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SURGICAL TREATMENT OF PATIENTS WITH BRONCHOPULMONARY CANCER AND MAJOR ANESTHETIC-SURGICAL RISK

321.13. – Surgery

Summary of the doctoral thesis for the habilitation in medical sciences

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This thesis was developed within the Department of Surgery No. 1 "Nicolae Anestiadi" of the State University of Medicine and Pharmacy "Nicolae Testemițanu" and the Consortium of the Doctoral School in the field of Medical Sciences.

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Summary

CONCEPTUAL FRAMEWORK OF THE RESEARCH

Relevance and Importance of the Topic Addressed. Among oncological diseases, the incidence of lung cancer is on the rise both globally and in the Republic of Moldova. In 2021, approximately 2,000,000 people worldwide were diagnosed with lung cancer, resulting in 1,800,000 deaths. According to the American Cancer Society, in 2022, 236,740 people (117,910 men and 118,830 women) were diagnosed with lung cancer in the U.S., and 130,180 people died (68,820 men and 61,360 women). Of all the deaths caused by oncological diseases, 25% are attributed to lung cancer. The risk of developing lung cancer significantly increases after the age of 40. Although lung cancer primarily affects individuals aged 50 to 70, recent trends indicate cases occurring in individuals under 40. The prevalence and mortality of lung cancer surpass the combined prevalence and mortality of colon, breast, and prostate cancers. According to the U.S. National Cancer Institute, one in 16 people will develop lung cancer in their lifetime; concerningly, 65% of lung cancer cases occur in individuals who have never smoked. The 5-year life expectancy from the time of lung cancer diagnosis is 22%. Even if lung cancer is diagnosed in the early stages, only 60% survive for five years.

According to the latest public data from the National Bureau of Statistics of the Republic of Moldova for 2022, mortality in malignant tumors takes the II place (approximately 14.6%), with 5,731 deaths recorded (in 2018 and 2012, there were 6,133 and 5,734 cases). Since 1982, lung cancer has been the leading cause in the oncological structure. In 2020, there were 565 new cases of lung cancer, rising to 812 cases (+44%) in 2021, making it the second most diagnosed malignant tumor. Contrary to the statistics from the USA, in the Republic of Moldova the 5- years survival rate from the moment of lung cancer diagnosis is 20-35%. According to available statistical data (1991-1997), the morbidity of lung cancer in the 30-34 age group increased fivefold (from 0.8 to 4.6 cases per 100,000 inhabitants), in the 35-39 age group it tripled (from 4.4 to 12.5 per 100,000), and in the 40-44 age group it doubled.

The conclusion is that this oncological condition represents a public health problem, imposing a significant financial and social burden on the state, and is tragic for patients and their families. Preventive measures, primary prophylaxis, risk group identification, screening, and early-stage diagnosis often fail to achieve their intended goals for various reasons. Although significant medical advances have been made in recent decades (molecular diagnostic techniques, imaging, surgery, intensive therapy, etc.), these have not substantially altered the prognosis or life expectancy of patients. Thus, one potentially achievable treatment strategy is to extend the patient’s lifespan (through chemotherapy, radiotherapy, or surgical treatment).

Surgery plays an important role in the diagnosis, staging and treatment of non-microcellular lung cancer. Pulmonary resection is the treatment of choice for stage I-II of non-microcellular lung cancer and an important component of multimodal treatment for stage IIIA. Essentially, surgical treatment involves standard resections (lobar, bilobar, pulmonary), with examination of the ipsilateral hilum and mediastinal lymph nodes. According to Lackey A. (2013), the goal of surgical treatment in early stages is to reduce morbidity and mortality. For more advanced stages of lung cancer or in patients with anesthetic-surgical risk, the focus is on correctly identifying patients for whom surgical treatment, combined with radiotherapy or chemotherapy, would provide a benefit. This underscores the importance of the issue addressed in the present research.

The issue of surgical treatment for lung cancer has been approached in 2019 by the European Society of Thoracic Surgeons, joining the ERAS Society, thoracic surgery section (which had addressed the issue in 2017). Accelerated postoperative recovery protocols have confirmed their utility in various surgical fields (colorectal, cardiac, orthopedic, etc.), including thoracic surgery. However, scientific publications addressing the ERAS strategy in thoracic surgery are based on non-randomized studies with significant methodological deficiencies and bias factors. Accordingly, the results and conclusions are very heterogeneous, and the need to standardize the recommendations remains a future goal. A very recent trend in perioperative patient management is the so-called prehabilitation (respiratory, cognitive, motor, etc.)—a set of measures, still insufficiently clearly defined, aimed at increasing the functional capacity (reserve) of the patient, enabling them to cope with surgical stress and the postoperative recovery period. The effects of other perioperative support techniques (e.g., fascial plane blocks, antifibrinolytic strategies to limit perioperative bleeding) on postoperative outcomes have yet to be reported in oncological thoracic surgery.

As a result, the possibility of developing and testing new perioperative management methods in oncological thoracic surgery is outlined within a new, multimodal, and integrated concept, which could make new categories of patients eligible for surgical treatment, especially those with advanced anesthetic-surgical risk, and/or improve postoperative outcomes for any patient undergoing intervention.

Purpose of the work: To develop a multimodal perioperative approach for patients with bronchopulmonary cancer and advanced anesthetic-surgical risk, which would allow the expansion of operability criteria to increase the life expectancy and reduce postoperative complications.

Research Objectives:

1. To estimate the own, developed methodology for the preoperative evaluation of patients with bronchopulmonary cancer and advanced anesthetic-surgical risk, justifying an individualized prehabilitation program to enhance preoperative biological reserves.
2. To characterize the clinical and paraclinical aspects and analyze the results of the traditional approach for patients with bronchopulmonary cancer and advanced anesthetic-surgical risk.
3. To conduct a comparative analysis of the clinical utility of the Charlson, Th-RCRI, ASA, and MET scores in the management of perioperative evolution and treatment results of patients with broncho-pulmonary cancer and advanced anesthetic-surgical risk.
4. To identify, describe, and analyze the determinants of perioperative mortality in patients with bronchopulmonary cancer and advanced anesthetic-surgical risk to optimize the management of related risks.
5. To assess the role of ultrasound-guided fascial plane blocks in the thoracic region in accelerating postoperative recovery to homeostasis in patients with bronchopulmonary cancer and advanced anesthetic-surgical risk.
6. To evaluate the impact of intraoperative bleeding reduction strategies on the postoperative recovery of patients with bronchopulmonary cancer and advanced anesthetic-surgical risk.

7. To analyze postoperative outcomes with the development of a rational diagnostic-therapeutic algorithm for patients with bronchopulmonary cancer.

Methodology of Scientific Research

The study design is bidirectional (retrospective and prospective), cohort-based. The research protocol was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy "Nicolae Testemițanu" in the Republic of Moldova (minutes report no. 4 from 12.11.2020).

To achieve the research objectives and tasks, were studied two patient cohorts. The first cohort, collected retrospectively from the database of the Oncology Institute, included patients with lung cancer and advanced anesthetic risk who met the inclusion and exclusion criteria for the study, but had not undergone surgical treatment due to contraindications based on traditional approaches. The second cohort was formed prospectively, adhering to the same inclusion and exclusion criteria, but included patients who benefited from a newly proposed conceptual approach (elements of prehabilitation and accelerated postoperative rehabilitation, anterior fascial plane analgesia, intraoperative antifibrinolysis, stratification, and parametrization of risks based on integrated severity scores (ASA, Th-RCRI, MET, Charlson)). The surgical patients were divided into two subgroups: survivors and those who died during the early postoperative period, in order to identify differences, risk factors, and predictors of postoperative mortality. The series of surviving patients who underwent surgery based on the expanded criteria for surgical treatment was compared with the cohort of patients treated through traditional approaches (only chemotherapy and/or radiotherapy) in terms of the two-year survival rate.

The results obtained from descriptive and inferential statistical analysis were subsequently used as a basis for the mathematical-analytical statistics of the data. This served as an argument for the precise formulation of extended indications and contraindications for surgical interventions based on the identified and parametrized risk factors, as well as for the formulation of general practical recommendations. Specifically, two subcategories of patients with lung cancer and advanced anesthetic-surgical risk were identified and compared, which showed similar long-term results: (1) patients with stage III lung cancer and a Charlson score of 0-4 points, and (2) patients with stage I-II lung cancer and a Charlson score of 5-12 points.

The required number of patients to test or reject the formulated research hypotheses was calculated using G*Power software v. 3.1.9.6 (developed by Franz Faul, University of Kiel, Germany, 1992-2020), based on the primary outcome criterion of a minimum 15% difference in the two-year survival rate between cohorts. Accordingly, the total number of patients needed was estimated to be 184 individuals. Statistical analysis of the data series was performed using GraphPad Prism software, version 9 trial (GraphPad Software, Boston, USA). The following statistical tests were applied: Fisher's exact test, Student's t-test, Spearman and Pearson correlation tests, ROC curves, Kaplan-Meier curves (with the Mantel-Cox test), multicollinearity testing, logistic regression, and probability calculation. The selection of tests was based on the formulated hypothesis, the normal or abnormal distribution of the data series, and the number of data series. The results are presented as mean and standard deviation (if applicable – 95% confidence interval of the mean), and relative (absolute) data. Statistical calculations were performed based on a study power of 80%, alpha error of 5%, beta error of 20%, and statistical significance of less than 0.05.

Novelty and Scientific Originality of the Results Obtained

The issue of surgical treatment in patients with lung cancer and advanced anesthetic-surgical risk has been addressed for the first time. These patients are traditionally treated only with chemotherapy or radiotherapy. It has been demonstrated that for well-defined categories of patients, surgical treatment is feasible, yielding significantly better postoperative results and a two-year survival prognosis, compared to the traditional approach. Specific risk factors have been established and parameterized to identify patients eligible for surgical treatment among those with increased anesthetic-surgical risk. Additionally, predictive models for perioperative mortality have been developed and tested, based on integrated severity scores. A perioperative management strategy has been created, which includes elements of prehabilitation, accelerated postoperative rehabilitation, intraoperative antifibrinolysis, and prior analgesic nerve blocks. These components work synergistically to enhance the body's resistance to surgical stress and facilitate the return to homeostasis.

Important Scientific Problem Addressed in the Thesis

A new conceptual approach to the eligibility and perioperative management of patients with lung cancer and advanced anesthetic-surgical risk has allowed for the expansion of operability criteria for some categories of patients previously considered inoperable. Mathematical models for predicting postoperative mortality risk, based on complex severity scores (Th-RCRI, Charlson, MET, and ASA) and the extent of planned pulmonary resection, enable the proposal of a reasonable treatment option (surgical or non-surgical). Patients with lung cancer and advanced anesthetic-surgical risk, operated based on the developed extended operability criteria and managed perioperatively with elements of prehabilitation and accelerated postoperative rehabilitation, significantly increase life expectancy compared to traditional approaches.

Theoretical Significance

The work provides a critical synthesis of the literature regarding elements of accelerated postoperative rehabilitation that, in the author's adaptation to oncological thoracic surgery, has allowed for the identification of categories of patients eligible for intervention among those previously deemed ineligible. The thesis offers theoretical, methodological, and practical support related to preoperative assessment, individualized prehabilitation programs, accelerated postoperative rehabilitation, and intra- and postoperative care for patients with bronchopulmonary cancer with increased anesthetic-surgical risk, which facilitate an increase in survival rates.

Practical Value of the Work

The proposed innovative approach allows for the expansion of operability criteria for patients with bronchopulmonary cancer and increased anesthetic-surgical risk. As a result, an additional segment of patients can benefit from surgical treatment for bronchopulmonary cancer, achieving significantly better clinical outcomes in terms of survival rates and life expectancy. The research findings provide straightforward practical recommendations for surgeons, anesthesiologists, and intensivists in evaluating and stratifying risks, types of prehabilitation, and preoperative preparation for elective surgical patients. The use of a previous serratus plane block in thoracic surgeries reduces postoperative pain intensity and improves ventilatory parameters. Reducing intraoperative bleeding through the systematic administration of tranexamic acid contributes to a faster return to homeostasis for the patient after surgery.

Implementation of Results in Practice

The research findings have been implemented in current clinical practice in the thoracic surgery department of the Emergency Medicine Institute in Chișinău, Republic of Moldova (Appendices No. 01-02).

Approval of the Thesis

The main postulates of the thesis have been reported and discussed at:

- The National Congress of Oncology (Poiana Brașov, Romania; 2023);
- The National Congress of Surgery (Eforie-Nord, Romania; May 24-27, 2023);
- The National Congress of Surgery (Eforie-Nord, Romania; May 24-27, 2023);
- The 30th Annual Congress of the World Society of Cardio-Vascular and Thoracic Surgeons (St. Petersburg, Russia; 2022);
- The National Congress of Surgery (Sinaia, Romania; June 8-11, 2022);
- The 13th Congress of the "Nicolae Anestiadi" Surgeons Association and the 3rd Congress of the "V.M. Guțu" Society of Endoscopy, Minimally Invasive Surgery, and Ultrasonography from the Republic of Moldova (Chișinău; September 18-20, 2019).

