Lung cancer-late stage at diagnosis in two comparative groups

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Abstract: - Bronchopulmonar cancer represents the main cause of death through neoplasia in numerous industrialized countries.We conducted a survey from January1999 to December 2005 on 116 patients admitted in Cluj Napoca Pneumology Clinical Hospital and we compared with a second group admitted in the Baia Mare Hospital (153 cases).We introduced in the study patients diagnosed with lung vancer and analized age, gender, environment of provenance,smoking status, exposure to professional noxes, the average time span from the inception of the clinical semeiology until diagnosis, confirmation of the neoplasia, diagnosis of hepatitis metastases. The survival rate of lung cancer patients depends on the moment of diagnoses. Statistical data and the analysis of the two groups included in the study, reveal that most patients went to the doctor in late stages and the surgical moment was excelled and for this reason we recommend an increase in the family physicians' attention with regard to patients who smoke and come in for consults even with minimal respiratory semeiology and to direct them as quickly as possible to a pneumology department .

Key-Words: - Bronchopulmonar cancer, lung cancer, early diagnosis, hepatic metastases

1 Introduction Bronchopulmonar cancer represents the main cause of death through neoplasia in numerous industrialized countries, and continues to remain a public health issue which concentrates considerable biological and therapeutic research efforts At the time of diagnosis, only 15% of patients have a local disease, 25% - 30% have a locoregional extended disease and over 55%have metastasized cancer

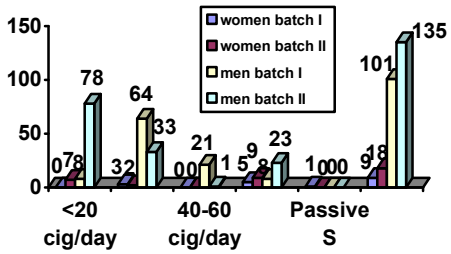
2 Problem Formulation We pursued two groups of patients:the first batch (batch I) consisted of 116 cases, hospitalized at the Cluj Napoca Clinic of Pneumology for a period of 6 years, from January1999 to December2005. The second batch (batch II) consisted of 153 cases with lung cancer, admitted at the Baia Mare Hospital of Pneumology in 2005. The patients underwent the following investigations: clinical examination, complete blood and biochemical tests chest X-rays, EKG, abdominal ultrasound, hepatic scintigraphy, chest CT, fibrobronchoscopy with brushing, bronchial and transbronchial biopsies, chest ultrasounds.We analized patient age, place of origin, smoker/non-smoker status time elapsed from the onset of symptoms to diagnosis, radiographic and CT finding, results of biopsy at fibrobronchoscopy comparative in both batches. **Criteria of inclusion:** patient first time diagnosed with broncho-pulmonary cancer, confirmed with broncho-pulmonary cancer histology or with unconfirmed broncho-pulmonary cancer histology; but the existence of the tumour was proven by fibronchoscope and by computer tomography in correlation with clinical and biological data, including the dosage of specific tumour markers.

3 Problem Solution-Results The relation between the gender patient and the apparition of pulmonary cancer in both batches: we observed the predominance of male in both group (batch I90,51% and 88,23% in batch II). **The correlation coefficient** calculated for both batches, **r = 0, 99** indicates that there is a correlation between the "male gender and the apparition of pulmonary cancer". In **batch I**, the **urban/rural** ratio = 1, 82 (~ 2 times) from the total number of cases, and in batch II, this proportion urban/rural = 1, 2 times. The age average was smaller within the urban environment in the first batch and greater in the second one; nevertheless this aspect is not significant. With

regard to the gender of the patients diagnosed with pulmonary cancer and their environment of provenance, one can notice the for females, the urban/rural ratio equals 1, 75 for batch I and 1, 57 for batch II while for men, the ratio is 1, 83 for batch I and 1, 17 for batch II.

The correlation coefficient between "male smoker and the total cases from batch I" is **r = 0, 99** indicating that there is a great connection between the male gender and the smoker category in the advent of cancer. When reported to women, **r = 0, 694563984** indicating there is a relative correlation between smoking and the female gender and the advent of cancer. **The correlation coefficient r = 0, 50**, between "the advent of cancer and lack of smoking" is smaller than the correlation coefficient between "smoking and the advent of cancer".

