UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA", BUCURESTI

DOCTORAL SCHOOL

MEDICINE

CLINICAL, PARACLINICAL AND HISTOPATHOLOGICAL STUDY OF THE EVOLUTION OF PATIENTS WITH VARIOUS LUNG TUMORS AFTER SURGERY AND CHEMORADIOTHERAPY TREATMENT

PHD THESIS ABSTRACT

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CONTENTS

Bronchopulmonary cancer continues to be a fairly widespread and aggressive disease, ranking second worldwide in 2020.

The motivation for choosing this PhD research is due to the fact that bronchopulmonary neoplasm is the leading cause of cancer death affecting mainly men, and data on patient survival after surgery and neoadjuvant treatment have not yet been reported in detail at regional or national level.

In this work we aimed to study a number of factors that might influence prognosis and survival in non-microcellular bronchopulmonary neoplasm. Thus, we analyzed a series of parameters such as: patient age, gender, histopathologic type, tumor stage, presence of bronchial invasion, and completeness of surgical resection.

The study was analyzed on a group of patients in which demographic, histopathological, clinical, therapeutic correlations have characteristics generated by both demographic and local/national medical behavior.

The working hypothesis started from the identification of statistical arguments in support of the hypothesis that there are personal, clinical or tumor parameters that could influence the survival of patients with bronchopulmonary neoplasm. We started from the premise that by analyzing these parameters, we could identify new tumor particularities, identify new data, all of which would be useful in the development of diagnostic and treatment algorithms. Thus, we have formed a representative group of patients with bronchopulmonary neoplasm.

GENERAL PART - CURRENT STATE OF KNOWLEDGE comprises two chapters.

The first chapter summarizes the epidemiology, risk factors, screening, histopathological classification, diagnosis, staging, and clinical and histopathological course of lung tumors.

The incidence, mortality, survival, risk factors, lung cancer screening, histopathological classification, clinical, imaging and histopathological diagnosis, staging of lung tumors, clinical, paraclinical and histopathological evaluation were reviewed.

In the second chapter were analyzed the surgical and neoadjuvant treatment, postoperative course, postoperative complications - immediate and late, course after neoadjuvant treatment and prognosis of non-microcellular lung cancer.

THE ORIGINAL PART - PERSONAL CONTRIBUTIONS comprises six chapters.

Chapter 3 presents the working hypothesis, aim, general objectives and research directions.

General aims and objectives

The aim of the study was to investigate a number of factors that might influence prognosis and survival in non-microcellular bronchopulmonary neoplasm. Also to detect possible correlations between various personal, clinical or tumor parameters with impact on the evolution and prognosis of bronchopulmonary neoplasm.

General objectives of the study

- Can a survival period for the patients with various lung tumors treated with curative intent be established by the restrictive median survival (RMST) estimated at 24 months, 60 months and over the entire follow-up period of the study?
- Can the impact of the studied variables on the research group be analyzed in terms of overall survival (OS)?

In order to analyze the study and fulfill the general objectives, we researched and tried to answer the following questions:

1. Can curative surgical resection increase long-term survival rates?
2. Can neo-adjuvant therapy/chemotherapy in initially inoperable stages improve survival in patients who have subsequently undergone surgery?
3. Does survival rate by histopathology type influence patient prognosis?
4. Is survival rate influenced by tumor size?
5. Does the stage and status of the tumor margins (R1) after incomplete resection influence the patient`s prognosis?
6. Can the status of neoplastic invasion of the bronchial tree preoperatively influence patient prognosis?
7. Can the preoperative bronchoscopic diagnosis influence the surgical indication?

Research directions:

To achieve the objectives of the doctoral research, we have compiled the following studies:

Study 1: Influence of demographic, anatomopathological and clinical characteristics on the evolution and prognosis of lung tumors operated with curative intent.

Study 2: Investigation of possible associations between demographic characteristics and anatomopathological features of bronchopulmonary neoplasms.

Study 3: Classical descriptive statistical analysis of the variables followed in the study.

Chapter 4 presents the general methodology of the research - database construction and statistical analysis, including, selection criteria for the patients included in the study, material and method used, data recording and statistical analysis of results.

General research methodology - database construction and statistical analysis

Our research consisted of a retrospective, observational, longitudinal, non-randomized study, which included a sample of **1537 patients diagnosed with bronchopulmonary neoplasm in curative surgical stage pre- and intra-operatively,** where surgical treatment with curative intent was used, conducted from January 2015 to December 2023 representative sample of a population of patients diagnosed with bronchopulmonary neoplasm, treated with curative surgey, in a tertiary center.

The target group consisted of patients diagnosed with bronchopulmonary neoplasm at the "Marius Nasta" Institute of Pneumophthiology – Bucharest, who at the time of diagnosis did not present with secondary remote determinations or other synchronous neoplasms. Cases were carefully selected because the main objective of the study involved the assessment of time to death (prognosis).