The results of the study were discussed and approved during the meeting of the Department of Surgery No. 1 "Nicolae Anestiadi," USMF "Nicolae Testemițanu" (minutes report No. 10 from 02.05.2024); and at the Scientific Seminar in the field – 321.13. Surgery; 321.14. Pediatric Surgery; 321.22. Urology and Andrology, USMF "Nicolae Testemițanu" (excerpt from minutes from 26.06.2024).

Publications on the Thesis Topic

The foundational materials of the thesis have been published in 24 scientific papers, including one monograph, 4 articles in international journals, 2 articles in indexed foreign journals, 3 articles in nationally indexed journals, 12 abstracts published in the proceedings of scientific events; 2 intellectual property objects, and oral presentations and communications at various international scientific events (2 in the country and 5 abroad).

Summary of the Thesis Sections

The thesis text is presented in 197 pages of core text, processed on a computer, consisting of the list of abbreviations, introduction, 7 chapters, general conclusions, practical recommendations, a bibliography of 310 sources, and 7 appendices. The illustrative material includes 48 tables and 53 figures.

Keywords

Bronchopulmonary cancer, anesthetic-surgical risk, ultrasound-guided fascial plane block, prehabilitation, extended operability criteria, accelerated rehabilitation protocols, survival rate.

THESIS CONTENT

1. SURGICAL TREATMENT OF BRONCHOPULMONARY CANCER IN PATIENTS WITH ADVANCED ANESTHESIOLOGICAL-SURGICAL RISK WITHIN A MULTIMODAL APPROACH TO PERIOPERATIVE MANAGEMENT

This chapter presents a critical analysis of recent and relevant scientific literature regarding the surgical treatment of bronchopulmonary cancer, including in patients with advanced anesthesiological-chirurgical risk. The chapter is structured into five sections. The first section reviews the epidemiology of bronchopulmonary cancer, based on data from the international GLOBOCAN platform as well as internal evidence from the Republic of Moldova. It mentions issues such as late diagnosis, reduced survival rates, and the limited efficacy of radiotherapy or chemotherapy treatments, whether used alone or in combination. Additionally, it highlights the extremely low proportion of patients who generally benefit from surgical treatment for bronchopulmonary cancer. The purely surgical aspects are discussed in the second section of the chapter, where the criteria for operability, indications, and contraindications for surgical treatment are addressed. The modern approach, based on the new concept of prehabilitation for frail patients aimed at increasing their preoperative biological reserve and ability to withstand surgical stress, is described in the third section. The inclusion of prehabilitation in ERAS-type programs has been associated with a reduction in postoperative morbidity and mortality, as well as hospital duration and costs, although this varies depending on the field of surgery and the experience of the surgical clinic adopting such an approach. The last two subsections (four and five) of the chapter focus on the anesthetic and perioperative care of patients undergoing thoracic surgeries, including oncological interventions. New technologies, based on ultrasound-guided administration of local anesthetics with or without adjuvants, enable the performance of analgesic blocks of sensory nerves passing through the muscular interfascial planes. In addition to remarkable postoperative analgesia, these technologies facilitate accelerated postoperative recovery. The summary of Chapter 1 identifies numerous understudied aspects or conflicting data reported in the literature that require clarification, as well as a reconceptualization of the surgical approach for patients with bronchopulmonary cancer and advanced anesthesiological-chirurgical risk.

2. MATERIALS AND RESEARCH METHODS

2.1. Study design

The research conducted for this thesis tested a new multimodal perioperative approach developed for patients with bronchopulmonary cancer and advanced anesthetic-surgical risk, aimed at expanding surgical operability criteria to increase life expectancy and reduce postoperative complications. From this perspective, the work consists of two main studies: 1) the first study, experimental, prospective, descriptive-analytical, and cohort-based, was carried out in the thoracic surgery department (Institute of Emergency Medicine), part of the Surgical Clinic of the Department of Surgery No. 1 “Nicolae Anestiadi”, USMF “Nicolae Testemițanu” in the Republic of Moldova during the years 2016-2024; 2) the second study, retrospective, descriptive-analytical, and cohort-based, was conducted based on medical records, with data extracted from the archive of the Oncology Institute in the Republic of Moldova. Data collection took place throughout 2022 and included eligible clinical cases according to predefined inclusion and exclusion criteria, treated and monitored during the years 2013-2020.

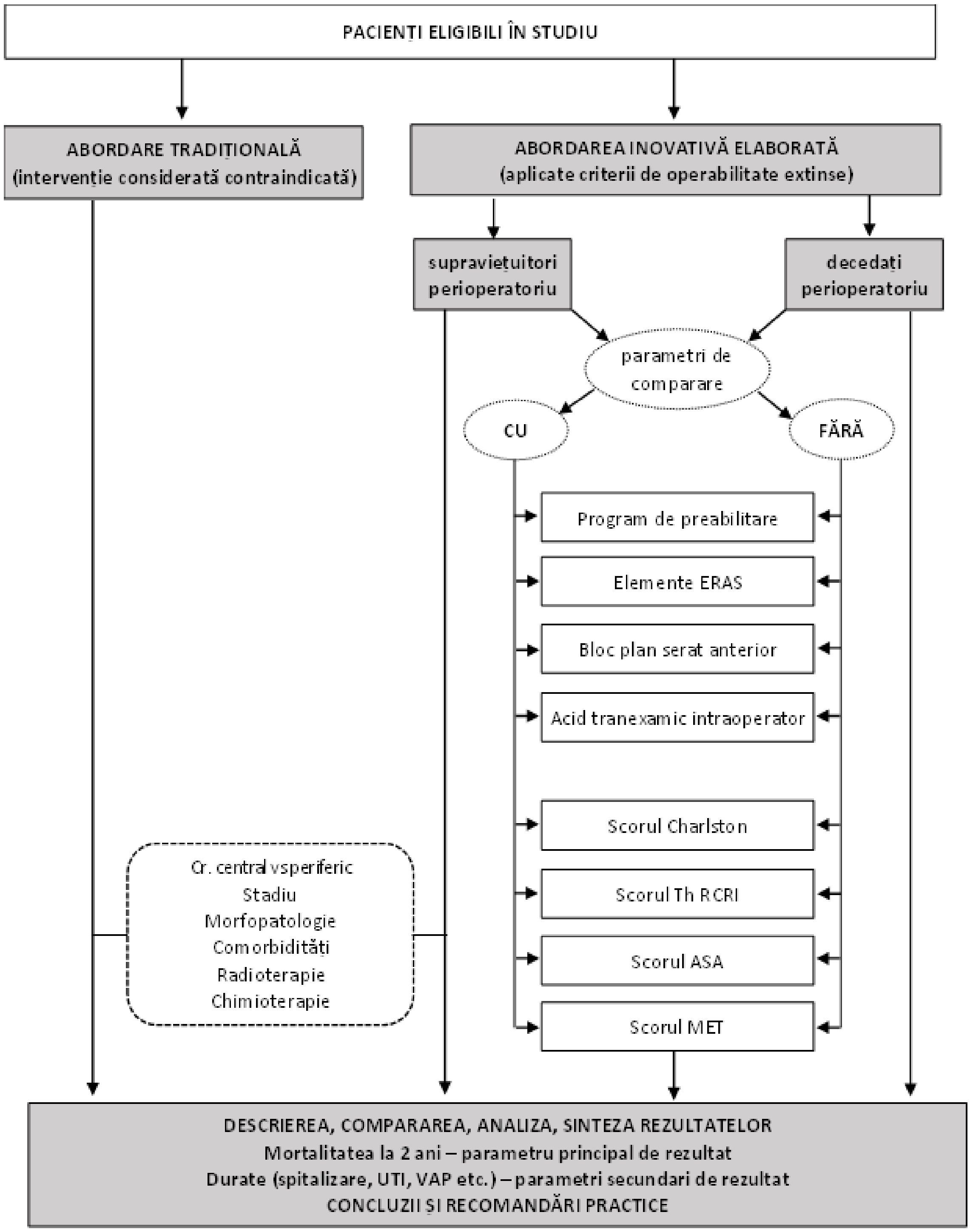

Figure 1. **General Design of the Research in the Thesis**

The main research hypothesis is based on findings from a critical literature synthesis. Specifically, this paper tested the influence of the developed innovative approach on survival rates and overall survival duration compared to the traditional approach in patients with lung cancer and advanced anesthetic-surgical risk. The innovative approach included the application of ERAS-type elements (combatting malnutrition, correcting preoperative anemia, avoiding incidental hypothermia in the operating room, multidimensional preoperative prehabilitation, multimodal pain management, intraoperative use of antifibrinolytics, etc.), as well as the implementation of new anesthesia techniques (e.g., ultrasound-guided fascial plane blocks) and surgical techniques (e.g., a new type of bronchial sealing suture proposed).

Thus, the inclusion criteria for the study were: 1) adult patients (over 18 years old); 2) bronchopulmonary cancer in stages I-IIIa; 3) preoperative diagnosis confirmed by pathological anatomy examination; 4) patients with preoperative anesthetic risk ASA II-III; 5) patients not previously operated on for bronchopulmonary cancer; 6) patient consent to participate in the research project. The exclusion criteria from the study were: 1) patients with bronchopulmonary cancer in stages IIIb-IV; 2) metastases from other tumor types in the lungs; 3) preoperative anesthetic risk ASA I and ASA IV, V; 4) patients with a history of cardiac and major vessel surgeries; 5) patients previously operated on for bronchopulmonary cancer; 6) absence of preoperative pathological anatomy examination; 7) patients with preoperative cognitive disorders; 8) patients abusing alcohol or using drugs; 9) patients who refused to participate in the research project.

The proposed and realized design of the research in this thesis is presented in the figure1.

Finally, to conclude on the feasibility of expanding the operability criteria for bronchopulmonary cancer, the multimodal innovative approach during the perioperative period on the 2-year survival rate and average survival duration, these key outcome parameters were compared between the retrospective cohort (traditionally approached, non-operated patients) and the series of surviving patients from the prospective cohort (Figure1).

2.2. Preoperative Assessment and Anesthetic-Surgical Risk Stratification

Preoperative respiratory assessment is based on three core elements: (1) respiratory biomechanics; (2) actual pulmonary parenchyma function; (3) cardiopulmonary functional reserve. Current guidelines for preoperative respiratory function assessment consider the most valid parameters: FEV1, DLCO (diffusion capacity of the lungs for carbon monoxide), and VO_{2max} (maximum oxygen consumption). Subsequently, depending on the estimated resection volume, functional resectability is estimated based on two derived parameters: ppoFEV1 and ppoDLCO, which are the theoretical postoperative values estimated from the patient's actual preoperative values, subtracting those volumes that are hypothetically provided by the volume of lung tissue to be removed [1, 2, 3].

The Goldman Risk Index (GRI) is one of the first risk scores for cardiac complication risks that was developed and widely disseminated in most fields of surgery, anesthesia, and intensive care. As a result, a score was created consisting of nine criteria, to which a specific point value was assigned if positive (Table 1).