BPC cases based on the number of cigarettes / day and their allotment on genders



In **batch I** we recorded 40 (34, 48%) confirmed cases of BPC with **exposure to professional noxes**, a great number was allotted to the exposure to **chemical agents** (13/40) **32, 5%**, followed by the exposure to **Ni, Cr, Ti, Si, Cu, Pb, Au, Zn** (10/40) 25%. **The correlation coefficient r = 0, 94** shows that there is a correlation between the „presence of insults and the advent of pulmonary cancer". In **batch II**, those exposed to professional insults represented **25, 49%** (39/153) of the cases with the greatest exposure **15, 68%** from batch II and **61, 53%** of cases with BPC and exposure to insults were allotted in the category of nonferrous minerals due to a mining specific geographical area while in all other regards, the exposure was similar.

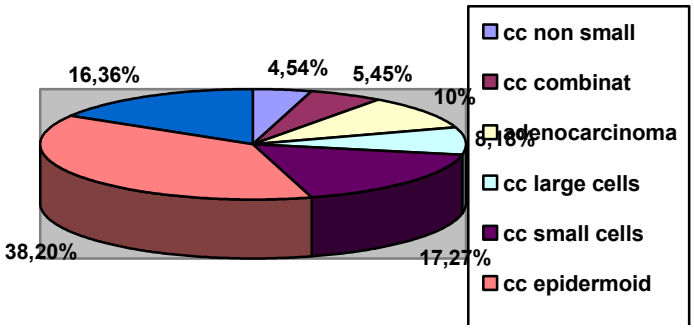
The coexistence of **heredocolateral antecedents (HCA)** of broncho-pulmonary cancer (BPC) was ascertained in **10, 9%** of which 10% were associated with smoking as risk factor while just one case 0, 9%) did not present any other risk factor as the patient was female and did not smoke. The average age of patients with this association was 57, 6 years. In batch **II**, we found 3 cases of BPC with HCA of pulmonary neoplasia (**2, 72%**) all among male smokers from the urban environment with an average age of 60, 33 years. **In batch I, the average time span from the inception of the clinical semeiology until admission into** the pneumology ward and the determination of a pulmonary cancer diagnosis was 12, 6 weeks (~ 3 months) with insignificant variations depending on the histological type., gender or the patient's environment of provenance;. Patients are mainly smokers and implicitly suffer from chronic cough and as a consequence they ignored this symptom or did not notice a change until another symptom like haemoptysis or the alteration of the general state appeared and at that moment they went in for consultation. Within **batch II** the interval between the advent of symptoms until presentation was smaller than for batch I. In batch II the interval between symptoms inception and presentation at the hospital was smaller than in the case of batch I(11, 6 weeks). The rural/urban difference within each batch and between batches I and II regarding the interval between clinical semeiology inception and the diagnose of cancer depending on the fact that the Pneumology hospital from Cluj is a university clinic so it is a clinic were patients come from all over the territory, some are patients who were treated previously without having a clear histopathology diagnosis and the clinic is the last place were they come for evaluation. In batch I we observed that the **predominant debut symptom** was cough 81,81%, followed by weight loss 60%, shortness of breath 58, 18%, thoracic pain 53, 63%, haemoptysis 27, 27%, and other symptoms in smaller percentage and 4 cases without respiratory clinical semeiology (3, 63%). In **batch II** we found that the predominant debut symptom was still cough 88, 23%, followed by thoracic pain 62, 74%, weight loss 52, 94%, shortness of breath 45, 75%, haemoptysis 24, 83%, and other

symptoms in smaller percentages; also there were 2 cases with no clinical respiratory semeiology (1, 3%). The analysis of symptoms of BPC cases from both batches in relation with smoking has revealed a coefficient p = 0, 01 (< 0, 05) indicating that there is a significant connection between "smoking and the number of symptoms". Of the 116 patients in batch I we performed FB for 111 (95, 68%), basically for all patients whose histological type was determined **Bronchial biopsy** determined the histopathologic type in 84, 94% of cases; in all cases of epidermoid carcinoma, small cell carcinoma, combined carcinoma and non small cell carcinoma. In batch II, FB was performed in 77, 77% of cases (119/153) and among these cases the tumour was visualized in 81, 51% as the diagnose infusion of this method is greater even when material for the bronchial biopsy cannot be harvested. **Bronchial biopsy** was performed for a small number of cases (6) and for those patients who accepted the iteration of FB within another department with possibilities of biopsic harvesting. Statistically, **p = 0, 02** (<0, 05) indicating the fact that there is a connection between the fibronchoscope investigation and the diagnosis of pulmonary cancer. **The cytology of sputa** in batch II (it was not performed in batch I because most cases benefited from bronchial biopsies was made in 37,9% and was positive in 15,51% . **Bronchial aspirate** in batch II (was performed for a few of the cases of batch I, statistically insignificant)made in 67,32% and is positive in 16,5% (17 cases) **Bronchial brushing** in batch II (was performed for a few of the cases of batch I, statistically insignificant) was made in 11 cases and is positive in 81,81%

