CONTRIBUTIONS TO THE CLINICAL AND MORPHOLOGICAL STUDY IN LUNG CANCERS

Scientific coordinator:
Prof. Univ. Dr. Emil PLEŞEA

Ph D student:
Camelia MICU (DEMETRIAN)

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KEY WORDS:

✓ Lung cancer
✓ Histopatological type
✓ Immunohistochemistry
✓ Phenotype
ACTUAL KNOWLEDGE

The thoracic surgical pathology, including tumors of the lung had a number of changes in the last two decades, both due to the increasing incidence of lung cancer and the continuing evolution of thoracic surgery.

We know now deep enough of lung cancer pathology. Most histopathological classification of lung cancer, including the revised WHO classification, mentions four main types: squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. Are also described several histological subtypes and some rare forms.

New techniques, particularly immunohistochemistry, have provided a large amount of information about histogenesis, tumor differentiation and proliferation, information widely used to the classification of tumors.

Toate țesuturile epiteliale pulmonare, până la nivelul alveolelor inclusiv sunt de origine endodermică, iar elementele interstițiale sunt de origine mezodermică.

Lung cancer is one of the most common malignancy with a prognosis still very reserved. Approximately 65% of patients with NSCLC (non-small-cell lung carcinoma) presents for the first time to the physician with locally advanced or metastatic disease. Most cancer-related mortality is due to lung metastases.

Most cases are found in Europe and America and are strongly correlated with smoking. In average, a smoker increases his risk of developing lung cancer by 5 to 10 times, and in developed countries smoking is responsible for up to 80% of these cancers.

The prognosis of lung cancer remains one of the worst. Although the survival rate at 1 year (all stages) increased from 32% in 1973 to 41% in 1994, five years survival rate remained virtually unchanged at about 14%.
Among the risk factors, smoking has a leading role: it is responsible for 85% of lung cancer; incidence and mortality trends reflect changes in the consumption. We can say that smoking has made lung cancer from a rare disease in the early 1900s in the disease of the century the late 1990.

The second major risk factor is the exposure to radon, an odorless gas that has been suspected since the early twentieth century that could cause lung cancer to the miners working underground. Other environmental factors that can cause lung cancer are: arsenic, asbestos, nickel, polycyclic aromatic hydrocarbons, radon precursors, etc.

The biological characteristics of lung cancer are changing, pointing out an increased incidence of adenocarcinoma and a decreased incidence of squamous cell carcinoma.

Lung tumors have a wide variety of histological types with varying degrees of malignancy, from benign to those with a high degree of malignancy. Location of a lung carcinoma diagnosis is made by the pathologist. But there is no absolute pathological criterion allowing the assertion of the primitive character (bronchopulmonary origin and not metastatic) of a localised lung carcinoma.

The diagnosis of the primitive character of a lung tumor is made on a series of clinical, imaging, morphological and phenotype criteria. Of this so established diagnosis will depend further patient staging and future treatment.

It is worth mentioning the importance of interdisciplinary consultation for each new case.

Squamous cell cancer is the most common histological type of lung cancer in Western countries and also the histopathological type best correlated with smoking. Lung adenocarcinoma is the most common histological type of lung cancer found in Japan and some Asian countries and found also growing in the United States and other economically developed countries.
Small cell carcinoma has a complex histopathology and the highest degree of malignancy, despite its increased sensitivity to anticancer agents (chemotherapy) and radiotherapy. Male / female ratio is about 2:1, and the average age of patients at diagnosis is somewhat lower when compared to squamous cell carcinoma.

In lung cancer, as in other cancers, the three most important factors influencing the prognosis of patients are distant metastases, lymph node metastasis and local invasion, they constitute elements of the TNM classification.

The TNM system (2009, 7th edition) is the most commonly used today, using the most descriptive parameters such as:

- T: The tumor information
- N: Information involving regional lymph nodes
- M: Information about the presence of secondary tumors (metastases)

These parameters are quantified and finally combined to determine the clinical stage of the neoplastic process.
The base of the statistical study of the work was composed of a group of 364 patients admitted and operated in the Thoracic Surgery Department of the Centre Hospitalier d'Avignon (France) in a period of 5 years (01.01.2003-31.12.2007), with the clinical diagnosis, later confirmed histopathologically, of malignant tumor located in the lung parenchyma.

