



# Squamous Cell Lung Cancer in a Non-smoking Woman: A Case Report with Review of the Literature

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**Abstract:** Objective: The objective of this paper is to present, from a case, clinical parameters, imaging and anatomopathological assessments of the pulmonary squamous carcinomatous process in a non-smoking woman with a survival of more than 5 years. Case presentation: A 52-year-old patient who has had a pulmonary squamous carcinomatous process since 2014, revealed from a dry cough associated with mild dyspnoea without hemoptysis or chest pain. The imaging showed a left lung seat of two large masses, one of which extended towards the diaphragmatic dome, penetrating extensively into the abdomen, with a large abdominal contingent. Anatomopathological examination and the Immuno study -history -chemical evidence of a moderately differentiated squamous carcinoma infiltrating the lung. According to the TNM and AJCC 2016 classification, the patient was classified as T4N0M0 and she benefited from a navelbine cisplatin type chemotherapy with a minimal response of approximately 10% according to the RECIST criteria then two other lines of chemotherapy with initiation therapeutic pose. In 2019, she had a histologically confirmed metastatic relapse to the liver, treated with paclitaxel-carboplatin-type chemotherapy with clinical and radiological stability at assessment. Discussion: Squamous cell carcinoma is present in both smokers and non-smokers. Non-smoking females are two to three times more likely to develop lung cancer than non-smoking males, but female gender is a favourable risk factor. Conclusion: lung cancer in non-smoker females is becoming more and more frequent with genetic susceptibility as one of the etiological factors. The search for molecular alterations allows an increase in survival with the use of targeted therapies. Molecular biology is becoming an essential tool in the management of lung cancer with the presence of metastases.

**Keywords:** Squamous Cell, Lung, Non-smoking, Woman

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## 1. Introduction

Primary bronchopulmonary cancer has been the most common cancer pathology in the world for several years. About 85% of new bronchopulmonary cancers diagnosed worldwide are non-small cell bronchopulmonary cancers. The most common histological types, adenocarcinoma and the squamous cell carcinomatous process, account for 30 to 50% and 20 to 30% of non-small cell bronchopulmonary cancer [1].

Bronchopulmonary cancer is a cancerous pathology

strongly correlated with active smoking with 90% of cases occurring in smokers [1, 2]. The relative risk of bronchopulmonary cancer is 20 in the subject who smokes compared to patients who do not smoke [3]. However, this cancer is becoming increasingly common in non-smokers [4]. In a recent review of bronchial cancers diagnosed in the Lower Rhine over a period of 16 years, 1.4% of non-smokers in men and 28.9% of non-smokers in women were found [4].

Several causal factors have been identified to explain the appearance of bronchopulmonary cancer in people who do not smoke [1]. Among these, mutations are found in genes

that code for signaling proteins at both the initiation and maintenance of cell malignancy, which have been demonstrated in molecular and translational studies [1]. Adenocarcinoma and squamous cell lung cancer have different mutational profiles that allow them to respond differently to targeted therapies. Studies in the past have shown that EGFR, KRAS, HER2 and BRAF have recurrent mutations in adenocarcinoma [5, 6] and that they are particularly found in women, non-smokers and Asians with bronchopulmonary cancer pathology [7, 8]. The objective of this work is to present the peculiarities of this tumour in women exposed to passive smoking and survival at 5 years, which is rarely seen in clinical practice.

## 2. Observation

This is a 52-year-old woman with exposure to passive smoking, and no concept of comorbidities, consulted in February 2014 for a dry cough associated with mild dyspnea without hemoptysis or chest pain. Clinical examination noted good general condition, and pulmonary examination noted abolition of the vesicular murmur in the left lung field, no digital hippocytoma or supraclavicular adenopathy. The rest of the somatic examination was unremarkable.

The initial radiological work-up performed by thoracic CT scan noted a left lung with two large masses; one located at the apex and presenting calcifications measuring 110 x 78 mm along its two largest axes and largely necrotic, encroaching largely on the upper-middle mediastinum; the second one occupied almost the entire inferior lobe and partially the lingula, necrotic, largely multicompartamental, measuring 150 x 110 mm along its two largest axes, exophytic in appearance, with a large extension towards the diaphragmatic dome, encroaching largely on the abdomen,

with a large abdominal contingent located between the stomach medially, the spleen posteriorly and the colonic angle medially (Figure 1). The mediastinum study showed the absence of adenopathies but there was an extension by contiguity of the mass of the culmen and lingula towards the anterior contingent in intimate contact with the vascular structures of the mediastinum (trunk of the pulmonary artery and the aortic arch).

