The Importance of Histo-pathological Factors in Setting the Long Term Prognosis for Non-small Cell Lung Cancer

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Introduction: In the last decades, the rate of pulmonary cancer has risen alarmingly. Pulmonary cancer represents the main cause of death in women and men in the United States of America, 100,000 new cases being registered annually in men and 50,000 new cases in women. The purpose of our study is to evaluate the importance of histo-pathological factors in the long term outcome of patients operated for lung cancer.
Material and methods: In order to write the present paper, we carried out a retrospective observational study on a period of 6 years. We used the casuistry of the Surgical Clinic I of the County Emergency Clinical Hospital Tîrgu Mureş. We studied all the patients' papers who were admitted to Surgical Clinic I from the 1st of January 2005 till 31 December 2010. Further, we based our research on 197 patients that were admitted to Surgical Clinic I for bronchopulmonary tumors.
Results: We studied the importance of the T descriptor (tumor) from the TNM staging for establishing the long term prognosis. The value of p was 0.1676 so we didn't obtain any value of statistical importance. We also took into consideration the value of N from the TNM staging as a prediction factor for long term survival in patients who underwent surgical intervention for pulmonary cancer. The p parameter was 0.0152 so we can say that we obtained a direct connection between the stages of lymph nodes metastasis and long term survival rate.
Conclusions: Long time survival rate of the patients depends on the histological type of the tumor. Long term survival prediction rate is better if the patients are over 60 years, compared with patients under 60 years. The N descriptor can be considered an important prediction factor, while the T descriptor's value is useless. The existence of N's descriptor in more stages of the TNM classification shows its limits and encourages for further improvements.

Keywords: lung, cancer, prognosis, fistula, stump

Introduction

In the last decades, the rate of pulmonary cancer has risen alarmingly. Pulmonary cancer represents the main cause of death in women and in men in the United States of America, 100,000 new cases being registered annually in men and 50,000 new cases in women.

In Romania, the incidence of pulmonary cancer has risen drastically in the last 10 years, taking the first place for men and third for women (after breast and uterus cancer). If 20 years ago, statistics showed an average of men/women ratio of 9:1, nowadays it is 2:1.

Material and method

We carried out a retrospective observational study on a period of 6 years. We used the casuistry of the Surgical Clinic I of the County Emergency Clinical Hospital Tîrgu Mureş. We studied all the patients' papers who were admitted to our clinic from the 1st of January 2005 till 31 December 2010. Further, we based our research on 197 patients that were admitted to Surgical Clinic I for bronchopulmonary tumors.

Inclusion criteria

- All the patients included in the study were admitted and underwent surgical procedures in Surgical Clinic I for malignant bronchopulmonary pathology.
- From the patients that presented metastasis of bronchopulmonary cancer we took into consideration just the ones with singular cerebral metastasis, which prior to the admittance were surgically removed in a specialized service. These patients presented no other metastasis on other territory and were cleared to undergo thoracic surgery. The patients did not present neurological sequelae after the surgery, or before the admittance.

Exclusion criteria

- Patients with pulmonary malignant tumors at whom the preoperative investigations showed invasion in the mediastinum, heart, major vessels, trachea, esophagus, tracheal bifurcation, and malignant pleural liquid (diagnosed histologically).
- Patients with malignant pulmonary tumors with systemic metastasis.
- Patients with malignant pulmonary tumors with lymph nodes metastasis in contralateral mediastinal lymph nodes, contralateral hilum lymph nodes, scalene lymph nodes or supraclavicular lymph nodes.
- Patients operated in our clinic, diagnosed with pulmonary cancer with small cells.