The Revised Cardiac Risk Index (RCRI) assesses six independent variables associated with increased cardiac risk. These clinical risk factors include: high-risk surgery, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin-dependent diabetes and preoperative serum creatinine over 2 mg/dL (or over 177 µmol/L). The Revised Cardiac Risk Index (RCRI) was developed as a risk stratification tool for patients undergoing non-cardiac surgery; however, its development and validation included a relatively small number of patients undergoing thoracic surgery. A recalibration of the RCRI proposed by Brunelli and co-authors, known as the Thoracic Revised Cardiac Risk Index (ThRCRI), has emerged as a tool to predict postoperative cardiovascular complications in patients undergoing lung resections. The individual components of the ThRCRI (pneumonectomy, chronic kidney disease and cardiovascular disease) are known to be associated with an increased risk of mortality in the general population. In the ThRCRI, patients are classified into four risk groups based on their accumulated score: A (risk score of 0), B (risk score of 1 to 1.5), C (risk score of 2 to 2.5), and D (risk score greater than 2.5).[8]

Table 1. **Goldman risk index**

Criteria				**Score**
History				
• Myocardial infarction in the last 6 months				10
• Age 70 and above				5
Physical Examination				
• Jugular vein distension or S3				11
• Significant aortic stenosis				3
Electrocardiogram				
• Rhythm other than sinus with or without premature complexes on last ECG				7
• 5 ventricular premature complexes/min before surgery				7
Other Factors				
• Poor general physical condition				3
• Intra-abdominal, intrathoracic, or aortic surgery				3
• Emergency surgery				4
Total Points				**53**
Probability of life-threatening complications based on CRI points				
Class	Points	Minor or No Complications	Probability of Complications	Sudden Cardiac Death
I	0-5	99%	0,7%	0,2%
II	6-12	93%	5%	2%
III	13-25	86%	11%	2%
IV	26	22%	22%	56%

2.3. Description of surgical techniques applied through the lens of relevant clinical cases

Right pneumonectomy. Under general anesthesia, the patient is positioned in a supine position. An anterolateral thoracotomy is performed on the right through the fourth intercostal space. Upon revision, the upper lobe of the lung is found to be adherent to the thoracic wall and mediastinum, with adherence to the spine. In the region of segment S1, a hard, flat, immobile formation measuring 1×2 cm is palpated. A flat, elongated formation is also identified along the path of the oblique interlobar fissure. Multiple nodular formations are noted on the mediastinal pleura and multiple nodules are found on the visceral pleura of the upper, middle and lower lobes of the lung, as well as on the diaphragm—multiple nodules of varying sizes. The decision was made in favor of pneumonectomy with extensive lymphadenectomy. The preparation of the right pulmonary hilum was carried out, ligating the superior and inferior veins, as well as the peripheries. These were sutured and sectioned. The pulmonary artery was prepared, ligated, and sectioned, including the peripheries. Vascular pneumonectomy was performed with stable hemostasis. During the preparation of the main bronchus, adherence to the wall of the esophagus was determined, involving the vagus nerve. Extensive lymphadenectomy was performed, removing lymph nodes from the esophagus, the right main bronchus and at the tracheal bifurcation (lymph node groups 8, 10, and 7). A vagotomy was performed due to the involvement of the tumor process in the vagus nerve. A nasogastric tube was placed for postoperative monitoring of the esophagus. The right main bronchus was clamped, sectioned in stages and sutured in two layers with continuous suture (Innovator's Patent No. 6185). Stable hemostasis and airostasis were achieved and pneumonectomy was performed. The stump of the main bronchus was covered with mediastinal pleura. A 30 Fr silicon drain was placed, directed towards the right pleural dome. Thermal ablation of metastatic nodules on the mediastinal pleura and diaphragm was performed. The drain was secured and thoracorrhaphy was performed in anatomical layers. An aseptic dressing was applied. The drain was connected to the Bulau system. Intraoperative blood loss amounted to approximately 400 ml.

Left Pneumonectomy. Under general anesthesia, the patient was positioned in a prone position. A left posterolateral thoracotomy was performed, with layer-by-layer incision and hemostasis throughout. The entry into the left pleural cavity was through the VII intercostal space. Upon inspection, a volume formation was found projecting onto the central bronchus, adhering to the wall of the left main pulmonary artery and the superior pulmonary vein, with enlarged and firm parahilar and bifurcation lymph nodes (groups 10 and 7). There were metastatic foci in the upper and lower lobes of the lung, and a region with conglomerates of nodules on the diaphragm. A decision was made for pneumonectomy. The pulmonary ligament was severed and the hilum structures on the left were dissected along with lymphadenectomy of mediastinal lymph node groups 7, 10, 4L, 5, and 6. The peripheral structures of the left pulmonary hilum were prepared, the left vagus nerve was mobilized from the volume formation, and the central inferior vein was ligated, followed by peripheral ligation and suturing of the central segment. The central superior vein was ligated and then ligated peripherally, with central suturing and sectioning. The central pulmonary artery was ligated with peripheral ligation, and central suturing was performed, followed by sectioning. A vascular pneumonectomy was conducted with verification of hemostasis. The central bronchus of the left lung was prepared, clamped, and sectioned in stages, with suturing in two layers using continuous suture (Innovator Patent No. 6185) and treatment of the stump with a betadine solution. Pneumonectomy was performed with subsequent pleuralization of the left main bronchial stump. Hemostasis and air leakage were verified. A 28 Fr silicon drain was placed in the thorax, directed towards the left pleural dome. The drain was secured. Thermal ablation of the conglomerate of nodules on the pleural surface of the diaphragm was performed. Thoracorrhaphy was done layer by layer. Intraoperative blood loss was approximately 400 ml.

Transpericardial Pneumonectomy on the Left. Under general anesthesia, the patient was placed in a prone position. A left posterolateral thoracotomy was performed layer by layer, with hemostasis throughout. In the pleural cavity, multiple pleuro-pulmonary, diaphragmatic, and mediastinal adhesions were found. Pneumolysis was performed, though with technical difficulties. Upon inspection, a central tumor was identified anterior to the left pulmonary artery, approximately 3×3 cm in size, hard on palpation, immobile, and irregularly shaped. Additionally, two metastases in the lung measuring 2 and 3 mm were identified. The pulmonary hilum was prepared with identification and mobilization of the artery, vein, and bronchus on the left side. The pulmonary artery and vein were ligated centrally and peripherally, and sectioned. The bronchus was prepared, clamped, and sectioned with sutures applied in two layers. A 28 Fr drain was placed in the pleural cavity, oriented towards the pleural dome. It was secured, and checks for hemostasis, air leakage, and foreign bodies were performed. Thoracorrhaphy was done layer by layer. Intraoperative hemorrhage was estimated at 1600 ml.

Transpericardial Pneumonectomy on the Right Side. Under general anesthesia, the patient was positioned in the dorsal decubitus. Anterolateral thoracotomy on the right side with ongoing hemostasis. Access was gained to the pleural cavity on the right through the IV intercostal space. Upon revision, the middle and upper lobes were adherent to the parietal pleura, followed by pneumolysis with hemostasis. During further revision, a hard, irregular, immobile tumor process was palpated, centrally located between the confluence of the *azygos* vein and the superior vena cava, the right main bronchus, the right pulmonary artery, and the right superior pulmonary vein. With technical difficulties, preparation of the right pulmonary hilum was achieved; both pulmonary veins were centrally ligated and the peripheral sections were ligated down to their segmental portions. These were sutured and sectioned with stable hemostasis. The right pulmonary artery was ligated, followed by suturing and further sectioning. Stable hemostasis was achieved. The bronchus was prepared and separated from the tumor process, which also involved the *azygos* vein. It was clamped and sutured with continuous sutures in two layers, achieving stable aerostasis. The right bronchial stump was pleurized with mediastinal adipose tissue and thymic gland. Control was established for aerostasis and hemostasis. A 30 Fr silicon drain was applied, oriented towards the right pleural dome. This was fixed, and thoracorrhaphy was performed on anatomical layers. Intraoperative hemorrhage was approximately 1200 ml.

Right Upper Lobectomy. Under general anesthesia, the patient was positioned in the dorsal decubitus. Anterolateral thoracotomy on the right side with hemostasis ensured. Access was gained to the pleural cavity through the IV intercostal space. Upon revision, a mass of 1×1 cm was found in S3, immobile and hard to palpate; pleuro-pulmonary adhesions were present at the level of the upper lobe, followed by further pneumolysis. Mediastinal lymphadenopathy was observed. The upper lobe elements of the right lung were mobilized and prepared. The veins and arteries of the upper lobe were ligated, sutured, and sectioned. The bronchus of the upper lobe was prepared, clamped and sutured in two rows with pleurization of the bronchial stump. The pulmonary ligament was sectioned. Verification for hemostasis and aerostasis was performed. Two drains were applied in the right pleural cavity, oriented towards the right pleural dome. These were fixed, and thoracorrhaphy was performed on anatomical layers. The drain was connected to the Bulau system. Intraoperative hemorrhage was estimated at 300 ml.

Right Upper Bilobectomy. Under general anesthesia, an anterolateral thoracotomy was performed on the right side, layer by layer, with hemostasis achieved. The pleural cavity on the right was entered. Upon revision, a mass was identified in the interlobar fissure of the upper and middle lobes, near the pulmonary hilum; it was hard on palpation and immobile. The decision was made to perform a right upper bilobectomy. The peripheral and central veins and arteries of the upper and middle lobes were meticulously prepared, ligated and sectioned. The main bronchi of the upper and middle lobes were prepared. They were clamped, sutured, and sectioned using the Sweet technique. Stable hemostasis and aerostasis were obtained. Two drainage tubes (28 Fr and 26 Fr) were placed in the pleural cavity, oriented towards the pleural dome. The drains were secured and thoracoplasty was performed in anatomical layers. The drains were connected to the Bulau system. Intraoperative blood loss was estimated at approximately 1000 ml.

Middle Lobectomy. Under general anesthesia, the patient was placed in the dorsal position. An anterolateral thoracotomy was performed on the right side, layer by layer, with hemostasis maintained. The IV intercostal space was entered. Upon revision, a mass was found in the middle lobe. The decision was made for a middle lobectomy. The hilum elements were prepared with delimitation of the lobe from the oblique and horizontal fissures. The vascular elements and bronchus of the middle lobe were prepared. The hilum elements of the middle lobe were ligated and sectioned. Hemostasis and aerostasis were verified. A 24 Fr drainage tube was placed, oriented towards the right pleural dome. The drain was secured and thoracoplasty performed in layers. The drain was connected to the Bulau system. Intraoperative blood loss was approximately 150 ml.

Right Lower Lobectomy. Under general anesthesia, the patient was placed in the dorsal position. An anterolateral thoracotomy was performed on the right side in the V intercostal space, with incision through the anatomical layers, achieving hemostasis. Upon revision, thickening of the visceral pleura was determined. Multiple adhesions were noted in the basal and apical regions of the right lung, as well as in the mediastinum. Pneumolysis was performed and the right pulmonary ligament was sectioned. The inferior pulmonary lobe was mobilized through the fissure to the inferior lobe artery. The elements of the lower lobe and inferior pulmonary vein were prepared. Peripheral structures were prepared. The inferior pulmonary vein and right lower lobe artery were ligated and sutured centrally. A lymph node was removed from the anterior surface of the inferior lobe bronchus. The inferior lobe bronchus was clamped and sectioned. It was sutured in two layers with continuous suture. Stable aerostasis was achieved. Pulmonary decortication was performed. Two drainage tubes (24 Fr and 28 Fr) were placed, oriented towards the right pleural dome. The tubes were secured and thoracoplasty was performed in anatomical layers. The drains were connected to the Bulau system. Intraoperative blood loss was approximately 300 ml.

Left Upper Lobectomy. Under general anesthesia, the patient was placed in the dorsal position. An anterolateral thoracotomy was performed on the left side in the intercostal space, with incision through layers, achieving hemostasis throughout. Upon revision, a mass was identified in the left upper lobe, with adhesion to the anterior thoracic wall. Pneumolysis was performed and the tumor was detached from the thoracic wall. The elements of the pulmonary hilum and the left upper lobe were prepared, ligated and sectioned. The bronchus was clamped and sutured with continuous suture in two layers. Left mediastinal lymphadenectomy was performed. Tumor ablation was conducted. Two drainage tubes of 24 Fr and 28 Fr were introduced, oriented towards the left pleural dome. The tubes were secured and hemostasis and aerostasis were checked. Thoracoplasty was performed in anatomical layers. The drains were connected to the Bulau system. Intraoperative blood loss was approximately 200 ml.

Left Lower Lobectomy. Under general anesthesia, the surgical field was prepared and delineated. A posterolateral thoracotomy was performed, with layer-by-layer incision and hemostasis ensured. Upon revision, a volume formation was identified, palpable through the interlobar fissure (4×4 cm), with no signs of invasion into the upper lobe. The organs in the left pleural cavity showed no other abnormalities. The decision was made for a lower lobectomy. The pulmonary ligament was sectioned. The vascular elements of the left lower lobe were mobilized. The vein of the left lower lobe was identified, prepared along with its branches, ligated and sectioned. The artery of the left lower lobe was prepared along with its branches, ligated, sutured and sectioned. The main bronchus of the lower lobe was identified, clamped and sectioned using the Sweet method. Stable airostasis was achieved. A lymphadenectomy of a paraesophageal lymph node chain on the left was performed. A 28 Fr drainage tube was placed in the left pleural cavity, oriented toward the pleural dome and secured to the skin. Hemostasis, airostasis and re-expansion of the upper lobe were checked. Thoracorrhaphy was performed in anatomical layers. Intraoperative hemorrhage was approximately 500 ml.

Modified Bronchoplasty Technique for Pulmonary Resections. One of the important stages of pulmonary resections is the processing and suturing of the bronchial stump.

The issue of bronchial stump dehiscence, following pulmonary resections, necessitates the search and development of new techniques for processing and securely closing the lumen.

Between 2016 and 2019, patients who underwent pulmonary resections for lung cancer (n=68), where the Sweet technique for bronchoplasty was applied, exhibited a perioperative mortality of 2.94% and a postoperative mortality of 11.76%, with an incidence of bronchopleural fistula of 10.29% (7/68 patients). Among these 7 cases of bronchopleural fistulas, 2 were primary and 5 were secondary (occurring more than 3 weeks postoperatively). The management of patients with bronchopleural fistula is complicated and complex, requiring prolonged maintenance of pleural drainage tubes, as well as the application of pleural cavity lavage with antiseptic solutions and sometimes systemic antibiotic therapy according to bacteriological results (the most commonly recorded cultures in such cases are from *Pseudomonas aeruginosa*).

