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A combined imagistic and morphological approach of lung tumors: study on 64 cases

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Abstract

Lung cancer is currently one of the major health problems, being considered one of the most common causes of death by cancer worldwide. That is why establishing as early as possible a diagnosis in order to start an appropriate therapy still a challenge. The studied group consisted of 64 patients who were investigated following the next algorithm: chest X-ray, bronchoscopy, guided bronchial brushing and/or bronchoalveolar lavage followed by cytological examination and if possible, endobronchial biopsy followed by histopathological examination. Patients were usually men, aged over 60 years coming from an urban area, smokers and with symptoms evoking the presence of neoplasia. Tumors presented as large tumoral masses, placed centrally and with obvious local spread, protruding or pushing intraluminally with subsequent bronchial stenosis, usually complicated with ulceration and bleeding, which proved to be, when histopathological examination was possible, firstly squamous carcinomas and then small cell carcinomas. The imagistic investigation in conjunction with the cytological evaluation can establish the diagnosis of malignancy of centrally located lung tumors in almost 80% of cases. The diagnosis can be improved by increasing the number of biopsy sampling and/or by the immunohistochemical marking of the cytological samples.

Keywords: lung cancer, flexible bronchoscopy, cytology.

Introduction

Lung cancer is currently one of the most common malignancies, often discovered in advanced stages and having a poor prognosis without aggressive and precocious treatment. Therefore, lung cancer remains one of the greatest medical challenges with nearly 1.5 million of cases worldwide each year and is the most common cause of cancer death in the world [1–3]. Because most of patients are still discovered at an advanced stage, the current five-year survival rate is still very poor – only 15.6% in USA [4] – and thus, an early and precise diagnosis is imperative for lung cancer and crucial to determine optimal treatment [5, 6].

Bronchial endoscopy (bronchoscopy), with its variants, rigid – with precise indications but almost unused today for this purpose and flexible/fiberoptic bronchoscopy – currently considered the primary method for evaluating the tracheobronchial tree in patients with suspected lung cancer [7], contributes overwhelmingly in both diagnosis and treatment of lung cancer [8].

Flexible bronchoscopy is a very safe procedure. A retrospective study of 23 682 patients over a period of 11 years showed a mortality rate of 0.013% with a complication rate of 0.739% [9].

For diagnosis, the procedure allows the visualization and sampling of 95% of endobronchial, infiltrating and stenosing tumors and 68% of submucosal tumors [10]. Establishing the precise neoplasic etiology for endobronchial lesions is achieved using a variety of maneuvers under bronchoscopic control: biopsies, brushing, bronchoalveolar lavage (BLA), transbronchial punction without/under ultrasound guidance (EBUS) [11].

The value of cytological evaluation in the diagnosis of lung cancer is well established, the proportion of false-positive results being less than 1% [12–14]. A definitive diagnosis of cancer is established when cytological or histopathological examination highlights neoplastic cells, given that the literature shows that there is a good correlation between those tests, and the cytological diagnosis is unanimously accepted [12, 15].

The lesions extension is assessed accurately, the setting for operation indication in resectable cases being made currently only after bronchoscopic examination.

Regarding the treatment, it allows different therapeutic approaches. The therapeutic aspect of bronchoscopy in lung cancers is manifested in advanced inoperable tumors that occlude important segments of the bronchial tree. Various methods may result in recanalization of the endo-

bronchial lumen: resections using laser, crioablation, electrocoagulation or the endobronchial stenting.

The aim of this study was to emphasize the benefits that bronchial endoscopic examination combined with chest X-ray and pathological examination brings in the diagnosis of lung tumors.

Patients and Methods

Patients

The study group consisted of 64 cases with lung tumors that were endoscopically-investigated during the hospital admission with cytological assessment and, in some of the cases, histopathological examination.

The inclusion criteria for the patients in the study group were: the clinical symptoms suggestive for cancer and the radiological investigation which established the indication of endoscopic examination (Figure 1).

The study material was represented by: patient's medical charts, imagistic investigation records, cytological smears and records, biopsy samples and histopathological diagnosis records.

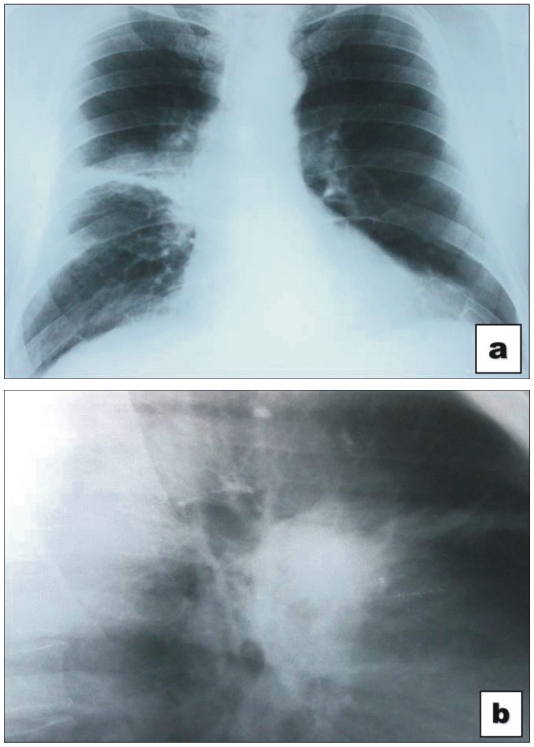

Figure 1 – ***X-ray images of a tumor with central location: (a) Anterior–posterior view; (b) Lateral view.***