In batch I, the cases where the histopathology diagnosis for confirmation could not be determined by bronchial biopsy, we tried to obtain histopathology confirmation by performing biopsies on other specimens: peripheral ganglions in 5 cases (4, 45%) from pleura in 2 cases (1, 81%), cutaneous tissue in 6 cases (5, 45%); liver 1 case (0, 9%); we tried to perform transthoracic and transbronchial biopsy for two cases but there was no biopsic confirmation. For 10 cases (9, 09%), the HP diagnosis was determined by histopathogical examination of the resection piece after surgery.

The highest percentage was attributed to epidermoid carcinoma The average age of patients from the 1st batch does not differ depending on the histological type as it was 56 years. In batch II the HP type could not be determined due to technical issues in 94, 11%: lack of a tuck for a bronchial biopsy, the diagnosis of pulmonary neoplasia was established by means of clinical biological and imagistic methods (X-ray- fibronchoscope-thoracic CT scan correlated with cytological bronchial aspirate, bronchial brushing with or without the cytology of the sputa, in some cases this provided certitude regarding the existence of neoplasic cells). The average age was similar within batch II – 55 years.

The allotment of cases from batch I depending of the HP type of the BPC



In batch I **we performed thoracic CT scan for 78 cases and 72 turned out to be BPC;** abdominal CT scan was performed at the same time with the thoracic CT scan in order to determined abdominal metastases. The cerebral CT scan was performed in 6 cases with confirmed BPC for patients with symptoms and in three cases it was positive; 2 cases initially and 1 case in evolution a year after diagnose. In batch II of 153 patients with BPC, thoracic CT scan was performed for 115 cases at the same time with abdominal CT scan. The cerebral CT scan was performed for 6 patients presenting symptoms and it was positive for cerebral metastases.

Of the 110 cases with BPC from batch I, 50 were subjected to abdominal ultrasounds and only 5 (10%) cases revealed secondary

abdominal determinations. This fact could be explained if we consider the human error factor related to the experience of the examiner. Of the 60 cases where the abdominal ultrasound was not performed 16 patients were subjected to abdominal CT scan, which detected metastases in 26, 66% of cases. Per total, abdominal metastases were confirmed in 21 (19, 09%) cases by completion of the ultrasound examination with abdominal CT scan. The second batch benefited of less ultrasounds (by 20%) but from those performed, the percentage of positive ones is much greater, 30% compared to just 10% in the first batch.

Of the 116 patients from batch I put under investigation, we dosed pulmonary tumour markers: ACE, NSE, Cyfra 21-1 and LDH for 31 patients, of which 3 women and 28 menThe statistical analysis of the correlation between the value Cyfra 21-1 and the size of the tumour with a correlation coefficient **r= 0, 210175** indicated that there is a low linear relation between the two variables. Also, the coefficient **p =0, 574332** (p > 0, 05) shows that the cyfra 21-1 value and the size of the tumour are independent. The correlation coefficient between cyfra 21-1 and the number of metastases is **r = 0, 08468**, resulting a low linear relation between the two variables. Just the same, the correlation coefficient between the number of packages of cigarettes smoked per year and the number of metastases for patients with cyfra 21-1 increased is **r = 0, 36870** resulting a decreased linear relation between the two variables