Histopathological interpretation was carried out in the Laboratory of Pathology of the same hospital.

From the main group the following subgroups were subsequently individualized, depending on the type of histopathological examination revealed:

• The Lot 1, the most consistent, of 348 patients with histopathological diagnosis of non-small cell lung carcinoma (NSCLC).

• The Lot 2, consisting of 5 patients with histopathological diagnosis of small cell lung carcinoma (SCLC).

• The Lot 3, consisting of 11 patients with histopathological diagnosis of carcinoid tumor.

The first group, the most consistent, was subdivided into three subgroups, consistent with NSCLC cancer subclassification:

• The subgroup 1A, consisting of 231 cases of adenocarcinoma.

• The subgroup 1B, consisting of 101 cases of squamous cell carcinoma.

• The subgroup 1C, consisting of 16 cases of subtypes less common of NSCLC (large cell undifferentiated carcinoma and large cell neuroendocrine carcinoma).
The study material was represented by two types of data sources. The first category was made up of medical evidence and documents, namely:

• The Epithor database (national database for thoracic surgery in France)
• Clinical observation sheets
• Surgical Protocols
• Records of histopathological diagnosis.

The second category was composed of histological preparations, block and archives from the Pathology Laboratory of the Centre Hospitalier d'Avignon (France).

The study was retrospective, and was structured in four chapters:

• The study of the general clinical context
• The pathological study
• The study of the correlations between histological type and sex, age, tumor location, surgery
• The study of phenotypic algorithm for cases undergoing immunohistochemistry

For the evaluation of microscopic parameters, were used fragments of lung parenchyma obtained intraoperatively after surgical resection.

In case of large postoperative parts (whole lung, pulmonary lobe, lung segment) were collected fragments of the suspected areas with macroscopic pathological appearance (tumor area), avoiding areas of tumor necrosis.

Lung tissue fragments were processed in the Pathology Laboratory of the Centre Hospitalier d'Avignon, initially stained with hematoxylin eosin only.

In cases where for the diagnosis was considered necessary to perform immunohistochemistry, immunohistochemical marking methods were performed.
RESULTS AND DISCUSSIONS

CHAPTER 2. GENERAL CLINICAL DATA ANALYSIS

The first parameter evaluated was distribution according to sex. Lung cancers were far more common in men, their number is almost 3.67 times higher than women.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Nr. of cases</th>
<th>%</th>
<th>M/F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>286</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>78</td>
<td>21</td>
<td>3.67</td>
</tr>
<tr>
<td>TOTAL</td>
<td>364</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Sex distribution for the entire lot

Gender distribution is maintained, generally defined the lots, except Lot 3, carcinoid tumors, which were found slightly predominant in women, consistent with the literature.
Patients included in the study group were mostly adults and especially elderly. Dispersion of the age was between 16 years, the youngest patient and 84 years, as was the oldest of patients. The age group which included most patients (107 patients, about 30% of the cases) was between 61 and 70 years, and grouping patients for periods of life we found that most involvement were in "elderly ".

Distribution by age remained generally the same in the lots and sublots studied, except for carcinoid tumors (group 3) that affected younger patients in accordance with literature data, showing a mean age of onset of 45-55 years for carcinoid tumors, occurring a decade earlier in typical carcinoids.

Annual distribution of cases reflected a slight tendency to increase in cases during the five years studied.

For the majority group (Group 1 - NSCLC) we analyzed the annual distribution related to sex in the most significant two subgroups (subgroup 1A - and subgroup 1B adenocarcinoma - squamous carcinomas), to ensure consistency with the literature.

Thus, for adenocarcinomas, has been a steady decrease both for the actual number of cases and the appropriate percentage for women, a situation which is contrary to literature data.

For squamous cell carcinoma we noticed an annual increase to the female population, a situation also contrary to literature data. We found no explanation for these findings although sufficient number of cases makes conclusions to be statistically significant.

Analyzing the evolution during the study of the number of cases of adenocarcinoma and squamous cell carcinoma in men, we found a slight increase in incidence of adenocarcinoma compared to squamous cell carcinoma.
For women the situation was opposite, with increasing number of cases of squamous carcinoma, against adenocarcinoma.