Methods

The study was retrospective. The parameters to be studied were grouped as following:

▪ ***Parameters defining the clinical profile*** (gender, age, social-economic status);

▪ ***Parameters defining the morphological profile*** (tumor site, gross aspect, local complications, cytological profile, histopathological type, local extension).

For the assessment of endoscopic aspects, a Pentax FB-18B5 fiberoptic bronchoscope was used. Patients were sedated with Diazepam, then local anesthesia with 10% Lidocaine spray and 2% Lidocaine solution (maximum dose, 20 mL) was applied. The device was inserted nasally or orally, with the patient in the supine position, as distally as possible towards the affected bronchus. After thorough inspection of the bronchial tree, either bronchial brushing (BB) or bronchoalveolar lavage (BAL) specimens and endobronchial biopsy specimens were collected for cytology and histopathology respectively. Samples were taken from areas showing abnormality.

BB was performed using straight brushes. BAL specimens' procedure consisted in the administration of 120 mL of saline solution, with recovering of approximately 50% of the material.

For the assessment of cytological profile, smears were obtained either directly from bronchial brushings or from centrifuged BAL sediments (cell spreads). In case of BAL, the fluid obtained was centrifuged for 10 minutes, at 2500 rot/min; then, the supernatant was removed and the sediment was spread on slides. The number of slides was variable depending on the amount of cytological material, but usually six slides. The prepared smears or cell spreads were fixed either by air-drying for MGG stain, or by immersing them in 95% ethyl alcohol, during five minutes, for Papanicolaou stain.

For the assessment of histopathological profile, biopsy tissue fragments were processed by the classical histological technique (fixation in 10% buffered formalin and paraffin embedding) and stained with classical techniques (Hematoxylin–Eosin).

All the above-mentioned parameters were recorded in "database" files created in and processed with the Microsoft Excel module from the Microsoft Office XP Professional software package.

Analysis of some of the parameters required a primary data filtering, consisting in definition of sets of specific categories:

▪ For age evaluation: age group (AG) AG1 = 0–9 years; AG2 = 10–19 years; AG3 = 20–29 years; AG4 = 30–39 years; AG5 = 40–49 years; AG6 = 50–59 years; AG7 = 60–69 years; AG8 = 70–79 years; and AG9 = 80–89 years.

▪ For site assessment: left lung (LL) and right lung (RL); upper, middle and lower bronchus (UB, MB, LB); bronchial wall (BW) and extrabronchial with invasion in bronchial wall (EBIB).

▪ For gross aspect: vegetant (V); vegetant and ulcerated (VU); ulcerated (U); infiltrating (I).

▪ For cytological assessment of smears: positive (P); doubtful (D); negative (N); inconclusive (Inc).

▪ For histopathological assessment: *WHO* classification of lung tumors [16]; non-small cell carcinoma (NSCLC); squamous carcinoma (SC); adenocarcinoma (ADK); large cell carcinoma (LCLC); small cell carcinoma (SCLC).

▪ For local complications: stenosis (ST); hemorrhage (Hem).

The graphs (charts) showing the evolution patterns of different assessed parameters and the comparisons between them were done with the "Graph" instrument included in the "Word" and "Excel" modules of the Microsoft Office XP Professional software package.

Results

Gender distribution

Neoplastic proliferations were discovered more frequently in males, with a male/female ratio of "3" (Table 1).

Table 1 – *Gender distribution and ratio*

Gender	No. of cases	%	M/F ratio
Males	48	75	3
Females	16	25	
TOTAL	64	100	

Age distribution

The tumor incidence had an ascending trend towards the elderly, the largest number of cases being observed in the sixth decade of age (Figure 2).

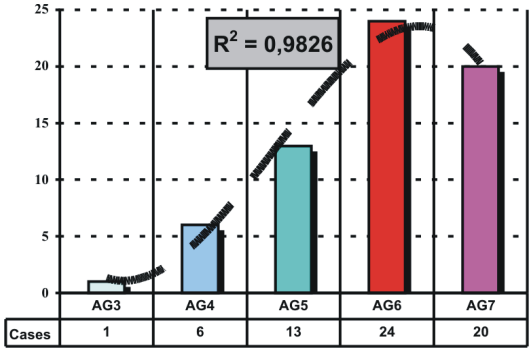

Figure 2 – *Age distribution.*

Social-economic status distribution

Lung neoplasia were almost twice more frequent in patients coming from urban areas (Table 2).