Hepatic metastases In batch I we can notice that: Histopatologic types epidermoid and adenocarcinoma have metastasized in the liver in equal proportions 33, 33%, the fifth case being a combined carcinoma with squamiferous cells and adenocarcinoma. We observed that the hepatic metastasis is correlated with the size of the tumour (4/6 = 66, 66%) but this has nothing to do with the number of hepatic metastases (small sized pulmonary tumour is associated with a unique metastases and vice-versa), statistically without significance due to the small number of cases. The epidermoid HP type metastasizes in the liver when the pulmonary tumour reaches a greater scale while adenocarcinomas metastasizes early when the primary tumour is small (2-3 cm) as it is a known fact that the epidermoid type metastasizes initially locoregional and undue at a distance, and adenocarcinomas metastasize early from a haematogenous point of view. In batch II we notice the percentage of correlation between the tumour size and hepatic metastasis is 66, 66% 6/9 cases with tumours > 6 cm). A correlation with the HP type cannot be made in this batch as it was not investigated enough. The prediction of hepatic metastases: the role of hepatic scintigraphy in the early detection of hepatic metastases in the batch under study: from the 110 cases of batch I diagnosed with BPC we performed planar hepatic scintigraphies, dynamic hepatic scintigraphies (angioscintigraphy: ASH) and SPECT tomoscintigraphy within the Department of Nuclear Medicine of the Medical Clinic no. III from Cluj Napoca for 12 patients, 2 women and 10 men, in relation with ultrasound examination and hepatic CT scan and for one case, we performed a hepatic Doppler ultrasound in order to disclose hepatic metastases in an infra-radiological phase. We performed planar hepatic scintigraphy and ASH in 12 cases, completed with SPECT tomoscintigraphy in 6 cases. We discovered hepatic metastases and confirmed them with ultrasound in 2 cases: one initially confirmed also by a hepatic biopsy (LIS spinocellular epidermoid carcinoma) and a case of positive ultrasound for hepatic metastases in evolution at 2 months after the first examination (LID mucinous carcinoma cu "seal ring" cells. From the total cases subjected to planar hepatic scintigraphy and SPECT (12 respectively 6) in 7 of them the scintigraphic examination was positive for secondary determinations and the IPH value was increased and the ultrasound examination was negative (58, 3%). Of the 7 cases with positive scintigraphic examination and negative ultrasound examination, for one case the scintigraphy proved to be false-positive and the Doppler hepatic ultrasound revealed a hepatic haemangioma while for the second case, the hepatic ultrasound disclosed the metastasis at a

subsequent examination 2 months later. Accordingly, per total, the planar hepatic scintigraphy examination combined with SPECT tomoscintigraphy was positive in 8 cases (8/12 = 66, 66%) and only one case was false-positive for metastases (hepatic haemangioma), true positive in 7 cases (7/12 = 58, 33% from the batch under examination and 7/11 = 63, 63% of the cases confirmed as having pulmonary cancer). The ultrasound – hepatic scintigraphy diagnosis correspondence was 5/12 cases 41, 66% and one case was ultrasound-scintigraphy positive during the first examination while for 4 cases both examinations were negative. Hepatic scintigraphy could predict by several months the apparition of hepatic metastases as it is useful even in cases where the diagnosis is doubtful, uncertain: primitive or secondary tumour, as well as in excluding the neoplasia diagnosis (the invalidated case was initially diagnosed as spinocellular epidermoid carcinoma by means of bronchial biopsy). Related to the size of the primary tumour, we noticed that there is no direct commensurate connection between the size of the tumour and the arterialized hepatic perfusion while the small sized tumours presented IPH > 55%. Statistically, r = 0, 171721 indicates that there is no correlation between IPH and the size of the primary pulmonary tumour. After observing this batch of patients, we concluded that the scintigraphic hepatic examination plays a role in predicting the advent of hepatic metastases with at least 2 months before there is a possibility of visualizing them by means of ultrasound and it also states better what the size of the tumour is (case with hepatic metastasis confirmed by biopsy). We cannot draw a conclusion with regard to the histopathological type of pulmonary cancer and the prediction of hepatic metastases because the number of cases included in the study is to small, but apparently there is no relation between these variables, conclusion confirmed by other imagistic studies with clinical applications (21,1). In order to confirm these observations, it is necessary to perform additional studies on a larger number of cases. Because the prediction of hepatic metastases advent or their early discovery would frame the case into another stage and would change the therapeutic attitude, hepatic scintigraphic examination may be included in the protocol of examinations suggested in view of pre-therapeutic staging. Angioscintigraphy revealed an arterial index of hepatic perfusion IPH = 80% denoting an important arterialisation of the hepatic perfusion and pleading for the existence of secondary hepatic determination. Figure 1- Case 1 – planar scintigraphy