After achieving a "sterile" pleural cavity, secondary suturing of the bronchial stump was performed on 2 patients. Spontaneous closure of the bronchopleural fistula was recorded in 1 patient who received the same management (systemic antibiotic therapy + pleural lavage).

From 2019 until 2023, when data collection for the thesis was completed, the modified bronchoplasty technique described in detail below was applied. A total of 3 cases of bronchopleural fistula were recorded, all of which were secondary (occurring more than 3 weeks post-surgery). Two patients underwent reoperation for bronchoplasty.

The specific technique developed for suturing and sealing the bronchial stump is as follows. The patient is intubated orotracheally and positioned appropriately (ventral, dorsal, or lateral decubitus, either right or left), depending on the type of surgical access planned. The bronchial stump is prepared and processed by clamping it distally. For suturing, a *Covidien GM323 BIOSYN Suture, Taper Point, Undyed, 30", Needle V-20, 1/2 Circle, Size 2-0, Violet* suture thread was used. The first suture is applied 5 mm from the clamp, with 3-4 knots made. One of the threads remains suspended, while the other continues suturing the bronchial stump. Gradually, with the help of a scalpel, the bronchial lumen is opened and secretions are aspirated with a suction device. The edges are periodically treated with a betadine solution.

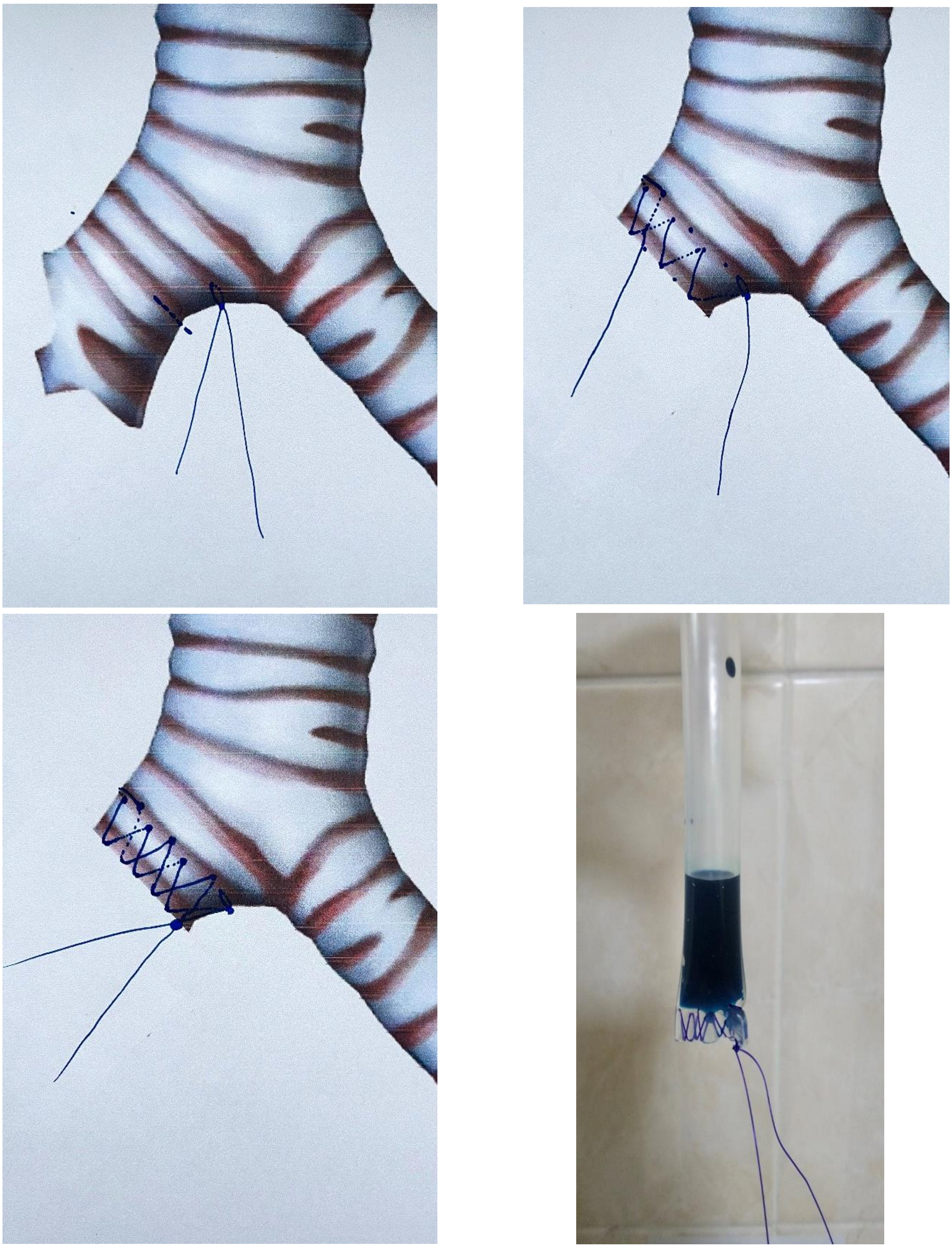

Figure 2. **Continuous bronchial suture of own elaboration** (schematic image and photograph of the leak test): A – application of the first suture; B – application of the first row of sutures; C – complete closure of the bronchial stump; D – demonstration of leak tightness ensured by the developed suture.

Sutures are applied as a continuous transfixion in 3 steps, with the anchoring thread passing over the edge of the bronchial stump. The last suture of the first row is applied so that it does not exceed the thickness of the bronchial wall; the second row is applied at a distance of 6-7 mm from the stump edge, with the needle passing through the midpoint of the distance between the previous suture points. Thus, by the return suture, an "X" is formed at the edge of the bronchial stump with each step (Figure 2).

The duration of the suturing procedure is 5-15 minutes, depending on the type of resection and the complexity of the case. This method has been applied to 117 patients: among them, 41 pneumonectomies and 76 lobectomies—most of the patients operated on for lung cancer, benign lung tumors (fibroleiomyoma, n=1; bronchiectasis, n=6), with no cases of dehiscence recorded in the first 3 weeks after the intervention.

The transpericardial approach (suturing and ligating) of the pulmonary vein. One of the challenging situations where meticulous processing of the pulmonary veins is necessary, is when the approached pulmonary vein is very short or the tumor process involving the affected segment does not provide adequate oncological safety margins. The transpericardial preparation of the pulmonary vein with ligation and suturing allows for the prevention of a vascular accident. The method consists of the following: Depending on the approached pulmonary vein and its mobility, meticulous transpericardial preparation is performed. After circular exposure, suturing is done by applying 2 transfixing sutures through the vein (its lumen being divided into 3 equal height planes), with a third circular suture around the vein, the threads being perpendicular to the vein and parallel to each other. The ligation of the threads is done with the formation of a bridge of a few mm when possible, followed by repeated circular ligation with knot application. For this method, Covidien VP523 – SUTURE, SURGIPRO-II, BLUE, 2/0, 36", V-20, 36/BX suture thread is used. The duration of the procedure is 7-20 minutes, depending on the type of resection and the complexity of the case. The implementation of this method has allowed for the creation of a safe venous vascular stump without incidents of dehiscence during the postoperative period. In total, during the period from 2016 to 2024, this method was applied to 5 patients operated on for lung cancer.

2.4. Anesthesia assistance and perioperative intensive therapy

Surgical interventions were performed under general anesthesia with inhaled agents, with controlled artificial pulmonary ventilation (with non-selective orotracheal intubation). Induction (the hypnotic component) was performed with propofol solution, bolus – 10-15 mg/kg, followed by a continuous infusion of 5-7 mg/kg/hour, adjusted according to the depth of anesthesia (FCC, TAS). The analgesic component was ensured through intravenous administration of fentanyl solution 0.03 mcg/kg at induction, followed by a continuous maintenance infusion of 0.01-0.02 mcg/kg, adjusted based on the patient’s heart rate and blood pressure, along with a single dose of 30-50 mg of ketamine intravenously. The opioid relay for ensuring intraoperative analgesia consisted of administering 10 mg of morphine intravenously as a slow bolus. Surgical muscle relaxation was achieved through the administration of atracurium solution (0.8-1 mg/kg). The inhalational component was maintained with Sevoflurane, at a concentration of 1.0-1.3 MAC, adjusted according to the patient's heart rate and blood pressure. Postoperatively, patients were transferred for awakening and temporary support of vital functions in the Intensive Care Unit on artificial pulmonary ventilation. After awakening and safe return to respiratory autonomy, patients were extubated and continued to breathe independently with additional O2 flow via facial mask.

2.5. Technique for performing ultrasound-guided interfascial thoracic blocks

The interfascial administration of local anesthetics in various volumes and concentrations, with or without adjuvants, has only been practiced in the last 20 years due to advancements in ultrasound technology, imaging algorithms, and the ability to finely visualize muscle tissue, fascia, and nerves.

Ultrasound-guided interfascial blocks at the thoracic level have been performed by the anesthesiologist as part of anesthesia and perioperative care, in accordance with standardized professional techniques described (https://www.nysora.com/pectoralis-serratus-plane-blocks/). Lidocaine 0.2% was used as the local anesthetic in a volume of 10-20 ml. The doses of local anesthetics in thoracic interfascial plane blocks: lidocaine or ropivacaine at a concentration of 0.2% (20 mg/ml). Volume: 0.2-0.4 ml/kg (extremes of 10-30 ml or 200-600 mg of Lidocaine or Ropivacaine in total). Reported data in the literature regarding the volume and concentration of the local anesthetic administered are extremely varied. The block is performed after induction of anesthesia and intubation of the trachea, until the incision.

2.6. Statistical Analysis of Data

The calculation of the necessary number of patients was performed using G*Power software version 3.1.9.6 (Franz Faul, University of Kiel, Germany, 1992-2020). The primary outcome parameter of the study, based on which the necessary number of complete datasets available for analysis was calculated, is the 2-year survival rate of patients. Thus, the survival rate of patients with lung cancer who meet the enrollment criteria for the study (the "classical approach/unresectable" group, sourced from the Oncology Institute) was 30%. The new proposed model for approaching these patients (the "innovative approach/extended operability criteria" group) aims to identify a 20% (0.2) difference in the 2-year survival rate, a difference considered clinically significant and one that entails reasonable additional risks associated with the surgical intervention itself and the perioperative period.

Thus, the following input parameters were selected from the G*Power software v.3.1.9.6:

- Test type: Z (since it assesses the difference between two independent proportions);
- One-tailed calculation (since only the increase in survival rate in p1 matters);
- Proportion 1 (estimated 2-year survival rate in the innovative approach): 0.50 (50%);
- Proportion 2 (observed 2-year survival rate in the traditional approach): 0.30 (30%);
- Alpha error: 0.05 (5%);
- Study power (1-beta error): 0.80 (80%);
- Allocation ratio N2/N1 (innovative group vs. traditional group): 1:1.

The calculated output parameters were:

- Critical Z (i.e., reaching the threshold of statistical significance): 1.64;
- Minimum sample size for group 1 (traditional approach): 74 patients (complete data sets);
- Minimum sample size for group 2 (innovative approach): 74 patients (complete data sets);
- Total sample size: 148 patients (complete data sets).

The graphic representation of the study sample calculation is presented in Figure 3.