The histopathological types distribution was the basis for dividing the groups of patients in the study. Choosing the initial lot split considered major epidemiological differences, mean age of onset, therapeutic attitude, aggressiveness and prognosis described in the literature between the three major types of lung cancer (NSCLC, SCLC, carcinoid tumors).

The other two groups - SCLC and carcinoids - were represented by a small number of cases (11 and 5 cases).

Analyzing all histological types encountered, we found that there are eight such types, ranging in number from 3 cases (atypical carcinoid) to 225 cases (adenocarcinoma).

It is noted that most patients with NSCLC were surprised in early stages, allowing potentially curable surgery (including up to stage IIIA): 270 cases, representing 78% of patients.

It explains the good results at least in the short term in terms of survival. Should be noted again that the origin of cases (patients operated in a thoracic surgery service) is the determining factor of the preponderance of early stages, a situation different from the real proportion of daily practice (including thoracic surgery service in which the study was conducted).

The studied cases were practically only those arriving in the operating room with radical surgical intent. The TNM staging applies only to NSCLC cancers.

But until definitive histopathological diagnosis was established after surgery, most of the SCLC cancers carcinoid tumors were staged initially (in time of surgery) according to the TNM staging.
We analyzed the distribution of patients according to WHO status before surgery. This indicator is one of the simplest to assess a person's autonomy, being used especially in the oncology.

It is noted the predominance of 89% of patients with a satisfactory WHO status (1 and 2), due to early diagnosis which led to a large number of radical surgery.

Analyzing from the same perspective the defined groups, we observed a similar distribution in the the majority of the lot (lot 1 - NSCLC) and WHO status even better for group 3 (carcinoids), explained by younger age of onset and low aggressiveness of these tumors.

Depending on anesthetic risk, measured by scale ASA (American Society of Anesthesiology), we noticed that most patients (85%) were enrolled in ASA classes 1 and 2, thus having a low anesthetic risk, which also contributed to the large number of radical surgery.

We also observed a similar distribution by WHO status and ASA anesthetic risk.

Analyzing the entire study group, we found a slight preponderance of the right lung affectation as compared to the left (54% to 46%). Because these percentages are very close to the proportion of the two lung volumes (55% - 45%), we believe that there was no predilection of cancer for a certain lung.

In terms of lobar location there is a more common location at the right and left upper lobes. For Group I (the most consistent), all three subgroups were noted for a predilection of localization in the upper lobes.

For group 2 (SCLC) the major location was in the left lung (especially left upper lobe), but again because the very small number of cases we can not draw any conclusion in this regard.
Carcinoid tumors were found particularly in the right lung (especially right upper lobe). Also, due to the small number of cases we can not issue a conclusion supported by statistically significant data.

There is a clear prevalence of the radical type surgery, (segmentectomy, lobectomy, bilobectomy, pneumonectomy), 320 cases (88%) benefiting from this type of surgery. Most interventions (93%) required thoracotomy approach as a way in line with most surgical gestures made (major lung resections - pneumonectomy, lobectomy, segmentectomy).

Only 7% of interventions were undertaken through thoracoscopy (minimally invasive method) and this approach was reserved to partial palliative resections or purely diagnostic procedures.

Most cases (86%) received a radical lymphadenectomy according to the oncological feature of to the majority of interventions. Consequently we have had a very precise description of the nodal involvement (N criterion in TNM classification).

Sampling lymph node biopsy (biopsy of a small fragment of a macroscopically suspect lymph node) was reserved for cases deemed unresectable and was practiced in only 4% of cases (15 patients).

Node involvement was established postoperatively after histopathological examination of all lymph nodes sampled (or biopsied) during surgery. We found that most (53%) had no nodal involvement because the tumors were caught in an early stage.

In accordance with the radical nature of the majority of the interventions, 80% of patients had no metastases (which were confirmed at a rate of only 11%).
The presence of a single metastases (adrenal, hepatic, brain or bone) is not a contraindication for radical surgery because it usually can be resected in another intervention (prior to or after lung resection) with good results.

Data collection was conducted in April 2008. At that time most of the patients enrolled in the study were alive (94%). The predominance of radical surgery led to a good survival rate, at least in the short term.

Of the few patients deceased until data collection, were relatively equal in number those with adenocarcinoma (12 patients) and those with squamous cell carcinoma (11 patients).