Table I. Distribution of patients based on the histological type of tumor

Histological type	Number of cases	Percentage
Epidermoid carcinoma	85	43.14%
Adenocarcinoma	68	34.51%
Undifferentiated carcinoma	5	2.53%
Adenosquamosus carcinoma	15	7.61%
Large cell carcinoma	5	2.53%
Carcinoid tumors	4	2.03%

Table II. Correlations between gender and type of tumor

Histological type	Percentage in men	Percentage in women
Carcinoid tumors	100%	0%
Epidermoid carcinoma	46.79%	29.58%
Adenocarcinoma	33.97%	36.58%
Undifferentiated carcinoma	2.56%	2.43%
Large cell carcinoma	2.56%	2.43%
Adenoscuamosus carcinoma	4.48%	19.51%

The TNM staging of these patients was realized postoperatively based on the histopathology examination. We used the TNM classification of lung cancer published in 2009. The statistic analysis was made using Microsoft Excel and Graph Pad software.

Results

Based on the observation papers of the patients and the statistical analysis, we obtained the following results.

From the total of 197 patients, 41 were women (20.81%) and 156 were men (79.18%). Most of the patients were in the 5th and 6th decade of life. The average age was 59.48 years. The average age in men was 57.07 years, and in women 60.12 years. The statistical value of p was 0.107, so there is no statistically significant difference between the patients' age between men and women.

We saw a relatively uniform distribution of the location of the primary tumor such as: left superior lobe (28 patients – 14.21%), right superior lobe (54 patients – 27.41%), right medial lobe (11 patients – 5.58%), left inferior lobe (27 patients – 13.70%), right inferior lobe (36 patients – 18.27%), left center (hilum) (27 patients – 13.70%), right center (hilum) (14 patients – 7.10%). The two main groups of patients were divided based on the surgical intervention that was applied to them. In group A there were 106 patients with the following types of procedures: 13 bilobectomies (12.27%), 52 lobectomies (49.06%) and 41 pneumonectomies (38.67%). In group B there were 91 patients with the following interventions: 54 wedge resections (59.34%) and 37 exploratory thoracotomies with biopsy (40.66%).

Based on the histology reports, most cases presented with epidermoid carcinoma (85 cases – 43.14%). We also found some other types of pulmonary tumors: carcinoid tumors (4 cases – 2.03%), large cell carcinoma (5 cases – 2.53%), non differential carcinoma (5 cases – 2.53%), adenosquamous carcinoma (15 cases – 7.61%) and adenocarcinoma (68 cases – 34.51%) (Table I).

In order to evaluate these correlations we studied separately the incidence of the histo-pathologic types of the tumors in men and women, the statistical analysis between the histo-pathological type and sex of the patients showing a certain connection between the type and the sex. The epidermoid carcinoma is more frequent in men compared to women (46.79% men, 29.58% women). The adenocarcinoma is more frequent in women compared to men (36.58% in women and 33.97% in men). We also had 4 cases of carcinoid tumors, all in men; we didn't find any significant statistical difference in the following: non differentiated carcinoma (2.56% in men, 2.43% in women), large cell carcinoma (2.56% in men, 2.43% in women) (Table II). It must be mentioned that we excluded the pulmonary metastasis from this particular analysis. The value of p was 0.0728, concluding that there isn't any statistically significant correlation between the gender and the type of the tumor.

As far as the relation between the histological type of the tumor and smoking as a risk factor is concerned, we obtained a statistically significant correlation in the following cases: ade-nocarcinoma (79.71% smokers), epidermoid carcinoma (77.64% smokers), adenosquamos carcinoma (80% smo-kers), non-differentiated carcinoma (100% smokers), large cell carcinoma (100% smokers), carcinoid tumors (100% smokers). In this case we also excluded patients with pulmonary metastasis. The value