Table 2 – *Tumor distribution and ratio according to the relationship with social-economic status*

Social-economic status	No. of cases	%	U/R ratio
Urban	41	64	1.8
Rural	23	36	
TOTAL	64	100	

All patients were declared smokers and presented a clinical picture evoking the cancer.

Tumor site

Lung and bronchial distribution

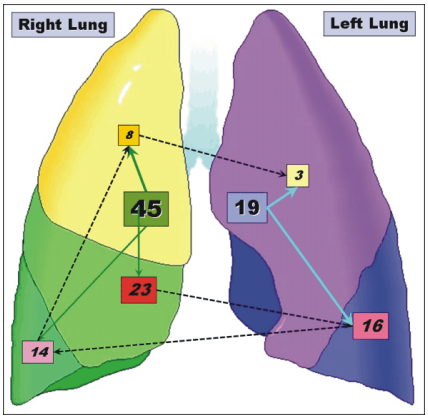

Figure 3 – *Lung and bronchial distribution of studied tumors.*

The studied tumors affected more frequently the right lung, with a right/left ratio of 2.3 (*i.e.*, 70% *vs.* 30%). The most affected lobes were the right middle one, followed by the left inferior one and the right inferior one (Figure 3).

Tumor relation with the bronchial wall

Almost two thirds of the tumors were supposed, on the radiological examinations, to develop from the bronchial wall (Table 3) whereas the rest of one third were "pushing" or infiltrating from outside the bronchial wall causing mainly bronchial stenosis with variable degree of obstruction (Figure 4).

Table 3 – *Tumor distribution according to the relationship with the bronchial wall*

Tumor site	No. of cases	%	B/EB ratio
Bronchial wall	42	65.6	1.9
Extrabronchial	22	34.4	
TOTAL	64	100	

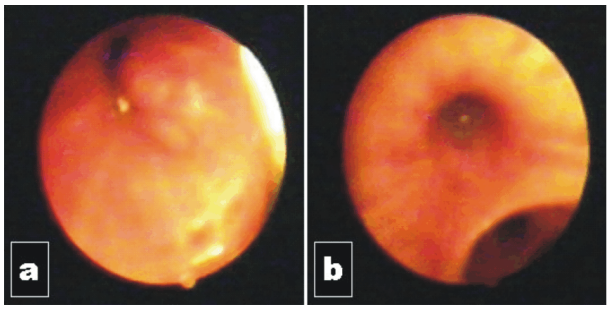

Figure 4 – *Extrabronchial tumor which compresses the bronchial wall and protrudes in the lumen causing partial obstruction of the medial basal segment of right lower bronchus.*

Gross aspect

Almost one half of studied tumors were seen, at the endoscopic examination, as protruding masses inside the bronchial lumen but which presented ulcerations in more than one half of them (Figures 5 and 6).

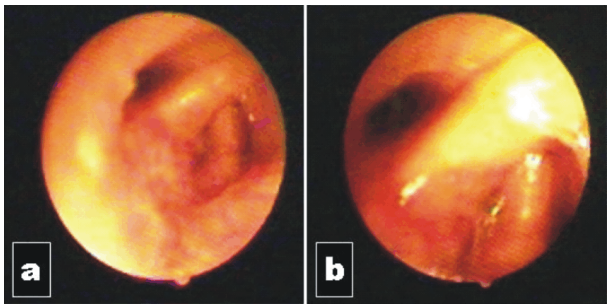

Figure 5 – *Vegetant tumor into the right lower lobe bronchus, which both protrudes in the lumen, causing partial obstruction, and infiltrates the posterior bronchial wall.*

The other almost one-half of the tumors had an infiltrating gross pattern in the bronchial wall, resulting in a variable degree of luminal stenosis (Figure 7). Only one tumor with infiltrating pattern was associated with ulceration. The ulcerating gross aspect was overall more frequent than the pure vegetant pattern. However, it was observed alone in only three cases. Except for those cases and the one mentioned above, the ulcerations were observed only on the surface of a protruding mass (Figure 8).