The patients admitted to the doctoral study were selected in accordance with the principles of the 1975 Declaration of Helsinki, updated in 2000, and the applicable national legislation. The protocol of the doctoral study was approved by the Ethics Committee of the Institute of Pneumophthiology "Marius Nasta" - Bucharest (No. 22062/27.09.2021).

The data collection was performed retrospectively for patients diagnosed and treated in the Thoracic Surgery Department of the "Marius Nasta" Institute of Pneumophthiology - Bucharest based on the observation sheets and electronic records.

Selection criteria for patients included in the study

The doctoral study consisted of an observational, retrospective analysis of medical records of patients diagnosed with bronchopulmonary neoplasm. Demographic aspects, neoadjuvant treatment, data on bronchoscopic evaluation, anatomopathological findings, surgical reports, data related to the histopathological type of bronchopulmonary neoplasms, degree of resectability, tumor differentiation, staging, were recorded in a database. We also monitored the time from the diagnosis, histopathologic type, neoadjuvant treatment, resectability until death.

Patients evaluated in this study were carefully selected using criteria in order to demonstrate the overall objectives and working hypotheses.

Inclusion criteria:

- age at admission over 18
- confirmed cases of primary bronchopulmonary neoplasm
- cases diagnosed with bronchopulmonary neoplasm who received curative surgical treatment
- patients treated and monitored at the Marius - Nasta Pneumophthiology Institute Bucharest, Thoracic Surgery Clinical Department in the period 01.01.2015-01.12.2023
- access to medical source documents, from which the information forming the variables studied could be extracted
- informed consent

The following data were collected for each patient:

- anthropometric (age 21-85 years, gender 1135 males, 402 females)
- date of diagnosis
- bronchoscopy
- neoadjuvant treatment

- degree of tumor resectability
- degree of differentiation
- definitive histopathologic examination
- tumor size after resection
- pTNM histopathologic staging
- date of death

Paraclinical examinations:

- Imaging: CT, MRI, PET-CT (imaging detection of lung tumors with the help of an artificial intelligence program by comparison).
- tumor: anatomo-histological
- exploratory: fibrobronchoscopic with autofluorescence
- EBUS TBNA

Histologic examinations: macroscopy and microscopy of the lung resection specimen and mediastinal lymph nodes were performed by an anatomopathologist. The following parameters were taken into account for the histopathological results: histological type, degree of differentiation, tumor size, staging of pTNM, degree of resectability.

The following three chapters present the three studies carried out for each, detailing the working hypotheses, specific objectives, material and method used.

Statistical analyses of the data are presented and the results are discussed.

Chapter 5 includes **Study 1** - Influence of demographic, anatomopathological and clinical characteristics on the evolution and prognosis of lung tumors operated with curative intent.

The group was composed of all patients diagnosed with primary bronchopulmonary neoplasm, who underwent curative surgery, whether or not they received neoadjuvant treatment. A total of 1537 subjects were enrolled and subsequently divided into several subgroups according to the parameter analyzed in order to demonstrate whether or not it can be considered a prognostic factor.

In the studied group we calculated OS, **Table 5.1**. Mortality was 53.28%, median survival was 52 months.

Table 5.1 Overall survival analysis on the whole batch:

Strata	N Deaths (%)	RMST	Median Survival (95% CI)
Global	819 / 1537 (53.28)	63.80	52.00 (47.00 to 60.00)