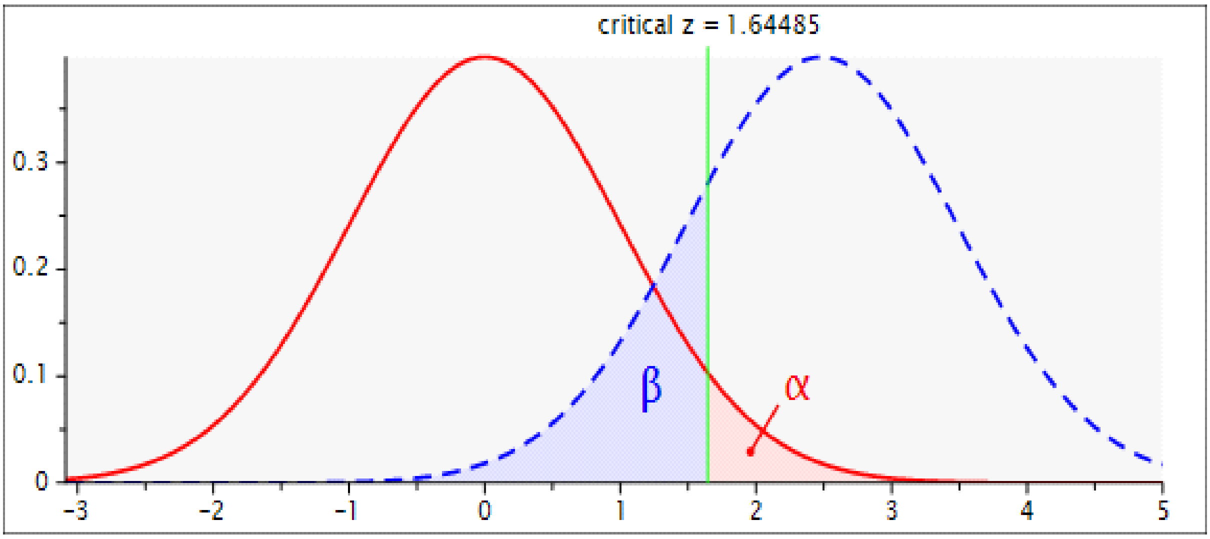

Figure 3. **The graphic representation of the required patient sample calculation to test the hypothesis that the innovative approach (extended operability criteria) can significantly improve the 2-year survival rate of patients with lung cancer with certain characteristics.**

Figure 3 presents a graph of the parameters used to calculate the study sample necessary for testing or rejecting the main research hypothesis, based on the primary outcome parameter: whether the innovative approach developed for preoperative assessment and management during the perioperative period, the expansion of operability criteria, the application of new therapeutic measures (e.g., intraoperative administration of antifibrinolytics, thoracic fascial plane blocks, prevention of incidental hypothermia, etc.), and the use of a new suturing technique significantly increases the 2-year survival rate and the duration of survival at 2 years, compared to patients with the same parameters who are treated traditionally (without surgery). Based on the set parameters, the critical value of the "Z" indicator was obtained (z=1.64). Thus, all statistical calculations performed estimated, through the lens of this critical Z value, the probabilities (p) of confirming or rejecting the null hypothesis. Based on the individual results of the evaluated parameters, trends, syntheses, and reasoning were drawn, which formed the basis for the final conclusions and practical recommendations made accordingly.

Figure 4 represents a graphical modeling of the study parameters based on the number of patients effectively enrolled in the research. The arrow indicates the number of 146 patients necessary to test the formulated hypothesis of the study (corresponding to the minimum standard parameters: 80% study power, 5% alpha error, 20% beta error, a patient allocation ratio of 1:1, and assumed survival proportions before the study began of 30% and 50% at 2 years, respectively). The statistical results obtained from the analysis of the data directly collected in the study can be compared with Figure 4 to assess the validity of the formulated conclusions.

In summarizing the chapter on materials, methods of research and statistical data analysis within the thesis, the research hypothesis was described, which was based on a critical analysis of recent scientific publications in the field. Subsequently, the study design and research methodology were developed. A detailed description of preoperative evaluation, identification and stratification of specific risks based on scores adapted to thoracic surgery was provided. For a more realistic presentation, the description of the surgical interventions performed was framed through specific clinical cases, encompassing all types of interventions for bronchopulmonary cancer. The anesthesia protocol, the technique of ultrasound-guided analgesic blocks of thoracic fascial planes and intraoperative and postoperative care were also described.

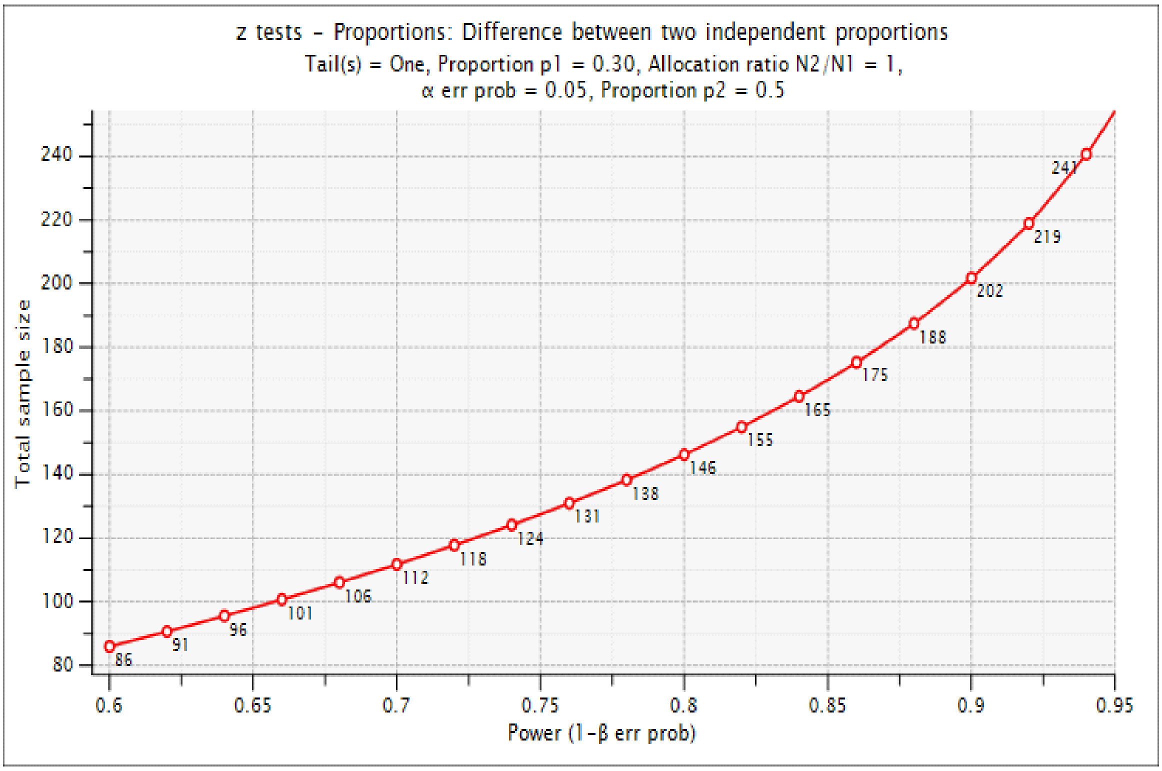

Figure 4. **Graphical representation of the relationship between the total number of enrolled patients and the study's power, based on the input parameters entered for calculation in G*Power v.3.1.9.6. The calculation is valid for the primary outcome parameter (2-year survival rate).**

Continuous data, arranged in two series with Gaussian distribution, were statistically compared using the two-tailed unpaired Student's t-test. The results were presented as mean and standard deviation or, where appropriate, as mean and 95% confidence interval of the mean (95% CI).

Continuous data arranged in three or more series were analyzed using Welch ANOVA for unequal variances. Individual differences between data series were analyzed using Dunnett's T3 test. In cases of equal variances, ANOVA with Bartlett's correction was applied.

Categorical data were analyzed using contingency tables. The statistical tests applied were Fisher's exact tests. Results were expressed as absolute (relative) values. For contingency tables larger than 2×2 lines, the applied statistical test was χ^2 for linear trends (Hantel-Maenzel).

Time durations (days, hours, minutes) were expressed through Kaplan-Meier curves, and the statistical tests applied for their comparison were Mantel-Cox (median comparison).

Correlational analysis between continuous data was conducted using the *(Pearson) r* test. A *(Pearson) r* value ≥0.6 was considered a strong correlation; a *(Pearson) r* value ≤0.3 was interpreted as no correlation, and a *(Pearson) r* between 0.3 and 0.6 was considered intermediate.

Correlational analysis between categorical data was conducted using the *(Spearman) r* test. A *(Spearman) r* value ≥0.6 was considered a strong correlation; a *(Spearman) r* value ≤0.3 was interpreted as no correlation, and a *(Spearman) r* between 0.3 and 0.6 was considered intermediate.

The sensitivity and specificity of the predictive model for postoperative mortality were analyzed and expressed through ROC curves.

The threshold for statistical significance was set at $p<0.05$.

Thus, among the strengths of the research in the thesis are the prospective design of the surgical patient cohort, the sufficient number of enrolled patients corresponding to the sample size calculation, the similarity of patient characteristics in comparison groups and the statistical tests adapted to the type of data, the number of data series and the normal or non-parametric distribution of the data, etc.

Potential bias factors in the study include the origin of the reference cohort from retrospective records collected in a different medical institution than the prospective data, the heterogeneity of secondary outcome parameters and the difficulty of measuring patient survival duration with greater accuracy than monthly intervals.

3. ANALYSIS OF THE RESULTS OF THE TRADITIONAL THERAPEUTIC APPROACHES IN PATIENTS WITH BRONCHOPULMONARY CANCER AND ADVANCED ANESTHETIC-SURGICAL RISK

3.1. Clinical and Paraclinical Characteristics of Patients with Bronchopulmonary Cancer and Advanced Anesthetic-Surgical Risk

This chapter characterizes patients with lung cancer treated according to traditional oncological therapeutic approaches (radiotherapy, chemotherapy, chemoradiotherapy, but without surgical intervention), thus representing the reference group for patients who have undergone surgical treatment. In this regard, necessary clinical cases were collected from the archive of the Oncology Institute between 2013 and 2020; this time period included the moment of registration, specialized treatment, and follow-up. The characterization of the collected group was carried out through the lens of the following paradigms (where paradigms, according to philosopher Thomas Kuhn, are universally recognized scientific achievements that provide model problems and solutions for a community of practitioners for a period): central lung cancer vs. peripheral lung cancer, Charlson Comorbidity Index score, and disease stage. Within the paradigms, the following were compared using descriptive statistics: symptomatology, comorbidities, diagnostic investigations performed, pathological pulmonary conditions associated with the underlying disease and the morphopathological picture.

Furthermore, the characteristics of the entire reference sample are presented, which will be stratified as necessary for comparisons across different subcategories. Thus, Table 2 presents a comparison of the frequency of specific clinical signs in patients with central vs. peripheral lung cancer.

The symptomatology of respiratory system involvement is usually nonspecific for various diseases, lung cancer being one of them. The vast majority of patients with lung cancer (about 8-9 out of 10) exhibited asthenia, dry cough, dyspnea and weight loss. Two-thirds reported chest pain and one in three experienced hemoptysis. Patients with central lung cancer did not show any difference in the spectrum or frequency of characteristic, but nonspecific clinical signs compared to those with peripheral lung cancer.

Table 2. **Comparison of the frequency of characteristic clinical signs between patients with central vs. peripheral lung cancer in the retrospective cohort**

Clinical Signs	**Central Lung Cancer (n=145)**	**Peripheral Lung Cancer (n=55)**	**p**
Asthenia	126/145 (86,9%)	50/55 (90,9%)	0,6263
Hemoptysis	53/145 (36,5%)	15/55 (27,2%)	0,2447
Chest Pain	98/145 (67,5%)	38/55 (69,9%)	0,8671
Cough	124/145 (85,5%)	49/55 (89,0%)	0,6451
Weight Loss	121/145 (83,4%)	49/55 (89,0%)	0,3809
Dyspnea	120/145 (83,45%)	43/55 (78,1%)	0,5408
Note: Statistical test applied: Fisher's exact test			

The comorbidities of patients in the reference cohort were also compared in terms of their spectrum and frequency between patients with central versus peripheral lung cancer (see Table 3).

Table 3. **Comparative analysis of comorbidities in patients with central vs. peripheral lung cancer**

Comorbidities	**Central Lung Cancer (n=145)**	**Peripheral Lung Cancer (n=55)**	**p**
COPD	117/145 (80,6%)	45/55 (81,8%)	>0,999
HTA	67/145 (46,2%)	28/55 (50,9%)	0,6348
Heart Failure	41/145 (28,2%)	19/55 (34,5%)	0,3929
Diabetes Mellitus	2/145 (1,38%)	2/55 (3,64%)	0,3038
Peripheral Vascular Disease	10/145 (6,9%)	5/55 (33,3%)	0,5616
Liver Disease	6/139 (4,14%)	4/55 (7,27%)	0,4669
Rheumatic Diseases	3/142 (2,07%)	3/52 (5,45%)	0,3492
Gastric/Duodenal Ulcer	6/145 (4,14%)	1/55 (1,82%)	0,6761
No Comorbidity	16/145 (11,0%)	6/55 (10,9%)	>0,999
Note: Statistical test applied: Fisher's exact test.			

The comorbidities of patients with lung cancer are generally typical of the general population, with a predominance of cardiovascular diseases (hypertension, peripheral vascular diseases, congestive heart failure), present in one in two patients. Chronic obstructive pulmonary disease, likely secondary to a long history of smoking, is significantly above the average for the population's age, affecting 8 out of 10 patients. Statistical tests did not identify any differences between these two data sets.

For primary diagnosis, diagnostic clarification and staging of the disease, patients undergo a series of paraclinical investigations, the structure and volume of which are mentioned in the respective National Clinical Protocols.

A significant portion of these investigations is part of High-Performance Services (HPS), for which there is a waiting list. Consequently, the time taken to establish a final diagnosis and stage the disease can be lengthy, which is detrimental to the patient when the illness is rapidly progressive (as is the case with broncho-pulmonary cancer).