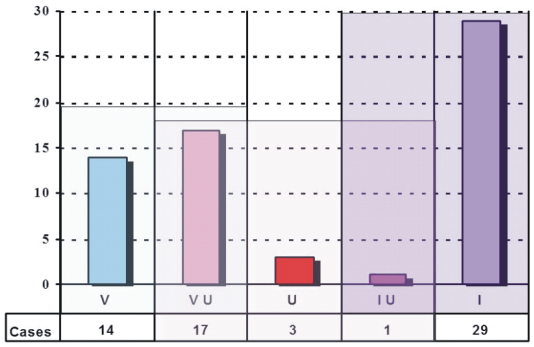

Figure 6 – ***Endoscopic gross aspect of studied tumors.***

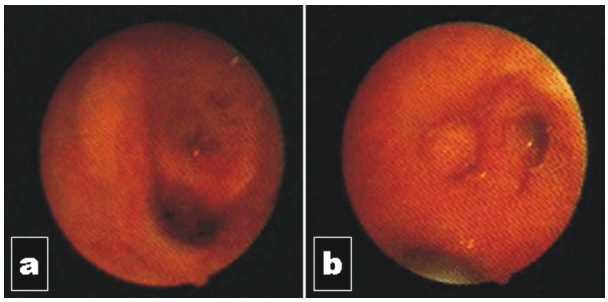

Figure 7 – ***Protruding tumor, with total obstruction of left lower bronchus and infiltration in the surrounding tissues.***

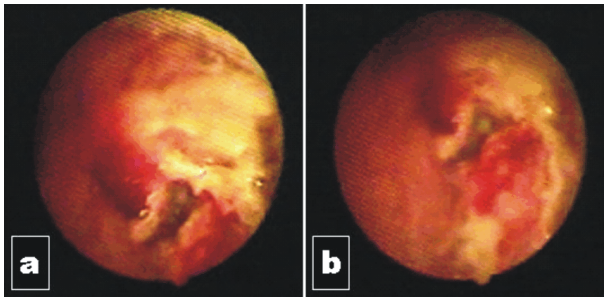

Figure 8 – ***Cauliflower like and ulcerated tumor with hemorrhagic areas and partial obstruction of the bronchial lumen.***

Complications

Local complications

The most frequent complication of studied tumors was the narrowing of the bronchial lumen, observed in almost 86% of cases (Figure 10), which evolved, in some cases, towards the total bronchial occlusion (Figure 9).

The bronchial stenosis was usually the only complication but it should be noticed that a significant number of the stenosing tumors presented also bleeding originating in the tumoral area (Figure 10).

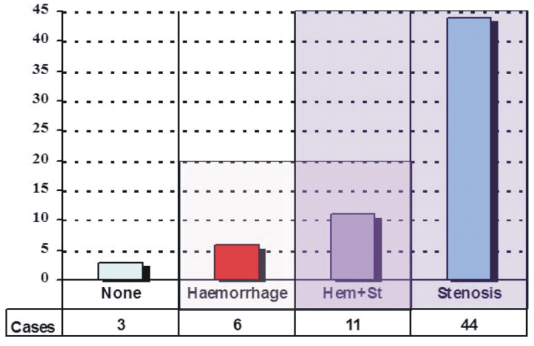

Figure 9 – ***Types of complications of studied tumors.***

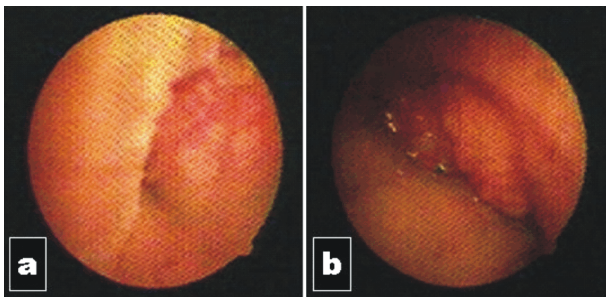

Figure 10 – ***Endobronchial tumor with total lumen occlusion in right middle lobe bronchus.***

The hemorrhage was the second important local complication, three times less frequent than stenosis and usually associated with it (two thirds of cases) than isolated (Figure 10).

Secondary pleurisies

Nine of the tumors were accompanied by a pleural effusion, which was, in all cases, homolateral.

Histological profile

Cytological examination

Cytology sampling techniques could not be performed in all cases. Thus, in four patients, the lesions were vegetant, cauliflower-like, friable and bleeding (in three of them from visible ulcerations of the tumor surface) which contraindicated both BB and BAL.

However, in most of the cases at least one of the two sampling techniques was possible, usually both of them (almost three quarters of the cases) (Table 4), thus allowing the cytological assessment.

Table 4 – ***Distribution of prelevation procedures***

Prelevation method		No. of cases	%	
Sampling technique	Brushing + BAL	47	73.4	96.8
	BAL	13	23.4	
No procedure		4	3.2	
TOTAL		64	100	

More than half of the smears revealed malignant features, being therefore considered as positive (Figures 11 and 12).

In five cases, the smears contained only normal epithelial cells, some reactive and inflammatory cells (Figure 13), which resulted in considering these samples as negative.

Besides these negative smears, there were another seven cases in which the cytological picture had not enough elements to raise at least the suspicion of malignancy.

