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THESIS

***THE ROLE OF
BRONHOSCOPY
IN THE DIAGNOSIS OF
LUNG CANCER***

ABSTRACT

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KEY WORDS

Lung cancer, X-ray examination, bronchoscopy, cytology, histology

BACKGROUND

Lung cancer is a disease with high mortality, the 5 years survival in Europe being of 10%, a little bit higher than the one in the developing countries, 8,9%. The geographical pattern of the lung cancer incidence and mortality is very much influenced by the exposure to smoking and the geographical pattern in women highlights the differences in the smoking history compared to the one for men. The percentage of lung cancer caused by smoking can be assessed by comparing the incidence (or the mortality) observed in different regions with known incidence (or mortality) according to the rate of non-smokers.

The lung cancer etiology is however multifactorial, the most important causes being: smoking and the pollution of the environment.

There are various histopathological types of lung cancer and considering the type of neoplastic cells there is an evolution, a prognostic and a different treatment for each of them. Most of the lung cancers are carcinomas – epithelial tumors that grow from the epithelial cells so that 2 major groups have been established with a high clinical relevance – non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [Bogdan, 2008; Zander, 2008].

Nearly 25% of lung carcinomas are asymptomatic and are diagnosed by mistake at an X-Ray evaluation. The signs and symptoms appear due to the local spread of the tumor, regional spread and the metastasis, having a diversity depending on the anatomic-clinical type, histological type and the stage of the cancer. The clinical events in lung cancer can be: - events determined by the local spread of the tumor and the intrathoracic development; events determined by the metastasis; - general, unspecified symptoms; paraneoplastic syndromes.

The thoraco-pulmonary X-Ray is the initial, routine evaluation in lung cancer. Considering the tumor type there are several locations and radiological features of lung cancer [Zaharia et al., 2000].

For the diagnosis and staging of lung cancer, the CT evaluation with or without contrast is fundamental allowing the highlight and the exact defining of the tumor, the mediastinal lymph nodes and the suspected tumor metastasis [Hansell, 2003].

The magnetic resonance imaging (MRI) is recommended in few locations of the lung tumor: the assessment of the apical tumors; pericardic spread; the assessment of the vascular spread of the mediastinal structures and the pleural effusion in the context of a malignant lung lesion.

PET examination is useful to differentiate the benign pulmonary focal anomalies from the malignant ones: solitary pulmonary nodules, pulmonary masses and poorly shaped opacities; staging, especially of NSCLC, in order to establish the diagnosis of mediastinal adenopathies and extrathoracic adenopathies; post-therapeutic monitoring of patients with LC [Chuong, 2005].

The bronchial endoscopy (bronchoscopy) represents the key examination for patients with suspicion of LC, providing a direct visualisation of tracheobronchial macroscopic alterations and the possibility of sampling by: aspirate, bronchial brush, bronchial lavage, fine needle aspiration and bronchial biopsy.

The flexible bronchoscopy is the most useful diagnostic investigation in LC allowing: the detection of preneoplastic lesions (dysplasia), early neoplastic lesions (in situ carcinoma and microinvasive carcinoma); establishing the histopathological type; TNM staging; evaluation of extension and operability of the tumour [Ulmeanu et al., 2009].

Depending on the lung cancer type, the staging is carried out in different ways. For TNM staging of SCLC there were established two groups [Collins, 2007]: limited

stage: it refers to the disease extended to the level of a half of the thorax which may be comprised in one single radiotherapy field, but are excluded the neoplasms accompanied by pleural and pericardial fluid; extended stage: the filling in of neoplasms that exceed the characteristics of the limited stage. The international staging for NSCLC is more complex taking into account the three factors: primary tumour, lymph nodes, remote metastases.

PERSONAL CONTRIBUTION

MATERIAL AND METHOD

The basis of the study of this work was formed by a group of 541 patients hospitalized with the suspicion of lung cancer. The inclusion criteria of patients in the group was the covering of the investigation algorithm: Clinical Examination, Radiological Examination, Bronchoscopic Examination, Cytologic Examination, Histologic Examination..

The study material was represented by two categories of data sources: the medical records of patients and the human biological material represented by cytologic smears and the obtained histopathological preparations.

The study was complex, descriptive, multidisciplinary, of retrospective type, carried out into two great directions: clinical study and morphological study.