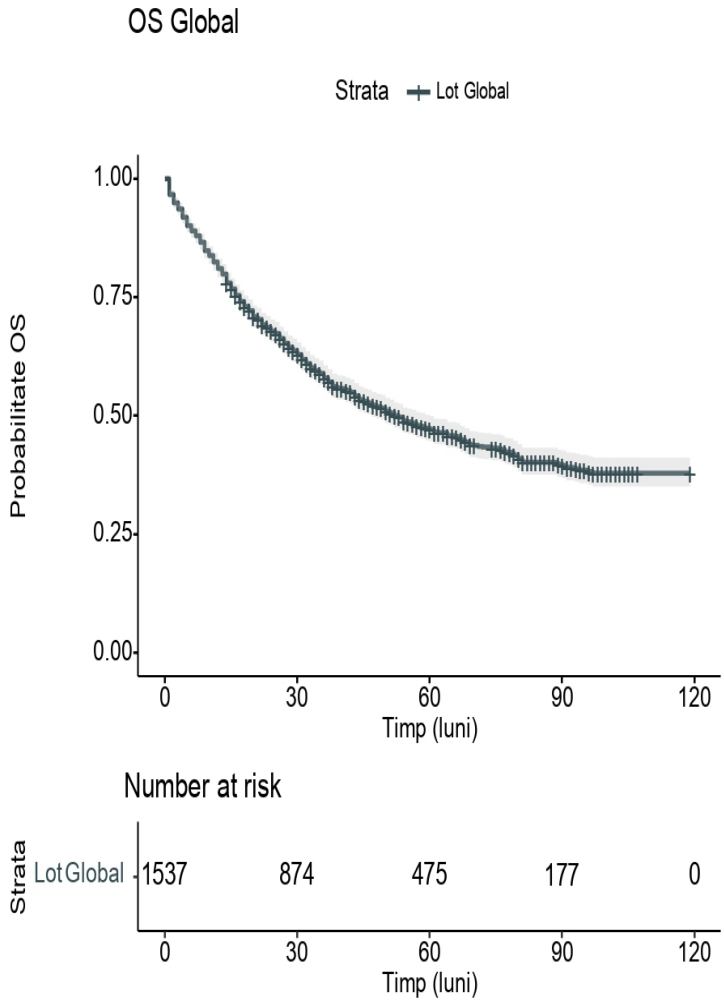

Figure 5.1 Survival curve (OS) for the whole batch

Source: own contribution.

We calculated mortality in months using the RMST function. In the patient cohort analyzed, mortality was 53.28%. Calculated overall survival was 63.80 months, while median survival was 52 months.

Chapter 6 contains **Study 2** - Investigation of possible associations between demographic and pathologic features of bronchopulmonary neoplasms.

Table 6.6 The association between neoplasm type and degree of differentiation (where information was available/it was possible to determine a degree of differentiation):

Variable	CARCINOID N = 99	ADK N = 724	LARGE CELLS N = 137	SCUAMOS N = 520	PLEOMORPHIC N = 57
Differentiation, n (%)					
G1	20 (67)	27 (8.2)	1 (5.0)	83 (28)	0 (0)
G2	10 (33)	202 (61)	2 (10)	132 (45)	2 (11)
G3	0 (0)	100 (30)	17 (85)	81 (27)	16 (89)
N/A	69	395	117	224	39

Table 6.7 Association between neoplasm type and resectability:

Variable	CARCINOID N = 99	ADK, N = 724	LARGE CELLS N = 137	SCUAMOS N = 520	PLEOMORPHIC N = 57
Resectability, n (%)					
R0	83 (84)	637 (88)	124 (91)	425 (82)	50 (88)
R1B	13 (13)	37 (5.1)	3 (2.2)	36 (6.9)	2 (3.5)

Variable	CARCINOID N = 99	ADK, N = 724	LARGE CELLS N = 137	SCUAMOS N = 520	PLEOMORPHIC N = 57
R1V	2 (2.0)	32 (4.4)	7 (5.1)	41 (7.9)	3 (5.3)
R1B+V	1 (1.0)	18 (2.5)	3 (2.2)	18 (3.5)	2 (3.5)

Chapter 7 contains **Study 3** - Classical descriptive statistical analysis of the variables followed in the study

Table 7.2 Multiple Cox regression (predictors with statistically significant influence):

Predictor	N	Deaths N	HR (95% CI)[1]	p-value
Age	1,535	818	1.02 (1.01 to 1.03)	<0.001
Gen				
F	402	158	-	
M	1,133	660	1.50 (1.25 to 1.81)	<0.001
Stage T				
T1	265	85	-	
T2	509	248	1.33 (1.03 to 1.71)	0.027
T3	438	257	1.53 (1.17 to 2.01)	0.002
T4	323	228	2.06 (1.47 to 2.87)	<0.001
Stage M				
M0	1,523	809	-	
M1	12	9	1.93 (0.99 to 3.77)	0.055

Predictor	N	Deaths N	HR (95% CI)[1]	p-value
Size	1,535	818	1.04 (1.00 to 1.08)	0.027
Tip				
Carcinoid	99	10	-	
ADK	723	399	6.10 (3.23 to 11.5)	<0.001
Big Cell	137	75	5.01 (2.57 to 9.79)	<0.001
Scuamos	519	289	4.76 (2.51 to 9.01)	<0.001
Pleomorphic	57	45	9.88 (4.91 to 19.9)	<0.001
Resectability				
R0	1,317	669	-	
R1 B+	91	59	1.91 (1.46 to 2.51)	<0.001
R1 V+	85	62	1.54 (1.18 to 2.01)	0.001
R1 B+&V+	42	28	1.85 (1.26 to 2.72)	0.002

[1] HR = Hazard Ratio, CI = Confidence Interval

The table reveals the following (statistically significant influences of each predictor, taking into account the action of all other predictors):

- A positive association between age and hazard of death, a 1-year increase in age is associated with a 2% increase in hazard of death.
- The hazard of death is 1.5 times higher in males.
- Compared with T1 tumors, T2 tumors have a 1.33 times higher hazard of death, T3 tumors have a 1.53 times higher hazard, while T4 tumors have a 2.06 times higher hazard.
- Stage M1 has (compared to M0) a 1.93 times higher hazard of death (the effect is, however, borderline statistically significant).
- A 10mm increase in tumor size is associated with a 4% increase in the risk of death.