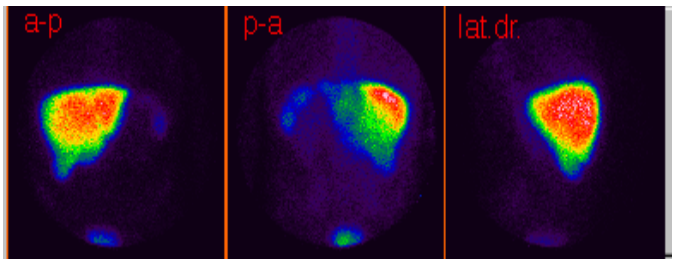
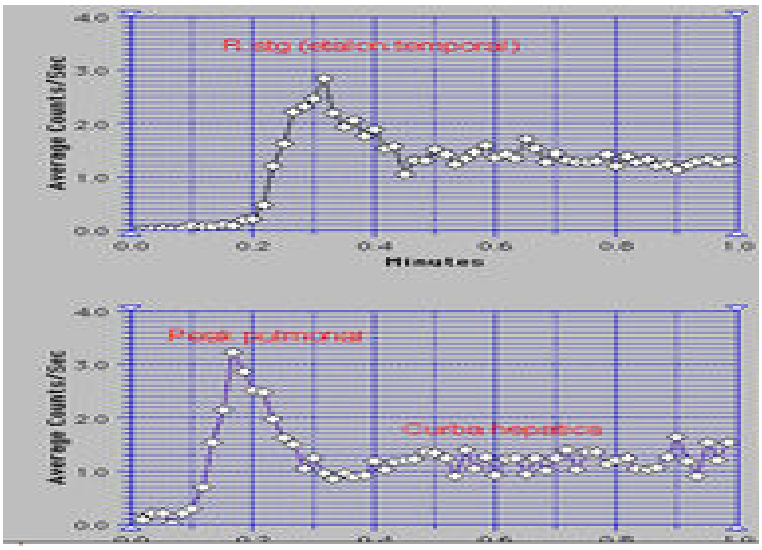
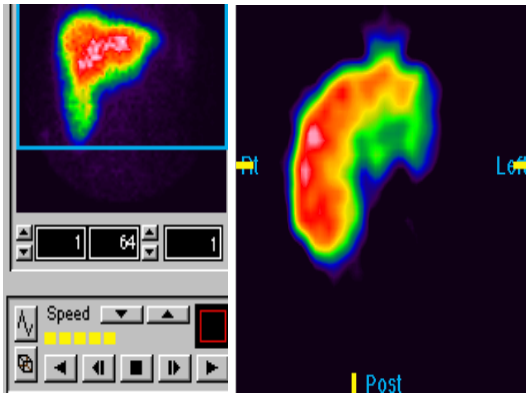


Figure 2- Case 1 – ASH



SPECT hepatic tomoscintigraphy confirms the non-homogenous attachment with a tendency towards lacunas in segments IV and V. Figure 2- Case 6 – SPECT



Dynamic hepatic scintigraphy was described as a method of improving the diagnosis specificity and sensibility of hepatic imagistic. This is based on the premise that the liver receives 20-30% of its blood reserve through the hepatic artery and the rest come from the hepatic vein. When tumours are present in the liver, they are dependent to grow and be viable to arterial blood. Due to this fact, the hepatic blood flow curve suffers a modification associated with an increase of the arterial blood perfused into the liver (74,2). Sarper et al, as well as Fleming et al described a scintigraphic method for evaluating the rate of the arterial flow reportable to the total hepatic blood flow. The hepatic perfusion index (IPH) was expressed as the ratio between the arterial flow and the total hepatic flow: IPH = $G_1/G_1 + G_2 = 0, 1 - 0, 4$. Patients without hepatic metastases were checked routinely ambulatory, clinically and by means of isotope imagistic and annual hepatic CT scans. The most important feature of this study is the fact that none of the patients with low IPH developed hepatic metastases yet and 18 of 29 patients with initially increased IPH values developed clinically visible hepatic metastases after one year. The consequence of this discovery is the fact that ~ 30% of patients should have been classified as having a more advanced stage "ab initio". An incorrect staging of the subgroup could lead to an inadequate stratification of therapy protocols and alterations of survival related data within studies regarding the natural history of the disease (2). In the group we studied, which consisted of patients with pulmonary tumours, the ultrasound advent of hepatic metastases related to scintigraphic investigation and determination of the hepatic perfusion by measuring the IPH value, appeared more rapidly than in the study presented previously (at 2 months). Of course, the confirmation of this observation needs additional studies. The practical advantages of dynamic scintigraphy are: it is not expensive ,it is non-invasive, sensitive and available in most hospitals, reproducibility and an interval of normal values were established. It seems that dynamic scintigraphy has an important role to play in the precise staging of gastro-intestinal cancer (2) while for pulmonary cancer there are no studies published in the specialized literature