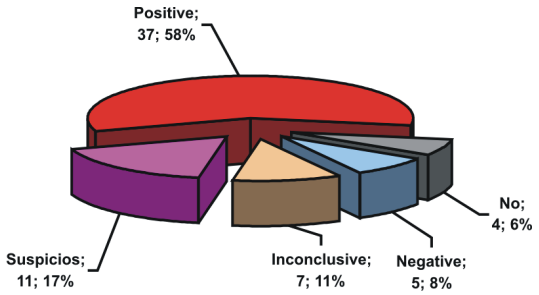

Figure 11 – ***Cytological types of smears.***

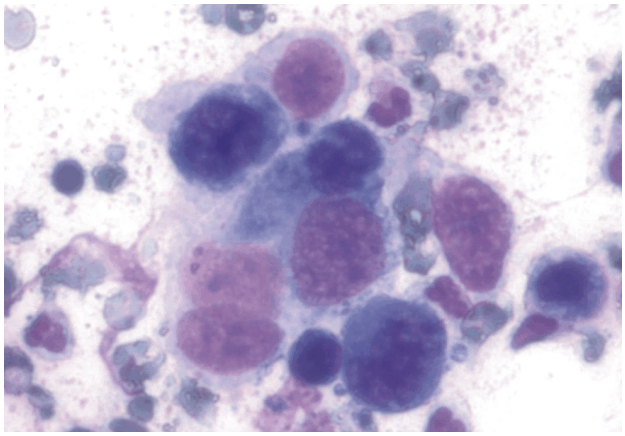

Figure 12 – ***Positive smear. MMG staining, ×400.***

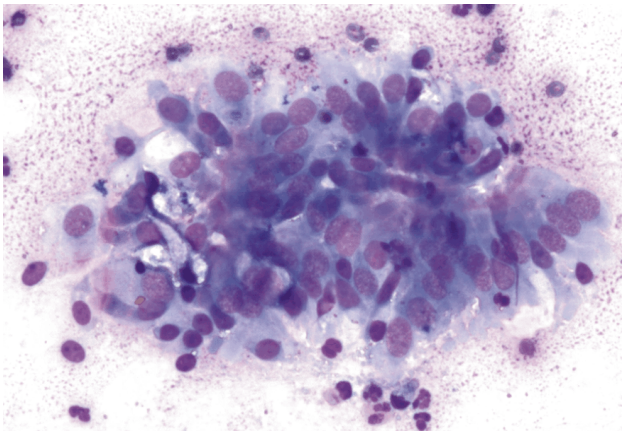

Figure 13 – ***Negative smear. MMG staining, ×200.***

Histopathological examination

While the cytological examination was possible in more than 90% of cases, the histological assessment was achieved in only 20 cases, representing almost one third of the cases, because of the tumor morphological status, *i.e.*, the pronounced stenosis, caused usually by extra-mucosal tumors, which were pushing a bronchial mucosa with intense hyperemia, or the presence of hemorrhages (Figure 14) or simply the friability of the hyperemic mucosa, all these contraindicating the biopsy.

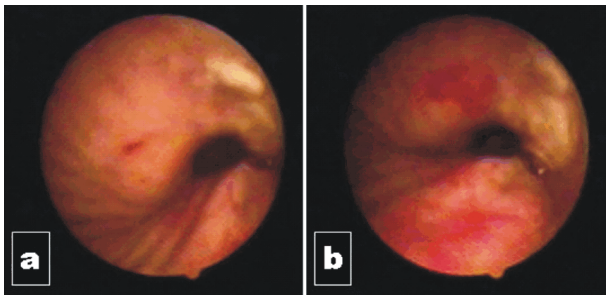

Figure 14 – ***Extrabronchial tumor, which infiltrates the bronchial wall and protrudes in the lumen causing partial obstruction. The underlying mucosa is hyperemic with areas of microhemorrhages due probably to a capillary fragility.***

More than half of the histologically assessed cases were squamous carcinomas (Figure 15), almost equally divided in poorly differentiated type (Figure 16a) and moderately differentiated type (Figure 16b).

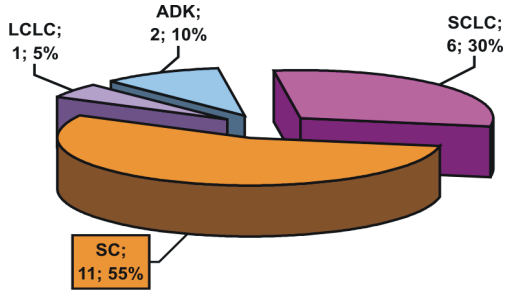

Figure 15 – ***Histopathological types.***

Another important contingent was represented by small cell carcinoma (Figure 16c), which was diagnosed in almost one third of the histologically assessed cases.

It should be noted also the presence in the group with histopathological examination of two cases of adeno-carcinoma and one case of large cell carcinoma.

Local extension

Radiological examination revealed an obvious local tumoral spread in the homolateral lung (Figure 17), in almost all cases (61/64 cases).