The anatomopathological examination and the immuno-histochemical study of the transparietal biopsy performed showed a moderately differentiated and infiltrating squamous cell carcinomatous process of the lung with the positivity of the anti P63 antibody (Figure 2). The extension workup made of bone scintigraphy and brain scan came back without any particularity. Abdominal ultrasound did not reveal any secondary lesions. The patient was classified as T4N0M0 Stage IIIA according to the TNM and AJCC classification.

The patient received six courses of Navelbine-Cisplatin-based chemotherapy, with post-treatment radiological evaluation by CT scan showing minimal regression (10% of RECIST criteria) of the left apical tumor mass measuring 80 x 74 x 50 mm and a stable appearance of the left lower lobar mass measuring 140 x 120 x 80 mm, largely necrotized. Second-line chemotherapy with 9 courses of Docetaxel was performed but clinical and radiological progression was noted. The patient was then put on Gemcitabine monotherapy on D1, D8 and D15 (9 courses) with clinical improvement and regression of the volume of the thoracic masses on CT scan. Therapeutic placement was decided in consultation with the patient with clinical and radiological monitoring. In December 2019, she presented a hepatic and bone metastatic relapse confirmed by a liver biopsy; she received a palliative chemotherapy based on Paclitaxel-Carboplatin six courses. Clinical and radiological evaluation showed stability.

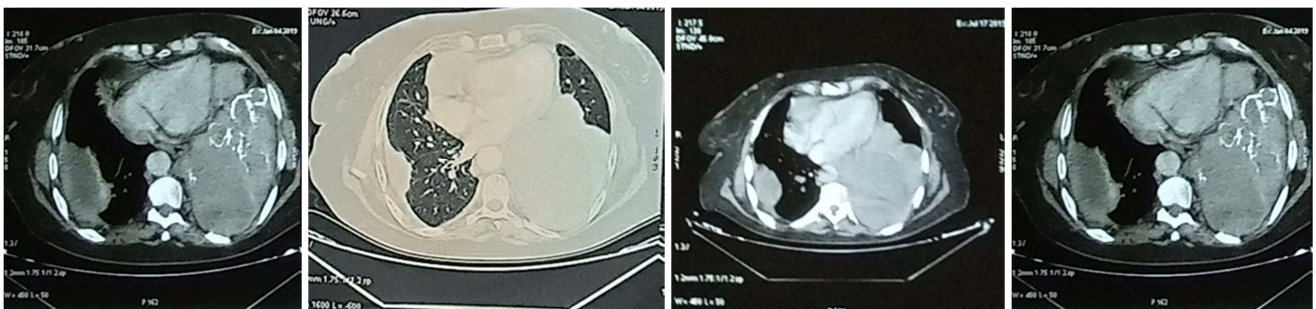


Figure 1. Thoracic transverse CT views.

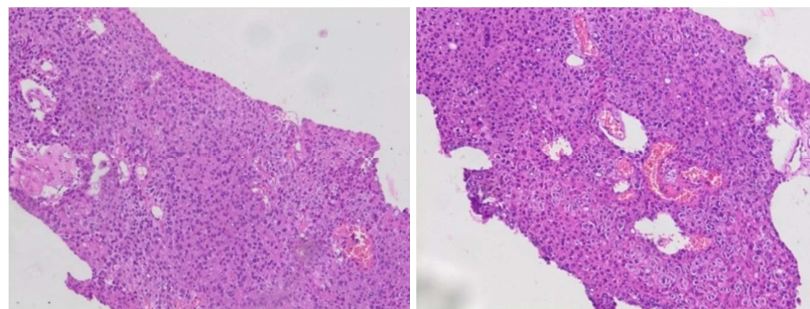


Figure 2. Histological aspect of liver metastasis from a squamous cell carcinomatous proliferation of the lung. G x 20.