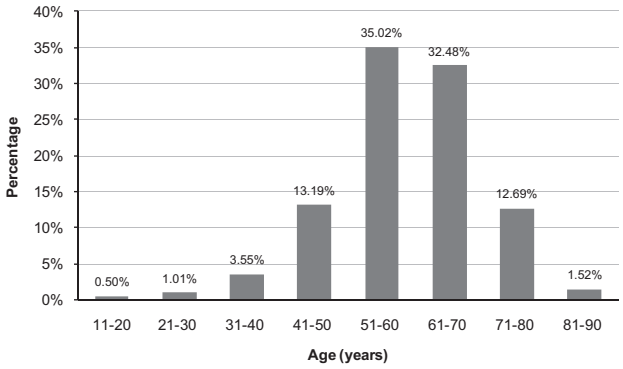

Fig. 1. Distribution of patients based on age groups

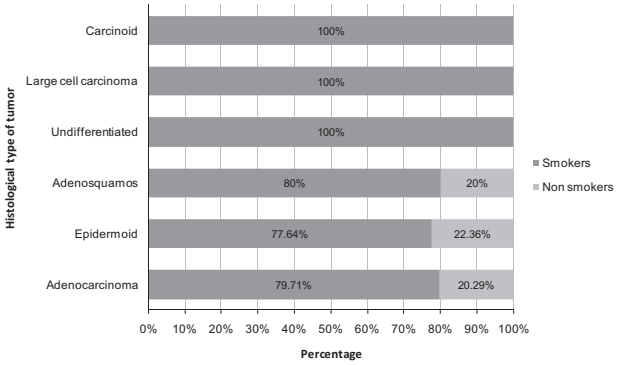

Fig. 2. Correlations between the histological type of tumor and smoking

Table III. Relationship between the type of intervention and the type of tumor

	Pneumectomy	Lobectomy	Bilobectomy	Wedge resections	Thoracotomy
Epidermoid carcinoma	70.73%	34.61%	30.76%	25.92%	54.05%
Adenocarcinoma	17.07%	48.07%	53.84%	42.59%	16.21%
Adenosquamosus carcinoma	7.31%	9.61%	7.69%	11.11%	0%
Large cell carcinoma	0%	1.92%	7.69%	0%	8.10%
Undifferentiated carcinoma	0%	0%	0%	0%	13.51%
Carcinoid tumors	4.87%	3.84%	0%	0%	0%

Table IV. The main causes of death

Cause of death	No. of cases	Percentage
Stroke	2	1.02%
Pulmonary embolism	2	1.02%
AMI	1	0.50%
Respiratory failure	2	1.02%
Acute renal failure	1	0.50%
Total	8	4.06%

of p was 0.6039, so there is no statistically significant correlation between the type of the tumor and smoking habit.

In our group, most of the patients were in an advanced stage of the disease, probably due to the late diagnosis of the bronchopulmonary cancer. From the total of 197 patients, 38 patients were in stage I (16 patients in stage IA – 8.12%, 22 patients in stage IB – 11.16%), 74 patients were in stage II (40 patients in IIA – 20.30%, 34 patients in IIB – 17.25%), 81 patients were in stage III (53 patients in IIIA – 26.90%, 28 patients in IIIB – 14.21%) and 4 patients were in stage IV (2.03%).

By analyzing the data in our study we realized a direct correlation between the dimensions of the tumors and the presence of lymph nodes metastasis. For this we split all the cases based on the tumor size – tumors under 1 cm – 13.64% presented lymph nodes metastasis, tumors between 1 and 2 cm – 65.07% presented lymph nodes metastasis, tumors between 2–3 cm – 85.50% presented lymph nodes metastasis, tumors over 3 cm – 90.69% presented lymph nodes metastasis. The value of p was 0.00000000005901 (p <0.0001), so than we can conclude there is a significant statistical connection between the lymph nodes metastasis and tumor size.