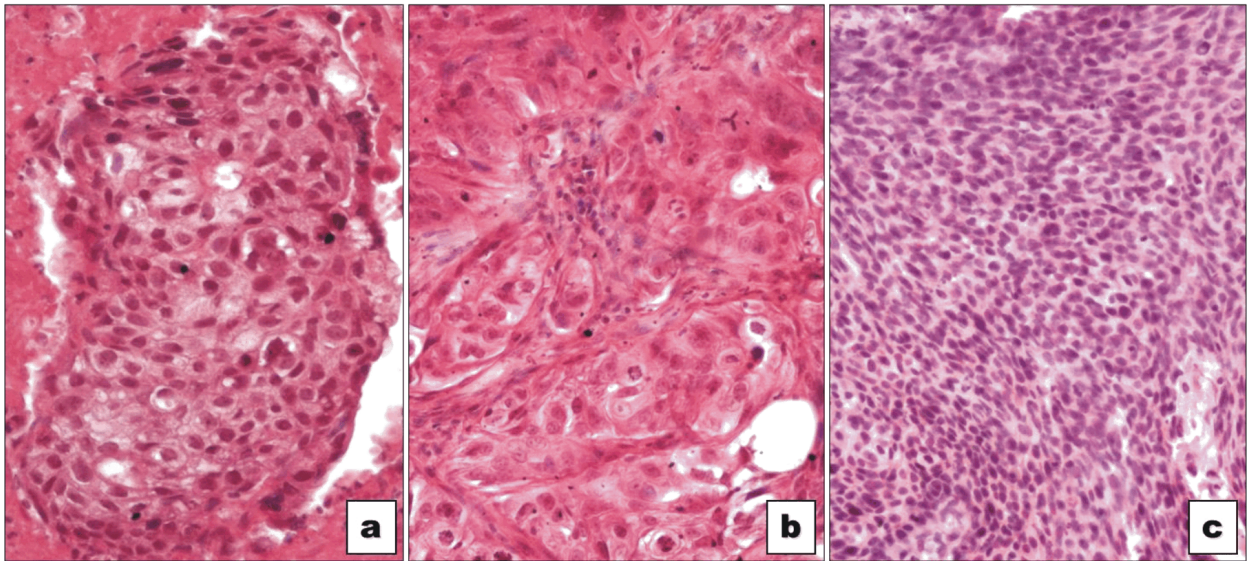

Figure 16 – ***(a) Poorly differentiated squamous carcinoma; (b) Moderately differentiated squamous carcinoma; (c) Small cell carcinoma. HE staining, ×200.***

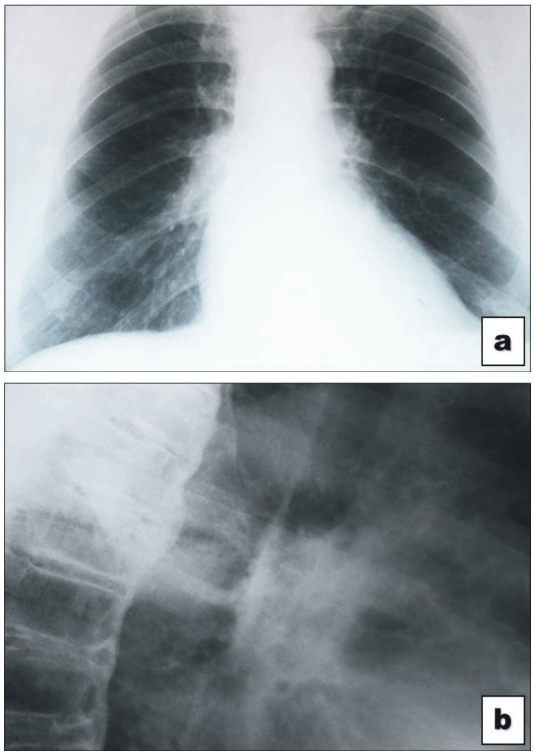

Figure 17 – ***Tumoral homolateral extension: (a) Anterior–posterior view; (b) Lateral view.***

Discussion

Clinical profile

The comparison of the age distribution in men and women showed that more than 80% of the men were aged over 60 years, whereas more than one third of women were younger than 60 years, in the sixth decade of life (Figure 18).

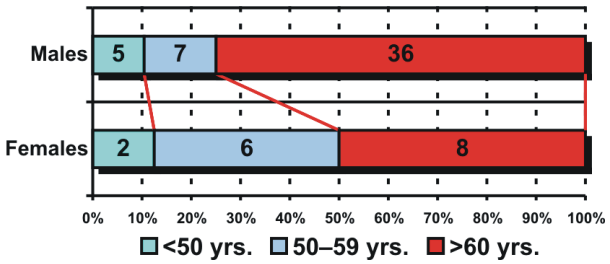

Figure 18 – ***Gender/age correlation.***

While both men and women were living in more than two thirds of cases from urban areas, the percentage of men coming from rural area was higher than that of women (Figure 19).