### 3. Discussion

Lung cancer in women exposed to passive smoking is becoming increasingly common. In fact, WORLD07, very first prospective series with a large number of women with a diagnosis of bronchopulmonary cancer who were followed in a cancer department at the level of university hospitals in Spain for 6 years, noted a proportion of 43.4% smokers, 39% non-smokers and 38.9% passive non-smokers, mainly at home [9]. Non-smoking females have a two to three times higher relative risk of developing bronchopulmonary cancer compared to non-smoking males, implying that other factors, such as exposure to tobacco (passive smoking) or the environment, who are key factors [9]. Also in France, Debieuvre [10] noted a female predominance. Our patient was exposed to passive smoking for at least 30 years at home. In addition Yangle Huang et al. [1] reported that 14.7% (95% CI, 12.1% to 17.4%) of the patients in their study were non-smokers, suggesting that bronchopulmonary squamous cell carcinoma is no longer solely a cancerous pathology of the smoker. Furthermore, the comparison of clinical and pathophysiological aspects of the broncho-pulmonary squamous carcinomatous processes and the mutational traits of known oncogens has shown that broncho-pulmonary squamous cell carcinomas in never-smokers are significantly different from those of the more common squamous cell carcinomas of the lung associated with cancer smoking. [1]. Oncogenic mutations, particularly oncogenic alterations in EGFR, appeared much more frequently in non-smokers, which is similar to the results of a previous study [11]. In this present case the PDL1 was between 1 and 49%.

Contrary arguments exist regarding the involvement of female hormones, in particular estrogens, as a causal factor and a factor in the spread of lung cancer [12, 13]. While many studies have shown that it could be predisposing factors [12], a recent study of the work of the Women's Health Initiative found little or no relationship between reproductive life history or the use of hormone replacement therapies and the risk of developing lung cancer [13]. Among patients with family cancer, bronchopulmonary cancer was the most common cancer in more than 30% of these patients [9]. In the present clinical observation, the notion of a personal and family history of bronchopulmonary cancer was not found in the patient.

For a long time, non-small cell bronchopulmonary cancers in non-smokers were not included in different clinical studies as a different subgroup of patients. In none of the major benchmark trials that studied and validated first-line or second-line chemotherapy treatment for advanced non-small cell lung cancer was smoking status not included. Thus, there are few data on response or survival in nonsmokers treated with conventional systemic therapies [14]. Retrospective studies report conflicting results on the response to chemotherapy in nonsmokers. In a Memorial Sloan-Kettering study, 2010 patients treated for stage IIIB/IV NSCLC were evaluated for survival based on smoking status. Their

survival median was inversely related to smoking status quantified in pack-years (PY): 17.8 months for non-smokers versus 14.6 months for patients with smoking below 15 PA and 10.8 months for smoking above 15 PA ( $p=0.03$ ) [15]. The treatments received by the patients were not detailed and neither was the EGFR mutation status. In another retrospective study of 4546 patients, including 724 non-smokers and 3842 smokers, treated for NSCLC stage I to IV, no difference in survival was found according to smoking status [14]. The hypothesis that nonsmokers respond differently to chemotherapy has not been clearly confirmed. On the other hand, if the population selection is biological (presence of an EGFR mutation), response rates to chemotherapy are generally better than those of EGFR wild-type patients [3, 16]. Female gender, regardless of histology and stage, is a good prognostic factor in bronchopulmonary cancer [9]. Spanish women in the WORLD07 study had a median overall survival of 24 months and a survival proportion of 50% in two years. 16.3 months is the median overall survival of patients with metastatic non-small cell lung cancer [9]. With its survival rates, this corroborates the superiority in survival among women; advantages of female gender also found in the Spanish Lung Group studies Cancer Group [9, 13] but in other studies [17]. In metastatic non-small cell lung cancer, a comparison of four first-line chemotherapy studies noted a statistically significant difference in median overall survival in females versus males (12.9 months vs. 9.3 months with a statistically significant  $p$ ) [9]. The median time to progression value for women was 6.8 months compared to 5.3 months for men. This time was statistically significant with a  $p<0.009$  [9].

Non-small cell lung cancer is becoming more common in many countries, which is a major public health problem. That requires the Development of prevention policy, diagnostic strategy and treatment of this pathology in both men and women. As research is part of the development of management policies, it must be innovative and address molecular biology lung cancer occurs in patients who have never smoked [9].

### 4. Conclusion

Lung cancer in non-smoker women, otherwise times not uncommon, is becoming more and more common. This increasingly high frequency is explained by several factors, among them we find activating mutations in the genes encoding signaling proteins. Chemotherapy plays an essential role in the management of broncho-pulmonary cancers, but survival is poor. With the advent of molecular biology leading to the search for oncogenic drivers, targeted therapies and immunotherapy are bringing a glimmer of hope for longer survival.

### Conflict of Interest

The authors declared no conflict of interest.

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