- Compared to carcinoid, ADK has 6.10 times higher hazard, large cell carcinoma 5 times higher, squamous cell carcinoma 4.76 times higher, pleiomorphic carcinoma 9.88 times higher.
- Compared to R0, R1 B+ has 1.91 times higher hazard, R1 V+ has 1.54 times higher hazard, R1 B+&V+ has 1.85 times higher hazard.

The final, eighth chapter is reserved for conclusions and **personal contributions**.

Conclusions

1. Surgical intervention is the main pillar for the oncologic patient, being the most important method for curative treatment. In our study, we statistically demonstrated that the mortality in the group was 53.28%, attributed to acute or short-term complications. The 60 months RMST was 39.84 months, which was considered superior to patients without operative indication.

2. In our study, patients who received neoadjuvant treatment did not show a statistically significant favorable outcome compared to those who did not. However, we believe that there is a need to integrate new radiotherapy techniques together with new oncologic therapies, such as targeted therapy and immunotherapy, in the approach to patients with lung neoplasm.

3. The most severe prognosis according to the histologic type detected was for pleomorphic carcinoma. (highest percentage of deaths), while the best prognosis was for carcinoid.

4. Tumor sizes greater than or equal to 4.6 cm influence a more sever prognosis for patients and survival.

5. R1 resection stage and positive resection margin status are negative prognostic factors in the patient's subsequent course, surveillance and treatment.

6. Tumor invasion at the level of the bronchial tree detected by bronchoscopy did not represent a factor of negative prognosis. The new possibilities and techniques of

bronchoscopy should be taken into account, which can more accurately demonstrate the presence of infiltration.

7. Bronchoscopy is essential in guiding the type of surgery applied.

Personal contributions:

Surgical treatment in NSCLC can ensure a good long-term survival rate and can still be considered the main option in this type of pathology. However, this depends on a number of parameters that directly influence long-term survival, such as tumor stage and size, the degree of histopathologic differentiation as well as the accuracy of surgical resectability, which may have effects beyond the standard period usually considered in oncology.

Our study aimed to track the overall calculated survival which was 63.80 months, while the median survival was 52 months. The time evolution, was calculated using RMST, showed 2-year survival of 19.71 months, while the overall RMST at 5 years was 39.84 months.

The presence of microscopic residual bronchial, vascular or associated microscopic residual tumor tissue negatively influences the prognosis and thus distant survival (R1) 218 patients (14.19%). Immediate postoperative mortality is higher in patients with advanced loacal tumors. The best prognosis was for neoplasms (R0), thus survival based on the resectability parameter was approximately 14.5 months higher in patients with R0 tumors.

A number of independent parameters such as age, sex or histologic type could influence long-term survival.

The identification of these prognostic parameters helps to identify patients at risk and consequently the use of adjuvant therapy. However, the study of survival-dependent parameters in NSCLC cancer remains an open field and a multidisciplinary approach is the most appropriate.

Following an accurate analysis of the staging of the patients included in the group, we observe a mean tumor size of approximately 4.6 cm. This corresponds to the pTNM classification in T2 (approximately 740 patients enrolled). The prognosis is more sever in patients with tumor sizes greater than or equal to 4.6 cm, with a higher percentage of deaths, RMST begin 26.40 month lower, and median survival being 58 months lower in patients with tumor sizes greater than or equal to 4.6 cm.

The peculiarity of the study was that the majority of patients (94%) (N=1444) received only curative surgical treatment and only a small percentage of 6% (N=94) of patients had neoadjuvant treatment associated with surgery.

The quality of the study and the prognostic parameters followed are directly influenced by and are closely related to the results of long-term surgical treatment.

The results of the study are broadly equivalent to the international literature. The characteristics of this doctoral research consist in the pluriperspectivistic paradigm of bronchopulmonary neoplasm investigated in a university clinical hospital (institute) over a period of 9 years.

It is very important the sequencing of therapeutic, surgical, oncologic and radiotherapeutic modalities, the discussion of cases in multidisciplinary committees, the aim being to cure patients with lung cancer without metastases.

The limitations of our study were:

- It is a unicentric trial, which may be considered a bias in enrolling patients in concordance with our clinic`s profile.
- The follow-up period through global survival analysis of the entire group, since the mortality rate in the group was 53,28%, RMST globally was 63,80 months, while the median survival was 52 months (as of December 1, 2023) and the global survival rate in the group was 46,72%.

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