The statistical analysis between the tumors' histological type and the type of the surgical intervention was calcula-ted because we tried to determine if a certain type of tumor has a disposition for a peripheral location (parenchyma) or central (endobronchial). We decided for this analysis because, concerning the tumors with endobronchial localization, typical pulmonary resection was made, when in the case with a peripheral location, a wedge resection was performed. Concerning the pneumonectomies, we found that 70.73% of the patients had epidermoid carcinoma, 17.07% had adenocarcinoma and 7.37% had adenosquamos carcinoma. In lobectomies – 48.07% had adenocarcinoma, 34.61% epidemoid carcinoma and 9.61% ade-nosquamos carcinoma. In bilobectomies the incidence of adenocarcinoma was 53.84% while the epidermoid carcinoma and adenosqamos carcinoma accounted for 30.76% and 7.69% of the cases. From the analysis of the wedge resections we noted that 42.59% had adenocarcinoma, 25.29% had epidermoid carcinoma and 20.37% presented with pulmonary metastasis. The statistical analysis in the cases with exploratory thoracotomies showed us that all the cases with undifferentiated carcinoma entered this cate-gory, meaning that all the patients presented themselves in a non-operable state. From these patients 54.05% presented with epidermoid carcinoma and 16.21% presented with adenocarcinoma (Table III). The value of p was 0.000000321(p <0.0001), so we have obtained a statistically significant connection between the histological type and the surgical intervention. This data proves that while the epidermoid carcinoma has the tendency to locate itself in a central area near the bronchial tree, the adenocarcinoma has the tendency for a peripheral growth.

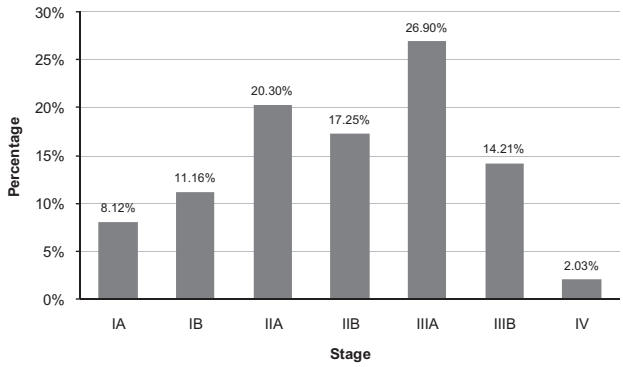

Fig. 3. Case distribution based on staging

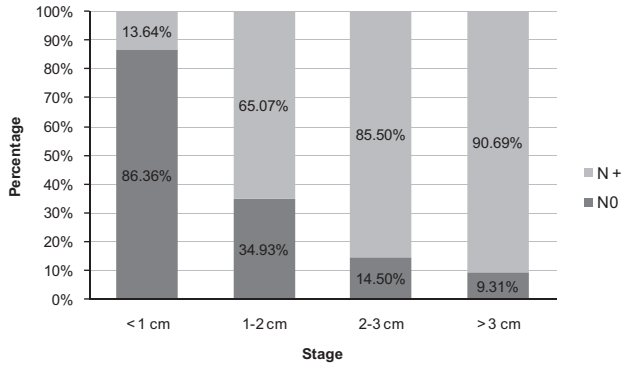

Fig. 4. Correlations between the size of the tumor and lymph nodes metastasis

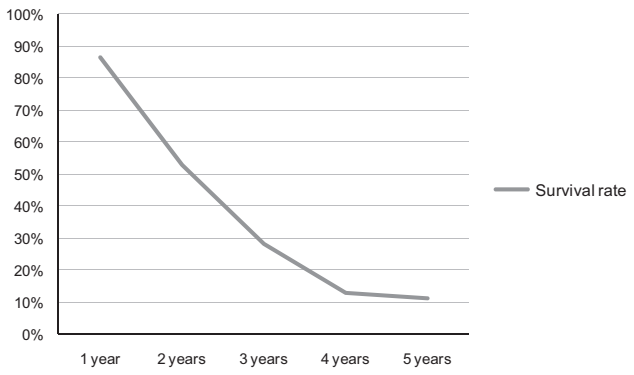

Fig. 5. Long term survival rate

In the study group we had 8 deaths (4.06%) in the first 30 days postoperatively. The main causes of death were: respiratory distress syndrome, cardiovascular disorders and one case of acute renal failure (table IV).