CHAPTER 3. CORRELATIONS BETWEEN CLINICAL PARAMETERS

Analyzing the distribution of patients by gender and age, we observed lung cancer more frequent in older men and at a younger age in women.

In terms of correlation between sex and WHO status, we observed a slightly higher proportion of female patients among those with a better status, although in the same category were the 2 patients with the worst status (WHO 4).

We analyzed the existence of some correlations between histological type of tumor and affected lymph nodes. It was noted that mediastinal lymphadenectomy is basically made in a very thorough manner in the thoracic surgery service where have been operated these cases.

The precise knowledge of nodal involvement and radical excision of the mediastinal lymph nodes are the most important prognostic factor for survival.
In the few cases where the operatory protocol or the pathological report did not mention anything about mediastinal lymph nodes, we considered the Nx criterion.

We noted that most cases without nodal involvement (N0) were the typical carcinoids category, which is consistent with the less aggressive character.

Another type of tumor that showed slight nodal involvement was CBA, where we observed for the majority the criterion N0 and just in one case N1.

Regarding the cases of SCLC in our study we found the absence of invaded nodes in all the 5 cases encountered, which is contrary to literature data.

It is known that histopathological type correlates with aggressiveness and hence with the appearance of metastases. In our study we encountered a number of 39 cases with metastases (11% of total).

Analyzing the presence of metastases in each histopathological type, we found that the vast majority (34 cases, ie 87% of all cases with metastases) were in subgroup 1A (adenocarcinomas). Other histological types (squamous cell, CBA, undifferentiated NSCLC) had a small number of cases with metastases (1 up to 2).

Data from this study are consistent with the literature that considers more aggressive adenocarcinoma than squamous cell carcinoma.

We analyzed the correlation between patient age and nodal involvement. We found that in adolescents only two cases had no nodal involvement. This is explained simply by histological type of tumor (typical carcinoid in both cases) and can not lead to any different conclusion.

In adults 73 patients (53%) had no nodal involvement while in the older group we found 142 such cases N0 or Nx (63%). We can say therefore that overall lung tumors were more aggressive in adults and elderly.
For the entire group the presence of metastases was quite rare (39 cases representing 10.71% of total). We tried to find a possible correlation between age and presence of metastases.

For adolescents the total absence of metastases can be explained again by the small number of cases (2 patients) and histological type (typical carcinoid) and allows no conclusions.

In adults 16% of cases presented metastases while in the elderly were found in 8% of cases. We conclude that metastatic phenomenon manifested itself more frequently in adults and elderly.

CHAPTER 4. PATHOLOGICAL STUDY

In the histopathological study, the first step was the division of the 364 cases of lung cancer cases according to histological type.

We noted that most cases (348 cases representing 96% of total) were non-small cell cancers and the remaining minority of cases was shared between small cell cancers (5 cases or 1%) and carcinoid tumors (11 cases representing 3%).

Histopathological diagnosis was possible without performing immunohistochemistry in a number of 152 cases, representing 42% of the total.

A total of 14 markers were used to specify the histological type. Of these only 3 were used in most of the cases: TTF1, CK7 and CK20.
CONCLUSIONS

1. Lung cancer is a major problem of health services because its incidence is increasing despite the efforts of the society to reduce risk factors.
2. The role of histopathological examination is defining the choice of treatment and establishing prognosis.
3. In our study, the lung cancer has shown the same known predilection for males and the sixth decade of life.
4. During the five years analyzed we found a slight increase of the number of cases of lung cancer.
5. The vast majority of neoplasms (96%) were NSCLC, of which predominantly adenocarcinoma (225 cases).
6. Most cases were found in early or less advanced stages, allowing in most cases (78%) radical surgical treatment.
7. In our study group we noted predilection for upper lobes of the tumor.
8. Surgery was performed with a few exceptions by open approach and included a thorough lymphadenectomy.
9. Metastases were seen in less than 11% of patients.
10. We found a survival rate of 94% on completion of the study.
11. A total of 212 cases required for the diagnosis the use of immunohistochemistry.
12. This was done using a large panel of 14 markers, but only 3 of them were used systematically (TTF1, CK7, CK20), demonstrating that immunohistochemical examination is very useful for the diagnosis.
13. An immunohistochemical investigation algorithm is required to avoid excessive use of resources.