The Morphological study, in its turn, has two main components, each one with two directions of investigation, namely: The Imaging Study, which comprised the Radiological Investigation and the Bronchial Endoscopic Investigation and the Morphopathologic Study which comprised the Cytologic Investigation and the Histologic Investigation.

The investigated parameters were as follows: Clinical Parameters (Temporary evolution, Gender, Age, the Environment of Origin) and the Morphological Parameters (Localization of Tumours and Suggestive Imaging Aspects radiologically determined; The morphologic aspect of lesions endoscopically determined; the cytological profile and the histological profile determined within the morphopathological exploration). The preliminary data regarding the clinical parameters as well as the morphological ones evaluated were introduced in the data base tables from the Microsoft Excel module from the Microsoft Office 2010 software package. To the extent possible, there were also statistically evaluated different correlations between the clinical and morphological common parameters. The radiological imagistic study consisted in the evaluation of the images obtained on the two standard incidences for the pulmonary radiological examination: antero-posterior incidence and lateral incidence. The endoscopic study was performed on all the patients admitted within the hospital by means of a videobronchoscope with double channel provided by accessory tucks for taking sample of material for the cytological and histological examinations. The performance of the bronchoscopic investigation had two main objectives: to visualise the macroscopic appearance of the tumour at the level of the bronchial wall and taking sample of biologic material at the level of the tumour formation for the microscopic morphologic examination.

The morphopathologic study had two component parts: the cytological examination of the cellular biologic material taken during the endoscopic examination on coloured smears by using the May Grumwald Giemsa method and the histological

examination of the fragments of bronchial wall taken also during the endoscopic examination on preparations coloured with H-E.

The processing of the preliminary data from the cases introduced into the data base was carried out by means of the same Microsoft Excel module from the Microsoft Office 2010 Professional software package. For the data processing there was used the module Data Analysis of the Microsoft Excel software, together with the XLSTAT sequence for MS Excel. The statistic device of evaluation included: the determination of the minimum and maximum values of the arithmetic means and of the standard deviation, test " χ^2 " and the determination of Sensitivity, Specificity and of predictive values both positive and negative. The diagrams (charts) illustrating the evolution tendencies of the different evaluated parameters as well as the statistic comparisons between these were carried out by means of the "Graph" instrument from the "Word" and "Excel" modules of the Microsoft Office XP Professional software package as well as the software of the type "add on" XLSTAT 2009 for the „Excel" module.

CLINICAL STUDY

The time evolution of the number of cases had a descendent trend along the studied time interval. The patients' **gender**. It could be noticed a frequency 8 times larger on men than on women. The patients' **age**. The dissipation range of the age of the studied batch was comprised between 35 years old, which is the age of the youngest patient and 97 years old, which was the age of the oldest patient, with a mean age of under 60 years old. The **Origin Environment**. There was no predilection for any of the origin environment.

MORPHOLOGICAL STUDY

Radiological evaluation. We have found a preponderance of the assignment of the right pulmonary mass as compared to the left one. The suggestive aspects of the studied batch, stressed out on the radiological images were as follows: the nodular, non homogenous appearance, with inaccurate limits, the pneumonic appearance, the atelectasis appearance and the infiltrative appearance. Most of the cases have shown a single characteristic appearance on radiography. **The bronchoscopic evaluation.** Most of the images visualised at the endobronchic level have highlighted a single macroscopic morphological appearance. Also, there was a significant contingent of patients on whom the bronchial wall did not show evocative macroscopic appearances for a tumour proliferation. Most of the unique bronchoscopic modifications were of the infiltrative type. **Cytological evaluation.** Almost half of the examined smears have highlighted agglomerations of desquamated cylindrical epithelial cells to which there were added cells of the inflammatory complex, usually lymphocytes, but several times there were identified, apart from these, PMN. In a little bit over half of the cases, the cellular population was dominated by cells having nuclear and cytoplasmic modifications evocative for the malignant phenotype. On a third of these cases, the cytological panel of the smear was also completed by cellular elements of the inflammatory complex. **Histological evaluation.** In the studied batch we have noticed an obvious predominance of the carcinomas without small cells, with a reduced percentage of carcinomas with small cells. Among the types of carcinomas without small cells (NSCLC) the most frequently met was the adenocarcinoma. In the specialty literature the weight of the different histological types of lung cancer shows variations from study to study and