Table 4. **Comparison of the types of paraclinical investigations conducted to establish and clarify the diagnosis of patients with central versus peripheral lung cancer**

Investigation Method	Central Lung Cancer (n=145)	Peripheral Lung Cancer (n=55)	p
Chest X-ray	143/145 (98,6%)	55/55 (100,0%)	>0,999
Computed Tomography	100/145 (68,9%)	39/55 (70,9%)	0,8643
Bronchoscopy	71/145 (48,9%)	23/55 (41,8%)	0,4284
ECG	32/145 (22,1%)	14/55 (25,45%)	0,7069
Echocardiography	17/145 (11,7%)	10/55 (18,18%)	0,2507
Spirometry	21/145 (14,4%)	9/55 (16,36%)	0,8248
Magnetic Resonance	5/145 (3,4%)	0/55 (0,00%)	0,3254
Abdominal Ultrasound	39/145 (26,9%)	16/55 (29,09%)	0,8594
Duplex Ultrasound	1/144% (0,6%)	1/55 (1,8%)	0,4754
Note: Statistical test applied: Fisher's exact test.			

Table 4 presents the volume and structure of the paraclinical investigations that patients benefited from, comparing cases of central *versus* peripheral cancer. Nine investigations are listed, of which four are high-performance.

3.2. Analysis of the results of traditional therapeutic approaches in patients with broncho-pulmonary cancer and advanced anesthetic-surgical risk

Since lung cancer is a disease with a very low probability of cure, regardless of the stage at which it is diagnosed, treatments are primarily aimed at increasing life expectancy. Thus, two important parameters arise from this: life expectancy (in months lived) from the moment the diagnosis is established, and the proportion of survivors at specific time intervals, usually set at 5 years.

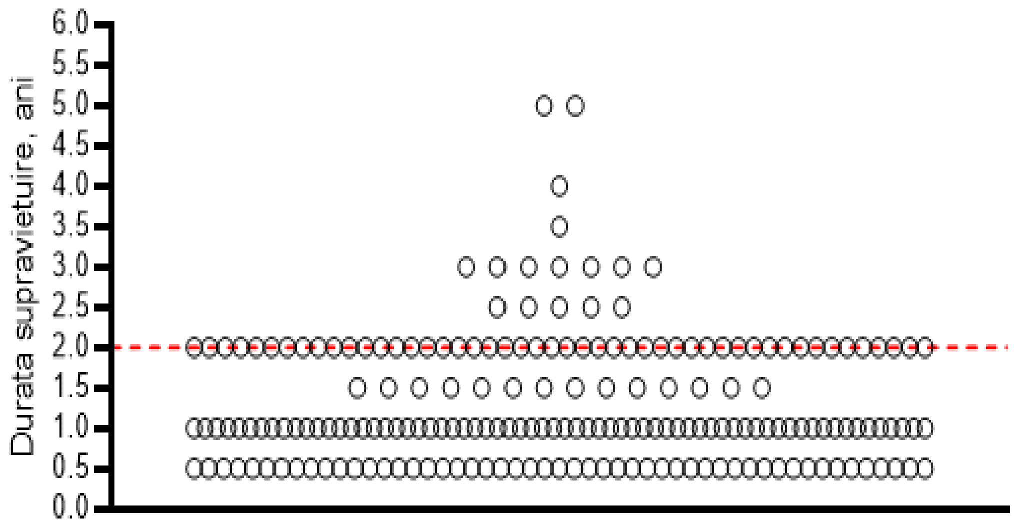

Figure 5. **Individual values of survival duration for patients with lung cancer from the moment of diagnosis establishment**

The results of traditional therapeutic approaches in patients with lung cancer, forming the reference group, will be presented through the lens of various covariates—depending on the stage of the disease at the time of diagnosis, the Charlson comorbidity index, and the presence or absence of pulmonary pathological conditions associated with lung cancer and the treatments performed. From this, the proportion of survivors at specific time points can be easily calculated and compared with data from the literature. Figure 5 presents the individual values of survival duration for patients in the entire reference group (n=200) after the establishment of the lung cancer diagnosis.

Table 5 presents the survival time of patients with lung cancer based on the stage of the disease established at the time of diagnosis, disaggregated by categories of severity of the Charlson comorbidity index.

Table 5. **Survival Duration by disease stage and comorbidity burden, expressed by the Charlson comorbidity index (CCI)**

Parameter	**Duration from "Year of Diagnosis" to "Year of Death," years**			
	Stage I n=2/200 (1%)	**Stage II** n=10/200 (5%)	**Stage III** n=51/200 (25,5%)	**Stage IV** n=137/200 (68,5%)
Charlson 0 points	-	-	0,8 (0,4 – 1,2)	0,9 (0,7 – 1,1)
Charlson 1-2 points	-	1,3 (0,6 – 2,1)	1,2 (0,9 – 1,5)	1,4 (1,1 – 1,6)
Charlson 3-4 points	1,7 (-7,7 – 11,2)	2,5 (-0,2 – 5,2)	1,2 (0,8 – 1,5)	1,4 (1,2 – 1,6)
Charlson 5≤ points	-	1,5*	1,6 (0,8 – 2,3)	1,2 (0,8 – 1,5)

Note: Data are expressed in years, with mean and 95% confidence interval (95%CI). Dashes indicate the absence of patients with the given characteristics in the study group (specific stage *versus* CCI score); * – one patient in the cohort with the given characteristics. The "Stage IV" column (gray color) – patients ineligible for surgical treatment. Yellow frame – patients with lung cancer and increased anesthetic-surgical risk.

Table 6. **Survival duration by disease stage and treatment applied (radiotherapy, chemotherapy, isolated or combined)**

Treatments	**Duration from "Year of Diagnosis" to "Year of Death," years**			
	Stage I n=2/200 (1%)	**Stage II** n=10/200 (5%)	**Stage III** n=51/200 (25,5%)	**Stage IV** n=137/200 (68,5%)
Radiotherapy (isolated)	2,5*	2,0*	-	2,0*
Chemotherapy (isolated)	-	-	0,9 (0,6 – 1,2)	1,4 (1,1 – 1,6)
Radio + Chemotherapy	-	-	1,6 (0,9 – 2,3)	2,2 (1,1 – 3,3)

Note: Data are expressed in years, with mean and 95% confidence interval (95%CI). Dashes indicate the absence of patients with the given characteristics in the study group (specific stage vs. treatment); * – one patient in the cohort with the given characteristics. The "Stage IV" column (gray color) – patients ineligible for surgical treatment.

It is also important to know the survival duration from the moment of lung cancer diagnosis based on the treatment applied—radiotherapy or chemotherapy. Similarly to Table 6, the number of patients in the cohort diagnosed in stages I and II of the disease does not allow for descriptive statistics, with the results reflecting a clinical case. Apparently, chemotherapy and radiotherapy, when applied in isolation, have no impact on survival duration; however, the combination of these methods allows for an average increase in life expectancy of about 6-8 months.

The short average survival durations from the moment of diagnosis (1.3-1.4 years) place pressure on fundamental research, in particular. In addition to radio- and chemotherapy, the development of anti-tumor immunotherapy is seen as a new direction in the non-surgical treatment of lung cancer.

4. ANALYSIS OF PERIOPERATIVE RISKS IN PATIENTS WITH BRONCHOPULMONARY CANCER AND THE DEVELOPMENT OF PREVENTIVE STRATEGIES TO ENSURE QUALITY AND SAFETY REQUIREMENTS IN MEDICAL-SURGICAL ACTS

4.1. General Characterization of Patients Surgically Treated for Bronchopulmonary Cancer

Patients with bronchopulmonary cancer who undergo multidisciplinary preoperative evaluation are very likely (1 in 3 cases) to present with a pathological condition associated with the cancer. Of the remaining 37 patients (38.9%), eight pathological conditions were identified. Among those treated surgically, patients had between 1 and 7 concomitant conditions, with the following distribution: 1 condition in 19/37 patients (51.4%), 2 conditions in 11/37 patients (29.7%), 3 conditions in 5/37 patients (13.5%), 4 conditions in 1/37 patients (2.7%), while no patients had 5 or 6 conditions, and 1/37 patients (2.7%) had 7 concurrent conditions.In conclusion, the vast majority of patients (35/37 – 94.6%) with pathological conditions associated with lung cancer, who were evaluated for surgery, had between one and three conditions typically linked to stage IIIA of the disease. As cancer progresses toward terminal stages (requiring palliative care), the number of associated pathological conditions is expected to rise, including malnutrition, clinical symptoms, and cancer-related pain.

There is a significant difference between the prospective group (surgically treated) and the reference group (retrospective, non-surgically treated) in the frequency of certain pathological processes associated with bronchopulmonary cancer. Specifically, conditions like pneumofibrosis and endobronchitis were statistically less common in the surgical group compared to the non-surgical group, while pulmonary emphysema, pleural effusion, and, at the statistical margin, foci of pulmonary atelectasis were more frequently observed in the prospective (surgically treated) group than in the retrospective (non-surgically treated) group.These differences could be explained by specific inclusion/exclusion criteria applied to patients evaluated for surgical treatment, the bias introduced by small-cell lung cancer (which was present in the retrospective non-surgical group but excluded from the prospective surgical group), the effects of chemo-radiotherapy, and, possibly, the different clinical pathways of the patients. A general characterization of the prospective study group includes a presentation of the types of thoracic surgical interventions performed (Table 7).

Approximately 43% of the patients underwent total pneumonectomy, with this procedure occurring nearly twice as often on the left side (61%). The necessity for such extensive surgical intervention was primarily due to the advanced stages of the disease at diagnosis.

Table 7. **Thoracic surgical interventions performed on patients in the prospective group with an innovative approach**

Surgical interventions	**Total (n=95)**
Pneumonectomy Right side Left side Total Of which, transpericardial	 16/41 (39%) 25/41 (61%) 41/95 (43%) 5/41 (12%)
Upper lobectomy Right side Left side Total	 10/26 (38%) 16/26 (62%) 26/95 (27%)
Middle lobectomy (right side only)	5/95 (5%)
Lower lobectomy Right side Left side Total	 10/14 (71%) 4/14 (29%) 14/95 (15%)
Superior bilobectomy (upper and middle lobes), right side only	2/95 (2%)
Inferior bilobectomy (lower and middle lobes), right side only	7/95 (7%)

Additionally, superior lobectomies were more frequently performed on the left side, accounting for 62% of all lobectomies. Overall, superior lobectomies were conducted in one out of every three patients.

4.2. Functional Characteristics and Preoperative Biological Reserve of the Respiratory System

The evaluation of the respiratory system's condition before surgery varies across the literature. Many pulmonary function alterations are linked to an increased risk of postoperative respiratory complications. However, relying solely on one parameter or test to determine an absolute contraindication for surgery is not justified. Generally, respiratory function tests should categorize patients into three groups: 1) those for whom surgery is contraindicated due to unacceptably high postoperative mortality or morbidity; 2) those with manageable risks related to postoperative respiratory complications, where preventive measures can reduce these risks to an acceptable level; and 3) patients with uncertain or inconclusive results who require further investigation.

In this study, we aim to predict the functional capacity of the remaining lung during the postoperative period based on preoperative functional parameters.

The predicted postoperative value of FEV1, termed ppoFEV1 (1-L), can be calculated using the formulas:

ppoFEV1 = FEV1 × (19 – S) / 19 (4.1)

or

ppoFEV1 = FEV1 × (1 - 5.3 × S) / 100 (4.2),

where S represents the number of lung segments to be surgically removed.

Subsequently, ppoFEV1 is expressed as a percentage of the normal FEV1 values for the patient:

ppoFEV1 (%) = ppoFEV1 (L) × 100 / FEV1 (L).

Figure 6 illustrates the actual preoperative forced expiratory volume in one second (FEV1) values alongside the predicted postoperative FEV1 (ppoFEV1), estimated based on the planned surgical volume, which ranges from segment resection to pneumonectomy. To highlight different interpretations of the results, the graphs are presented as paired individual values (A), group trends (B), and as percentages of the patient's FEV1, with the patient's value taken as 100%.

In Figure 6 (A), there is a broad range of FEV1 values among patients who underwent surgical treatment. The normal reference values for FEV1 are between 3.5-4.5 L for men and 2.5-3.25 L for women, indicated by the horizontal black dotted line in the image. For results to be considered normal, individual FEV1 values should fall between 80% and 120% of these reference values, which are influenced by factors such as age, body mass, muscle strength, height, and sex. In this patient cohort, FEV1 values ranged from 0.87 L to 3.68 L, with a mean of 2.51±0.78 (95% CI: 2.24-2.77) L. Statistically significant differences were found between men and women, with values of 2.70±0.73 L for men and 2.0±0.70 L for women ($t=2.57$, $p=0.0148$).