We evaluated the global survival rate at 1, 2, 3, 4, 5 years but also long term survival according to the stage of the pathology. Concerning the global survival rate, we calculated the following data: survival to 1 year – 86.66%, survival at 2 years 52.82%, at 3 years 28.20%, at 4 years 12.82%, at 5 years 11.28%.

Altogether we evaluated the survival rate calculated with the evolution stage of the disease and the average survival rate depending on the stage of the disease. Concerning the average of survival rate depending on the stage of the disease, the values are presented in the next table (table V).

In order to analyze the mortality depending on the stage in which the disease was diagnosed, we excluded from our group patients in stage IV (the 4 cases that weren't significant statistically). We realized that the differences between the survival rates are quite low at 1 year and 5 years, but at 2, 3 and 4 years the differences were significant. The value of p was <0.05, so we can accept that there is a statistically significance between the stage of the disease and long term survival.

We tried to study long term survival of the patients considering their age, so we divided them into two groups, group 1: 105 patients under 60 years (53.29%) and group 2: 92 patients over 60 years (46.71%). In group 1, the value of p was 0.1958 so we didn't obtain a significant result.

Table V. Average of survival (years) according to disease stage

Stage	Average of survival	Number of cases
IA	2.25	16
IB	2.70	27
IIA	2.16	25
IIB	1.97	44
IIIA	1.70	44
IIIB	1.02	35
IV	1.25	4

We also studied the long term survival of the patients over 60 years of age. For these patients, the value of p was 0.00006 (p <0.0001), therefore we can approve of having a significant correlation between the old age and the survival rates.

Another aspect that we tried to study was the importance of the T descriptor (tumor) from the TNM staging for establishing the long term prognosis. The value of p was 0.045533 (p <0.05) so we obtain a value of statistical importance.

We also took into consideration the value of N descriptor from the TNM staging as a prediction factor for long term survival in the patients that underwent surgical intervention for pulmonary cancer. The p parameter was 0.0152 so we can say that we obtained a direct connection between the presence of lymph nodes metastasis and long term survival rate.

Discussions

The histological type of the tumor plays a very important role in the natural evolution of lung cancer, also in deciding its prognosis. At this hour, the highest lymphatic invasion is described for the small cell carcinoma, followed by adenocarcinoma and epidermoid carcinoma. The best rate in long term survival is held by the epidermoid carcinoma [1].

Reed (1988) considers that epidermoid carcinoma has a better prognosis than adenocarcinoma and large cell carcinoma. At this moment, it is considered that smoking, as a risk factor, is responsible for the onset of the epidermoid carcinoma [2]. That is probably why in our published statistics, a high incidence is held by the epidermoid carcino-