from region to region. In different bronchoscopic studies [Olaru et al 2013; Rabahi et al 2012; Choudhury et al 2012; Sahin and Yıldız 2011; Rawat et al 2007; Buccheri et al 1991; Koss et al 1999], the squamous carcinoma is considered as the most frequently met type of lung cancer. Our results concord with those communicated by other authors who report that in the USA, Japan and most of the Western European countries, the adenocarcinoma is the most frequently met type of pulmonary malignant neoplasia, and is ranked the 1st, after the squamous carcinoma, in the Eastern European countries (Chart 9.16) [Kenfield et al 2008; Riquet et al 2006; Subramanian and Govindan 2007]. It must also be underlined in the end the existence of the contingent which is more than significant of cases (almost half) in which the histological panel of the biopsy piece did not include cellular elements of malignant proliferation but only the presence of an inflammatory infiltration at the level of the bronchial mucous membrane.

STUDY OF THE CLINICAL AND MORPHOLOGICAL CORRELATIONS

In the overwhelming majority of the cases the algorithm of the imagistic and morphological diagnosis was completely covered, namely in each patient there could be carried out all the patients, namely: the radiological investigation as the first step, which was followed by the bronchoscopy performance, time during which there could be achieved first of all the direct macroscopic evaluation of the lesions and secondly, there could be taken biologic material both for the cytological morphological examination and for the histological and morphological examination.

Among the correlations between the results of the different investigation techniques, the **radiography** was correlated with the tumours localisation, with the results of the cytological examination and with the results of the histopathological examination. But this examination showed a reduced specificity, together with a lower positive predictive value due to the tumour emplacement, placed either in the vicinity of the bronchia that it compresses or partially invasive in the external bronchial wall which it infiltrated or caused an inflammatory reaction to the invasion rank, it did not reach up to the level of the mucous membrane so as to be "intercepted" by the biopsy tuck. Also there was a reduced number of cases in which the tumour probably located at the level of the bronchial wall and in an incipient stage, it was not identified either by the radiological examination or by the histopathological examination of the mucous membrane biopsy. Another correlation highly significant was registered between the results of the cytological and histopathological examinations.

The results of the endoscopic examination were correlated with the tumour localisation, with the results of the radiological examination and with the results of the cytological and histological examinations. The endoscopic examination showed a very high negative predictive value, signalling the capacity of the endoscopic examination to also forecast situations in which the tumour did not reach up to the level of the bronchial mucous membrane. Also, the positive predictive specificity and value were higher than on the radiological examination, due to the higher concordance between the endoscopic and histological examination.

CONCLUSIONS

Our study has led to the following conclusions:

The clinical profile of the patients included in the study is that of a man, usually, having the age a little bit under 60 years old, originating equally from the rural and urban environments.

The statistic comparative analysis of the three clinical parameters did not highlight any specific trait of the pulmonary tumours spread depending upon each of them influenced by the others.

The diagnosis algorithm complementary to the clinical examination, made of the methods of radiological and endoscopic imagistic investigation and the methods of microscopic cytological and histological investigation was completely covered in the overwhelming majority of cases, except a very reduced number of cases in which the side effects or incidents appeared during the endoscopic investigation did not allow the taking of samples of biologic material for the cytological or histological examination.

The results of the radiological investigation, the first step of the complementary algorithm were correlated with the tumour localisation but especially with the results of the cytological and histological examination on the piece of the taken bronchial biopsy.

The positive predictive specificity and value of the radiological examination as compared to the histological examination results were more reduced and respectively lower, due to the emplacement specific traits of the studied tumours which either did not reach up to the level of the mucous membrane so as to be "intercepted" by the biopsy tuck because they were either located in the vicinity of the bronchia that it compressed or they partially invaded the external bronchial wall by infiltrating it or causing an inflammatory response to the invasion rank, or they were not identified either at the radiologic level or the histopathologic one because they were in an incipient stage of development strictly at the level of the bronchial wall.

The cytological and histopathologic examinations indicated a very high level of concordance, signalling either the presence of a tumour or the inflammatory response developed in the bronchial mucous membrane adjacent to the tumour.

Finally, the endoscopic examination which represented the second step in the investigation algorithm had results which were significantly correlated with the tumours location but the most important, which were highly significantly correlated with the results of the other investigation methods within the algorithm.

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