As shown in the figure, the absolute value of FEV1 indicates significant changes in the pulmonary function of the study patients, which are influenced by underlying diseases, pathological lung conditions associated with lung cancer, and comorbidities such as COPD and obesity. Only 20% of both women and men had FEV1 values within the physiological range. Furthermore, a conventional FEV1 threshold of 1.5 L serves as a critical cutoff, indicating an exponentially increased risk of severe postoperative complications, as marked by the red dotted line in the image. From this perspective, 14% of all patients (one in six) had FEV1 values below this critical threshold.

Given these low preoperative FEV1 values, further reduced by the underlying pathology and patient comorbidities, the estimated postoperative FEV1 values (ppoFEV1) are expected to be even lower following surgery. In the studied patients, the very low ppoFEV1 relative to FEV1 is primarily due to the advanced stages of the disease and the necessity for procedures such as pneumonectomies and bilobectomies. Additionally, an even greater number of patients fall below the 1.5 L threshold (as shown in Figures 6 A and B).

In the studied patient group, the estimated postoperative forced expiratory volume in one second (ppoFEV1) was 1.28±0.58 L (95% CI 1.09 – 1.48), which is significantly lower than the preoperative FEV1 values ($p \leq 0.0001$). About 70% of the patients had a ppoFEV1 below 1.5 L, indicating that most were at increased risk for anesthesia and surgery. The percentage of ppoFEV1 relative to preoperative FEV1 (set at 100%) shows a significant reduction in lung capacity (see Figure 6). Among these patients, 59% had a ppoFEV1 below 50% of their preoperative values, distinguishing those who underwent pneumonectomy (PE) from those who had lobectomy (LE).

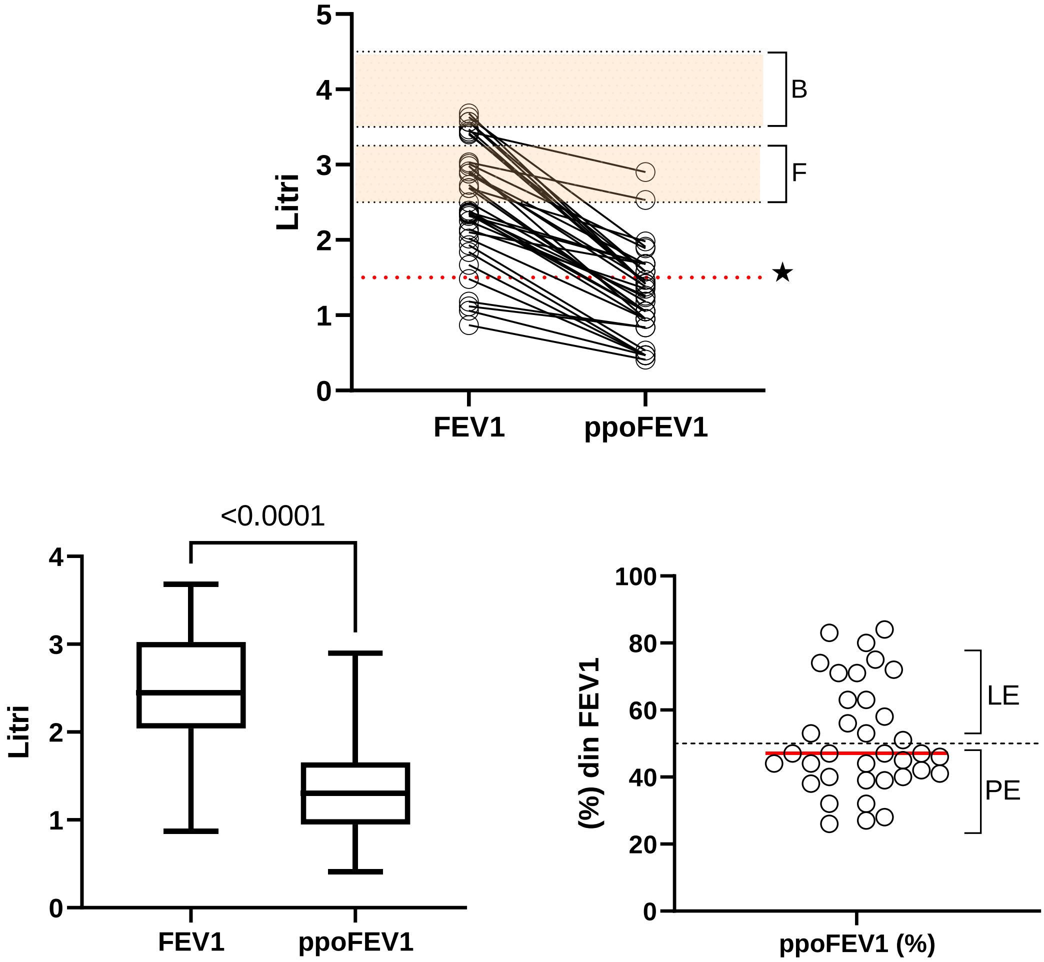

Figure 6. **Shows the actual forced expiratory volume in one second (FEV1) and the estimated postoperative FEV1 (ppoFEV1) following pulmonary resection. The data is presented in three formats: (A) individual paired values; (B) group trends; and (C) relative values expressed as a percentage of FEV1, with the individual patient's value set as 100%.**

Note: B = men; F = women; LE = lobectomy; PE = pneumonectomy. The red dotted line indicates the FEV1 threshold of 1.5 liters, which is reported in the literature to be associated with a high risk of postoperative mortality. The black dotted line represents a 50% reduction in forced expiratory volume in one second.

Another key spirometry measure is forced vital capacity (FVC), which indicates the maximum volume of air a patient can forcibly exhale after taking a deep breath. Normal values are 4.75 to 5.5 L for men and 3.25 to 3.75 L for women. This measure helps differentiate between restrictive and obstructive lung diseases.

Figure 7 shows the individual FVC values and their frequency distribution in the patient group. The average FVC was 3.1±0.88 L (95% CI: 2.79 – 3.38 L). Additionally, a significant number of patients (10% of women and 19% of men) had FVC values below the normal reference range.

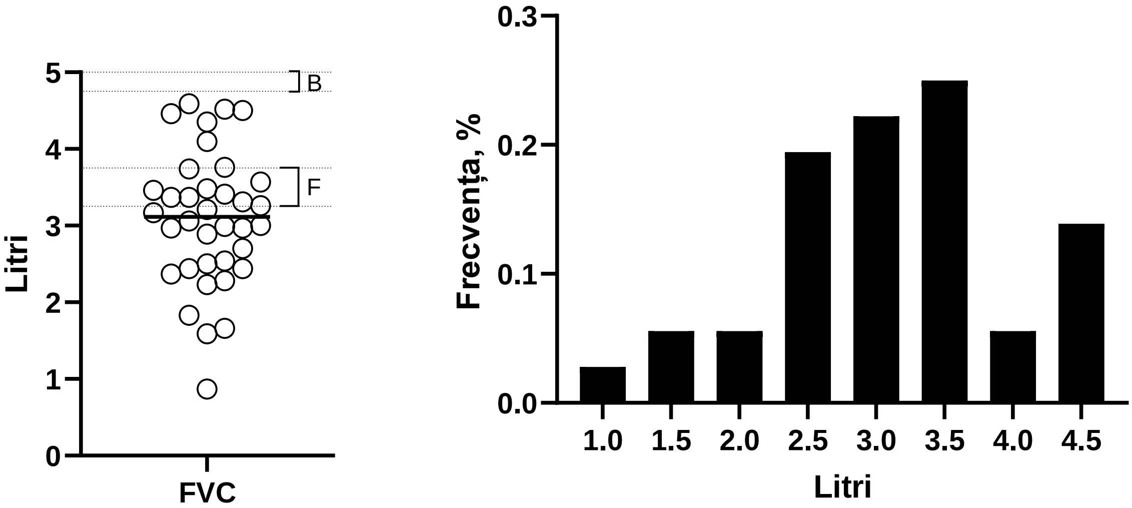

Figure 7 **Illustrates the individual values of forced vital capacity (FVC) among the study patients (A), alongside a histogram that shows the distribution of these values, indicating the reference ranges for men (B) and women (F).**

Many published studies have struggled to demonstrate the effectiveness of spirometry parameters alone in predicting postoperative complications or mortality following thoracotomy. Methodological limitations, such as small sample sizes, retrospective designs, and selective outcome measures, have impacted these findings. Furthermore, definitive cutoff values for spirometry metrics, especially FEV1, that could clearly separate risks of complications and mortality are still lacking.Spirometry tests have only accurately identified about one-third of patients who subsequently experienced postoperative complications, including atrial fibrillation, acute congestive heart failure, and pneumonia. Notably, a significant proportion of patients with abnormal spirometry results still achieved satisfactory postoperative outcomes. Therefore, it is prudent not to contraindicate surgical treatment for lung cancer based solely on spirometry results, as this could lead to a higher risk of mortality from metastatic disease.

4.3. Cardiovascular risk in bronchopulmonary cancer patients in the perioperative period

Postoperative cardiac complications are the second leading cause of morbidity and mortality in patients undergoing thoracic surgery. Conditions such as coronary artery disease, congestive heart failure, atherosclerosis, and arrhythmias are commonly found among smokers and are often associated with pulmonary comorbidities, particularly chronic obstructive pulmonary disease (COPD).To assess preoperative cardiovascular risk and stratify postoperative risk, patients underwent a comprehensive clinical examination, including the collection of medical history. Following this, they received electrocardiography and echocardiography evaluations. The results of these assessments (normal vs. abnormal) for patients who underwent surgical treatment for lung cancer are presented in Table 8.

Table 8. **Hemodynamic, Clinical, and Echocardiographic Indicators Recorded in Patients with Bronchopulmonary Cancer from the Prospective Study (Surgically Treated)**

Parameter	Normal Values*	Data presentation	Recorded Values	Abnormal results
PAS, mmHg	hypotension: ≤90 normal ≤120 elevated: 120-129 Hypertension st. 1: 130-139 Hypertension st. 2: 140≤ Hypertensive crisis: 180≤	M ± SD Min; Max 95% CI	128,9 ± 12,4 100; 190 126,4 – 131,4	64/95 (67,4%) – supranormal, of which: elevated: 37/95 (39%) Hypertension st.1: 22/95 (23%) Hypertension st.2: 4/95 (4,2%) Hypertensive crisis: 1 (1,1%)
PAD, mmHg	normal: ≤80 elevated: 80≤ Hypertension st. 1: 80-89 Hypertension st. 2: 90-100 Hypertensive crisis: 100≤	M ± SD Min; Max 95% CI	82,3 ± 7,1 60; 110 80,9 – 83,7	29/95 (44,6%) – supranormal, of which: Hypertension st.1: 26/95 (27%) Hypertension st.2: 2/95 (2,1%) Hypertensive crisis: 1/95 (1,1%)
MAP, mmHg	73-93 critical: 65	M ± SD Min; Max 95% CI	97,8 ± 8,6 73; 137 96,1 – 99,6	supranormal: 63/95 (66,3%)
HR, bpm	60-100* 60-90***	M ± SD Min; Max 95% CI	81,4 56; 120 79,4 – 83,4	7/95 (7,4%) – tachycardia*** 3/95 (3,2%) – tachycardia*
SpO2, %	95%≤	M ± SD Min; Max 95% CI	97,5 ± 1,3 92; 99 97,1 – 97,8	1/95 (1,1%) – moderately reduced (92%)
LVEF*, %	normal: 50-70 lightly reduced: 41-49 redused: ≤40 critical: ≤30	M ± SD Min; Max 95% CI	56,0 ± 6,2 32; 70 54,1 – 57,9	1/95 (1,1%) – lightly reduced (41 mm Hg).
PASP*, mmHg	normal: ≤20 HP: 25≤** Severe PH: 35≤** critical: 70≤	M ± SD Min; Max 95% CI	25,2 ± 6,5 12; 46 23,0 – 27,4	22/95 (23,2%) – PH 2/95 (2,1%) –severe PH 5/95 (5,3%) – borderline*

Note: Reference values are according to the American Heart Association: MAP – mean arterial pressure; HR – heart rate; PASP – pulmonary artery systolic pressure; PH – pulmonary hypertension. LVEF – left ventricular ejection fraction. SpO2 – oxygen saturation of hemoglobin (in ambient air), measured by pulse oximetry. * – estimates obtained through Doppler echocardiography. ** – definition of PH according to AHA; *** – definition according to PCN-395 “Supraventricular Tachycardias” (2021). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) values should be interpreted together within their respective categories. MAP = (SBP + 2 × DBP) / 3. According to: www.hearth.org/bplevels.