4.Discussion Early discovery of broncho-pulmonary neoplasm was accomplished only for a small number of cases from both groups. Programs for the systematic tracking down of pulmonary cancer deployed in the '70s have confirmed the unique role of standard x-ray, with rough rays, for front and profile, completed by the cytological examination of the expectoration. But they demonstrated that for an important number of cases, lesions can be found on previous x-rays (3,4). We can notice that thoracic CT scan improves the diagnosis performance of pulmonary x-rays, detecting significant mediastinal adenopathies and classifying them in another stage. By increasing the resolution of modern CT scanners, the needs for screening examination for pulmonary cancer on a large scale and diagnosis studies, we can notice an increased need for reproducible analysis and accuracy of a large number of images. **Detection of the nodule** is one of the main challenges of CT imagistic because they can be overlooked due to their reduced size, to a relatively low contrast or their localization in an area with complex anatomy (5). It is expected that recent discoveries in computer aided diagnosis schemes (CAD) will help radiology in problems related to thoracic imagistic. In this era of the CT multi-detector, thoracic applications of the greatest interest include detection and measuring of pulmonary nodules' volume (5). According to Kersemans et al (6), pulmonary nodules are split into 3 groups based on their size: 1- 10 mm^3; 10 – 50 mm^3; over 50 mm^3. The CAD system does not detect nodules with a diameter under 4 mm (7) but the CAD system used by Lee et all was designed to detect nodules with diameters between 4 and 20 mm (5), this approach is practical in screening in order to obtain a true-positive rate sufficiently high without increasing the false-positive rate (5). It is thought reasonable that most pulmonary nodules under 5 mm are benign because they are normal pulmonary lymphatic ganglions or small granulomas (5, 7) and radiologists rarely miss seeing nodules with diameter of 20 mm or more (5). In order to

reach these aims in interpreting thoracic CT scan images is necessary not only to improve the detection of the pulmonary nodule, but also to find other schemes for a global approach of thoracic imagistic and of management methods (5). With a superb spatial resolution of modern "multislice" CT scanners and their ability to complete a thoracic scan during one breath, the software algorithms for computer aided detection (CAD) of pulmonary nodules has reached high levels of sensitivity and moderate false positive rates (8,9 **Important features of the patients' history include:**

1.the risk of malignancy increases with age: **(** 6 – 3% risk from 35 to 39 years**;**7 – 15% risk from 40 to 49 years **;** 8 – 43% risk from 50 to 59 years**;**9 – Risk greater than 50% over 60 years)**2.smoking history 3.malignancy history 4.travel history** – for benign lesions (histoplasmosis, blastomycoisis)5.**Occupational risk factors for malignancy –** exposure to asbestos, radon, nickel, chrome, vinyl chlorine, polycyclic hydrocarbons. **6.History of tuberculosis or pulmonary mycosis. 5.Conclusion**

The use of hepatic scintigraphy for the early diagnosis of hepatic metastases needs additional studies for the confirmation of cost efficiency because the number of cases included in the study was too small and compared to abdominal ultrasound, widely used today, the cost is higher. The ultrasound and CT scan result depends on the experience of the examining practitioner while planar hepatic scintigraphic examination combined with angioscintigraphy and SPECT tomoscintigraphy offer precise results with a possibility to calculate IPH. The survival rate of BPC patients depends on the moment of diagnoses. Statistical data and the analysis of the two groups included in the study, reveal that most patients went to the doctor in late stages and the surgical moment was excelled and for this reason I recommend an increase in the family physicians' attention with regard to patients who smoke and come in for consults even with minimal respiratory semeiology and to direct them as quickly as possible to a pneumology department.

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