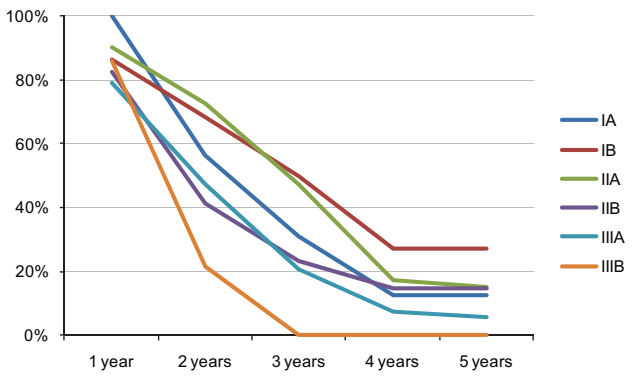

Fig. 6. Survival based on disease stage

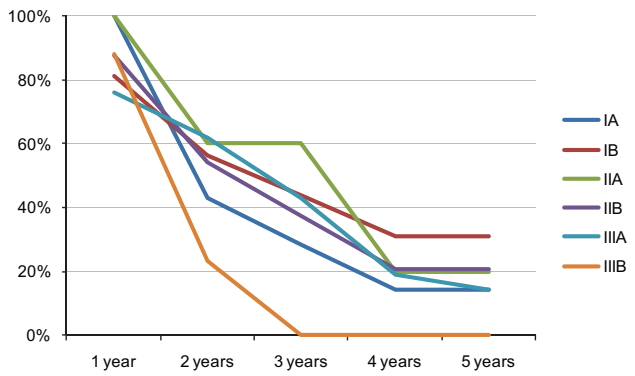

Fig. 7. Long term survival in patients under 60 years old

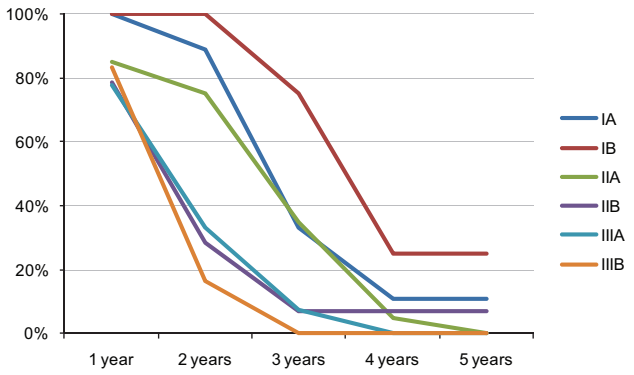

Fig. 8. Long term survival in patients over 60 years old

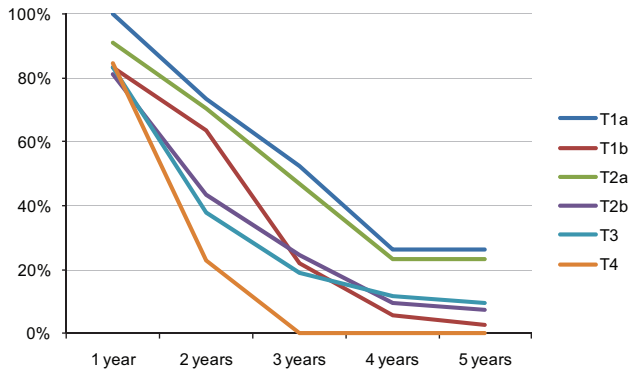

Fig. 9. Survival rates of patients according to the valule of the T descriptor

ma. Perrot (2000) considers that epidermoid carcinoma's incidence is higher in men compared to women, and the incidence of adenocarcinma is higher in women than in men, the same observations we concluded by running this study [3], the carcinoid tumors are more frequent in men, but we couldn't find a statistical significance for not finding any cases of carcinoid tumors in women.

In an article published in 1990, Ishida sustained that the possibility for a tumor to have lymph nodes metastasis at the moment of surgical intervention is directly correlated with the size of the tumor [4]. The same data we obtained in our statistics, the higher the tumor, the higher the possibility of having lymph nodes metastasis.

From our statistics we realized that the epidermoid carcinoma has a higher tendency for a central location, and that the adenocarcinoma and adenosquamos carcinoma are frequently located in the middle bronchus and peripheral regions of the lung. Carcinoid tumors have the tendency to locate themselves in a central area, rather than in the periphery.