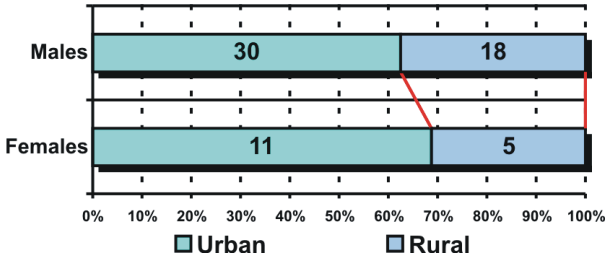

Figure 19 – ***Gender/social-economic status correlation.***

The percentage of patients aged over 60 years coming from rural areas was higher than that of patients in the same decades of life coming from urban areas (Figure 20).

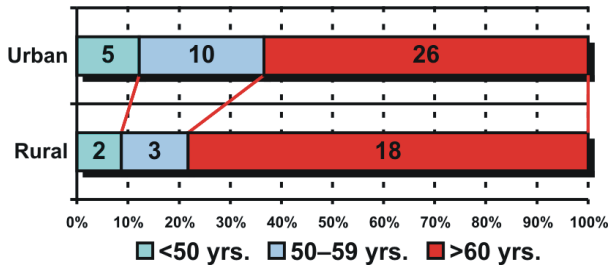

Figure 20 – ***Social-economic status/age correlation.***

In brief, a sketch of the patient in the studied group, investigated by fiberoptic bronchoscopy, could be: "usually a man, aged over 60 years coming from an urban area and older if he was from rural area, usually smoker and with symptoms evoking the presence of neoplasia". Our data are in accordance with the general evaluation of lung cancer incidence in the literature, evaluation that has variations depending on various factors such as period of time or histological type [17–19]. Thus, whereas male to female ratio was of 3:1 in our study, Rabahi MF *et al.* reported a ratio of 1.46:1 [11]. However, if these data are compared to those of the mid-20th century, when the male to female ratio was 10:1 [20], the progressive increase in incidence in females when compared with males becomes obvious.

Morphological profile

Tumor site

As Table 5 shows, the distribution of studied tumors in the pulmonary parenchyma was different from other published data, which report a higher frequency in the upper lobes of both lungs, with a slight predominance in the right upper lobe [11, 21].

Table 5 – ***Comparison of tumor site distribution with other studies***

Study	RLg [%]			LLg [%]	
	RUL	*RML*	*RLL*	*LUL*	*LLL*
Present study		70.3		29.7	
	12.5	*35.9*	21.9	4.7	25
Sahin F and Yıldız P (2011)		51.5		48.5	
	34.6	16.9		32.1	16.4
Rabahi MF *et al.* (2012)		68		32	
	28	30	10	20	12

RLg – Right lung; LLg – Left lung; RUL – Right upper lobe; RML – Right middle lobe; RLL – Right lower lobe; LUL – Left upper lobe; LLL – Left lower lobe.

However, Buccheri G *et al.* (1991) were mentioning the central sites of the right lung between the most affected sites, together with the upper lobes [22]. This different distribution in the studied group could be explained probably by the reduced number of cases as compared to the other studies.

The relation with bronchial wall, as revealed both by radiological examination and bronchial endoscopy, was similar to that observed by other authors (Figure 21) [21].

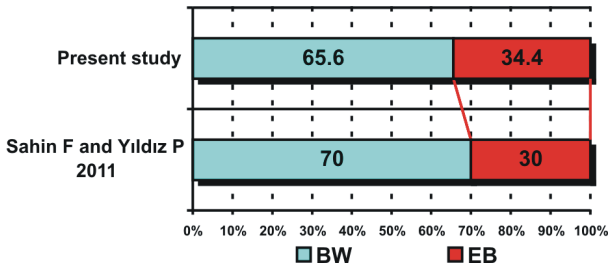

Figure 21 – ***Comparison with other studies of the relation with bronchial wall.***

Tumor gross aspect

A particularity of the studied group was the presence in almost all cases of what we defined as tumor complication, *i.e.*, stenosis of bronchial lumen, bleeding or, in some cases, both of them. Stenosis was mainly determined by infiltrating tumors but there was a significant contingent of protruding tumors whose dimensions caused quite often the total obstruction of the bronchial lumen (Figure 22).

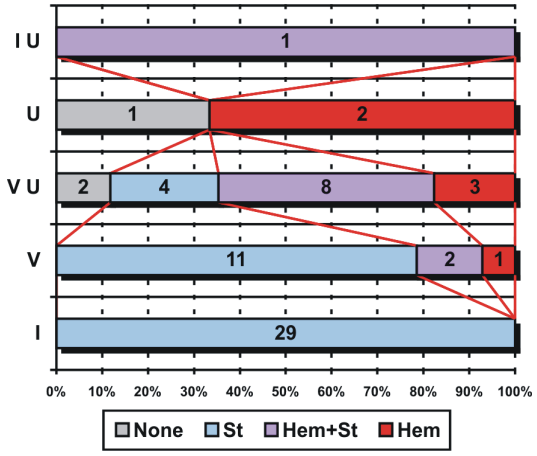

Figure 22 – ***Relationship between gross aspect and local complication.***

The presence of hemorrhage was usually related to the phenomenon of ulceration although there were three ulcerated lesions that were not bleeding and also three vegentant lesions with no ulceration but accompanied by small hemorrhages, determined by the friability of an obviously vascularized mucosa overlaying the tumor.

Histological profile

The gross aspect of most of the studied tumors was an important constraint in histological evaluation. Even in the case of cytological assessment, the sampling techniques have not been possible in more than 6% of cases not to mention about the reduced contingent of cases – only one third – where the biopsy could be done.

If the findings in the cytological assessment classified as inconclusive would be considered negative, and those classified as being suggestive of malignancy would be considered positive, and if the four cases with no cytology would be excluded, then the cytological examination proved to be useful for the diagnosis in 80% of cases.

If only the cases with histological evaluation are taken into consideration, then the sensitivity of the cytological examination is 90% (18 true positive cases and only two false negative cases) (Table 6).

Table 6 – ***Sensitivity of cytological examination in the histopathologically-assessed group***

	HP–	HP+	Total
Cyto–	0	2	***2***
Cyto+	0	18	***18***
TOTAL	***0***	***20***	**20**

This value is comparable with that obtained by Choudhury M *et al.* (2012) [23]. The only difference is that the Indian researchers analyzed separately the two ways of sampling whereas in our study we used in as many cases as possible the both techniques and were the brushing was contraindicated at least BAL was done.

The histopathological investigation, when possible, established the final diagnosis. As many other broncho-scopic studies have reported before [11, 21–25], **squamous cell carcinoma** was the most common histological type in our studied group (Figure 23).

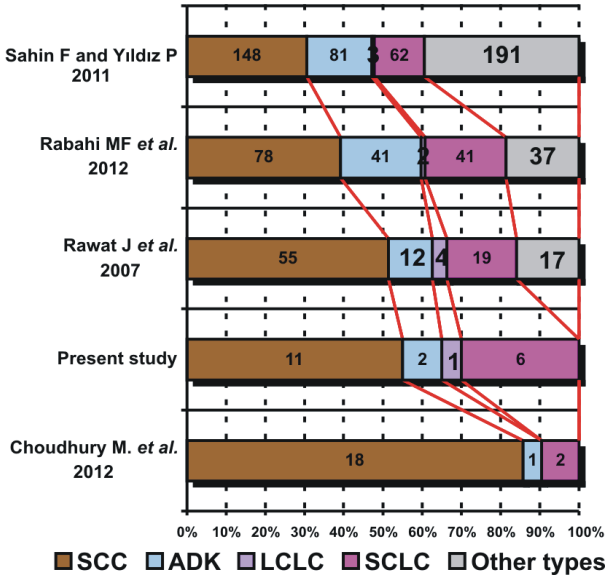

Figure 23 – ***Comparison of histopathological distribution with other studies.***

In all cases, the gross aspect was similar to that described in the literature [22, 26, 27], *i.e.*, an endo-bronchial cauliflower like mass, with an ulceration on its rough surface, in almost half of cases which was covered with necrotic material.

Small cell carcinoma, occupied the second position, as other studies also reported (Figure 23) and presented a characteristic aspect of tumoral mass, covered by an intact mucosa only with narrowing of the longitudinal folds over the tumoral mass.

The presence of the two cases of adenocarcinoma is in accordance with the other published data, which say that even this type of malignancy is one of the most common histological types of primary lung cancer, being the most frequent lung carcinoma in USA, Japan and the majority of western countries and the second, after squamous carcinoma in Eastern European countries [28, 29], its location is mostly peripheral, the endobronchial extension being very rare [30, 31]. In both cases, the tumors appeared as sessile masses, "pushing" the mucosa into the bronchial lumen and, thus, narrowing it.

In brief, the morphological profile of studied tumors could be: a large tumoral mass, placed centrally and with

obvious local spread suspected of malignancy on the chest X-ray, revealed on endoscopic examination as an intraluminal protruding or pushing process with subsequent bronchial stenosis, usually complicated with ulceration and bleeding, confirmed as malignancy by cytological evaluation in almost all cases, but precised as histological type in only one third of the cases.

Conclusions

The imagistic investigation, including here chest X-ray and bronchoscopy, in conjunction with the cytological evaluation of BB and/or BAL samples obtained during endoscopic examination can establish the diagnosis of malignancy of central bronchogenic tumors and tumors with central location and bronchial extension in around 80% of cases. The improvement of the diagnosis is depending on the improvement of the possibility of biopsy sampling for every tumor visualized endoscopically and/or on the completion of the cytological examination with an immunohistochemical marking either on the BB or BAL smear or on cellular blocks obtained from BAL.

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