All the patients in our study who presented undifferentiated carcinoma were in an inoperable clinical stage, which proves an extremely aggressive evolution. The analysis of the patients with inoperable tumors made us acknowledge that 54.05% of these patients had epidermoid carcinoma, while only 16.21% had adenocarcinoma and 8.10% had large cell carcinoma, this fact can make us think that the

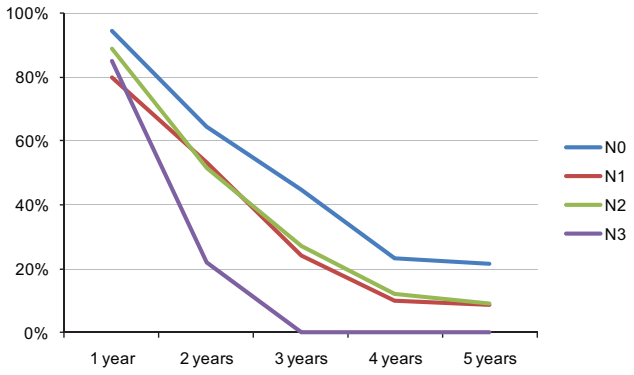

Fig. 10. Survival rates of patients according to the value of the N descriptor

asymptomatic period of the patients with epidermal carcinoma is longer than the one for the adenocarcinoma, giving the fact that also it is less aggressive than the latter.

There are differences noted in the literature regarding the long term survival after the surgically operated lung cancer. In a 2010 published study, Holmberg compares the 5 year survival rate in England, Norway and Sweden. The average survival rates for 5 years were as following: for men – 6.5% in England, 9.3% in Norway and 11.3% in Sweden and for women – 8.4% in England, 13.5% in Norway and 15.9% in Sweden. The author explains that the differences are being given by the health care system development and the sanitary education of the population [5]. In 2010, Oskarsdottir published a study on a group of patients at which only lobectomy was made, with a survival rate of 43.5% [6].

In the literature, the survival rate for 5 years differs a great deal from one author to another. These differences are given by the inequality of the study groups based on demographics, medical centers and, most importantly, the general sanitary education and healthcare access for the population in certain territories. In our case, Romania has a low healthcare level development. That is why, by Romanian authors, the statistics are smaller for the long term survival rate compared with another centers specialized in thoracic surgery.

Naruke (1988) published a statistic with patients operated with pulmonary cancer. He describes the rate of survival at 5 years, correlated with the stage of the disease, getting the following results: stage IA – 68.5%, IB – 59%, IIA – 54.1%, IIB – 40%, IIIA – 17.7% [7]. If we are to compare ourselves with Naruke's statistic, our published values are inferior most likely because of the statements we made prior to this.

Concerning patients' age and their long term prognosis, we noticed that the histological stage is a prognostic factor more sensible if associated with the age. In our study we obtained a significant statistical correlation for patients over 60 years of age, compared to the ones under 60 years. Therefore, we can conclude that the prediction rate for long term survival is getting better if the age is over 60 years. By

analyzing the long term survival rates, we noticed that the survival curves overlap with T1–T3 values and in T4 is inferior. So the value of the T descriptor cannot be used as a sole prognostic factor. The same observations were made by Martini (1992) and Watanabe (1991) [8,9].

If we analyze the N descriptor we learn that the survival curves are different for each of N's values, this holding a statistical significance. From here we can say that the value of N can be considered as an asset for predicting the long term survival in patients suffering from pulmonary cancer. In an article published in 1990, Tshuchiya highlights the importance of lymph nodes metastasis in patients' prognostic for the long term outcome and also the resection rate for pulmonary cancer [10].

If we study the TNM classification which is being used worldwide, we will notice that some stages (IIB, IIIA, IIIB, IV) have more combinations of T and N descriptors. Therefore, it is possible to have patients with different N values in the same staging. N being an important prognostic factor, this might not be considered helpful. That's exactly why the TNM classification should be revised in order to get a better prognostic value.

Conclusions

The dimension of the tumor holds a significant place; the bigger the tumor, the higher the chances for lymph node metastasis. The long time survival rate of the patients depends on the stage of the disease. Long term survival prediction rate is better if the patients are over 60 years, compared with the patients that are under 60 years. The N descriptor can be considered an important prediction factor, while the value of T descriptor is lower. The exis-tence of the N and T descriptors in more stages of the TNM classification shows its limits and encourages for further improvements.

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