4.4. Common Laboratory Parameters in Preoperative Evaluation of Patients with Bronchopulmonary Cancer

Some of the most common laboratory parameters, such as the complete blood count and standard blood biochemistry, provide important insights into the patient’s current health status and serve as indicators for medium- and long-term prognosis.In the preoperative evaluation, one in five patients showed signs of anemia, while 4% had hemoconcentration. Leukocytosis was observed in one out of every four patients, whereas leukopenia was rarely encountered and had minimal clinical significance. A key finding was that patients with leukocytosis had significantly shorter survival times compared to those without it.In our patient series, no differences were identified in postoperative mortality, median survival duration, or the two-year survival rate when comparing patients with and without leukocytosis ($\chi2=0.65$; $p=0.4209$). The most plausible explanation for this lack of difference is the high proportion of patients diagnosed with advanced-stage bronchopulmonary cancer, which is associated with a markedly reduced life expectancy.

Hemostatic disorders in oncology patients have been recognized for over 100 years. These disorders are common among cancer patients and can range from hypo- to hypercoagulable states, leading to thrombotic complications. Depending on the coagulation parameter assessed, abnormal values have been found in 10% to 33% of patients, encompassing both hypo- and hypercoagulable conditions; however, not all of these abnormalities hold clinical significance.

The last relevant indicators in the preoperative evaluation of cancer patients are laboratory results that do not directly contraindicate surgery but help establish prognosis. These indicators include:Hemoglobin Level: Anemia can often be corrected before surgery, but it is linked to poorer long-term outcomes. Leukocyte Count: High white blood cell counts (leukocytosis), when not due to a bacterial infection, can indicate a reserved prognosis. Fibrinogen Level: Levels above 4-5 g/L suggest a cautious outlook, while levels of 7 g/L or higher indicate a significant risk of thromboembolic complications. Blood Glucose: High glucose levels, especially those not related to diabetes, can indicate aggressive tumor activity (known as the Warburg effect).

These parameters, organized in a decision-making framework, can assist thoracic surgeons and patients in making informed choices about whether to proceed with surgical treatment for lung cancer.

5. EVALUATION OF THE EFFECTS OF ULTRASOUND-GUIDED FASCIAL PLANE BLOCKS AND INTRAOPERATIVE ADMINISTRATION OF TRANEXAMIC ACID ON BIOLOGICAL PARAMETERS AND POSTOPERATIVE OUTCOMES IN PATIENTS WITH BRONCHOPULMONARY CANCER

5.1. Description of the intraoperative and postoperative effects of ultrasound-guided interfascial plane blocks in the surgical approach to bronchopulmonary cancer within the ERAS framework.

Ultrasound-guided interfascial blocks represent a regional anesthesia technique that can be used in oncological pulmonary surgery to ensure intraoperative and postoperative pain management. Different types of blocks (serratus anterior, PECS 1, PECS 2) provide analgesia for the thoracic wall and adjacent structures.

One of the main benefits of ultrasound-guided interfascial blocks is the improvement of postoperative pain. By providing prolonged analgesia to the thoracic wall and surrounding structures, the block can significantly reduce the intensity of postoperative pain. This can enhance patient comfort, facilitate early mobilization, and decrease the need for systemic opioids in the postoperative period. Patients who benefit from effective regional anesthesia techniques often require lower doses of systemic opioids for managing postoperative pain. This can help minimize opioid-related side effects, such as respiratory depression, sedation, constipation, and nausea, thereby improving recovery and overall patient satisfaction.

Another described benefit of ultrasound-guided fascial plane blocks is the faster recovery and mobilization of the patient, which is a positive outcome of more effective pain control.

5.2. Description of the effects of intraoperative administration of tranexamic acid on intraoperative and postoperative bleeding, as well as other relevant parameters.

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that exerts its effect by competitively inhibiting the activation of plasminogen to plasmin, which ultimately inhibits fibrinolysis. In the context of surgery, including thoracic surgery for lung cancer, TXA has been studied for its potential to reduce intraoperative and postoperative bleeding, as well as other relevant parameters.

Although the reduction of intraoperative and postoperative hemorrhage volume has been demonstrated in numerous studies on other types of surgeries, the study conducted found no statistically significant differences between patients who received intraoperative TXA and those who did not.

6. ANALYSIS OF RESULTS AFTER SURGICAL TREATMENT OF PATIENTS WITH BRONCHOPULMONARY CANCER AND ADVANCED ANESTHETIC-SURGICAL RISK THROUGH PRISMA OF DURATION PARAMETERS AND DIFFERENT COVARIATES.

6.1. Analysis of general time-related outcomes after surgical treatment of patients with bronchopulmonary cancer and advanced anesthetic-surgical risk.

The recording and analysis of time-related parameters in processes or conditions are important indicators that serve two main purposes: they help optimize the performance of hospitals and their functional units, while also indirectly reflecting the severity of the treated cases and the necessary allocation of human, material, and financial resources. These parameters correlate, to varying degrees, but in a statistically significant manner, with the mortality rate observed at various time points (e.g., traditionally at 30, 60, and 90 days, 6 months, and annually). Specifically, in the context of perioperative medicine, three key parameters are crucial: 1) length of hospital stay, defined as the duration from the date and time of discharge to the date and time of admission, usually expressed in days; 2) duration of stay in the intensive care unit (ICU), calculated as the time from the date and time of transfer to the ward minus the date and time of admission to the ICU, typically expressed in hours; and 3) duration of mechanical ventilation, which is the time from the date and time of extubation minus the date and time of intubation, usually expressed in minutes.

Figure 8 presents the lengths of hospital stay, expressed through Kaplan-Meier curves, for patients with lung cancer and advanced anesthetic-surgical risk who died after surgery, compared to those who survived.

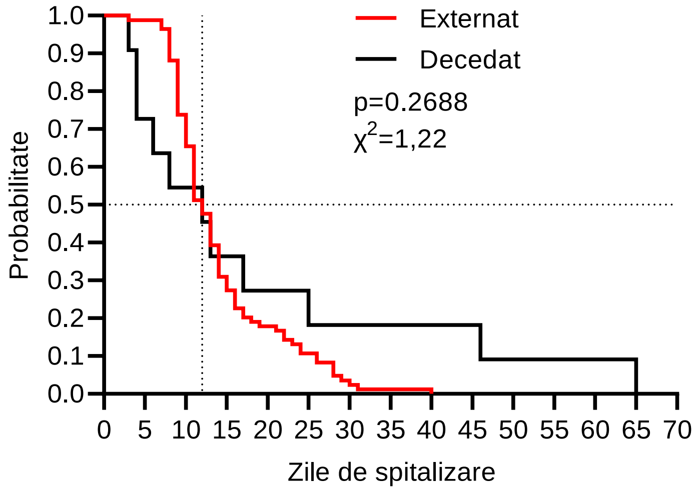

Figure 8. **Kaplan-Meier curves of hospital stays for patients who were discharged versus those who died.**

The Mantel-Cox analysis of hospital stays found equal median lengths of stay (12 days vs. 12 days, χ^2=1.22; p=0.2688) among deceased versus surviving patients.

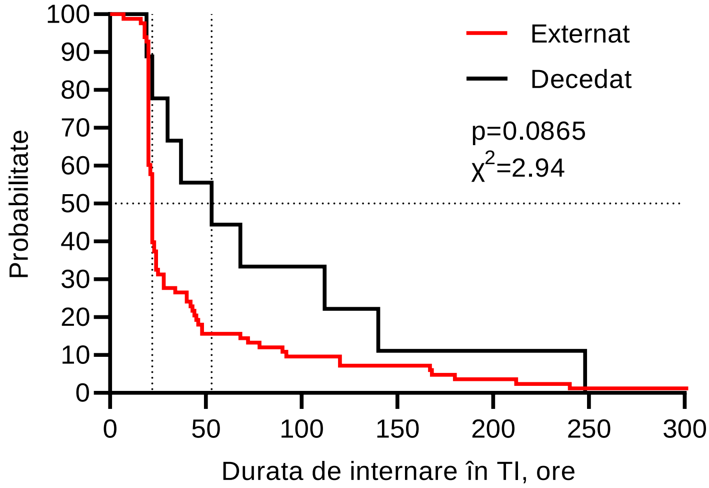

Figure 9. **Kaplan-Meier curves of postoperative intensive care unit stay durations for patients who were discharged versus those who died.**

The durations of stay in the intensive care unit (Figure 9) for patients who died after surgery, compared to those who survived, were not statistically significantly different (χ^2=2.94; p=0.0865), although the medians appeared to be different (63 hours vs. 22 hours). It is likely that enrolling a larger number of patients in the study to specifically test this hypothesis would reach the threshold of statistical significance. For this reason, it can be suggested that patients who died tended to have a longer stay in the intensive care unit.

In contrast, the durations of mechanical ventilation were significantly different between postoperative patients who died and those who survived (1160 hours versus 240 hours, χ^2=17.73; p=0.0001) (Figure 10). The inability to return to respiratory independence, followed by successful weaning from the ventilator and effective spontaneous breathing, was observed in patients who died. These patients required ventilation nearly five times longer than those who survived postoperatively.

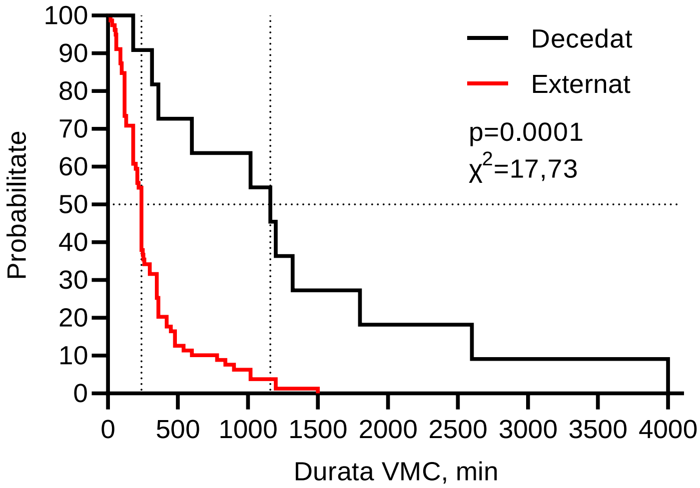

Figure 10. **Kaplan-Meier curves of postoperative continuous mechanical ventilation durations for patients who were discharged versus those who died.**

6.2. Analysis of time-related parameters after surgical treatment of patients with bronchopulmonary cancer and advanced anesthetic-surgical risk through the lens of severity scores.

To identify which specific characteristics were associated with negative outcomes (in this context—death after surgery or delayed return to homeostasis), the series of deceased patients was compared with the series of surviving patients using the Th-RCRI, MET, and Charlson severity scores. These scores are complex and are calculated based on several unique indicators.

Table 9 provides an ergonomic overview of the role of each score (specifically, its distinguishing value used in this study) in identifying clinically, logistically, or medico-economically significant differences among patients with lung cancer at various stages of progression and with different comorbidities. It highlights the ability to detect differences in intensive care unit stay durations and mechanical ventilation durations based on the Th-RCRI score (Class A vs. Class B) for both deceased and surviving patients. The CCI score was the only one that reached statistical significance in differentiating hospital stay durations.

The MET and ASA scores were unable to distinguish any of the tested durations, and therefore, they cannot be considered useful for predicting longer or shorter lengths of hospital stay, intensive care unit admission, or postoperative mechanical ventilation in patients with lung cancer and increased anesthetic-surgical risk.

Table 9. **Comparative summary table of results based on their statistical significance, according to the tested severity score and differentiation between survivors and deceased after surgery.**

Score (*x vs. y*)	**Tested Durations**	**Difference survivor *vs.* deceased**	
Pstoperative outcome survivor deceased	LOS	(green)	p=0,2688
	ICU	(yellow)	p=0,0865
	VAP	(red)	p=0,0001
Th-RCRI	LOS	(green)	p=0,6774

class A class B	ICU		p=0,0025
	VAP		p=0,0001
MET MET 4-6 MET 7-10	LOS		p=0,7041
	ICU		p=0,3688
	VAP		p=0,9551
CCI CCI 0-4 CCI 5-12	LOS		p=0,0536
	ICU		p=0,6573
	VAP		p=0,4293
ASA ASA II ASA III	LOS		p=0,8815
	ICU		p=0,3112
	VAP		p=0,0930

Note: Th-RCRI – revised cardiac risk score, adapted for thoracic surgery; MET – metabolic equivalent of task; CCI – Charlson comorbidity index; ASA – American Society of Anesthesiologists score; LOS – length of hospital stay; ICU – intensive care unit; VAP – mechanical ventilation.Color coding: Red – statistically significant ($p<0.05$); Yellow – borderline statistical significance (p=0.05-0.10); Green – statistically insignificant (p=0.1-1.0).

7. ANALYSIS OF POSTOPERATIVE RESULTS AND ARGUMENTATION OF EXTENDED OPERABILITY CRITERIA IN PATIENTS WITH BRONCHOPULMONARY CANCER AND ADVANCED ANESTHETIC-SURGICAL RISK

7.1. Analysis of postoperative outcomes in relation to preoperative pulmonary function and residual postoperative lung function.

The analysis of postoperative outcomes concerning pulmonary function involved comparing data from patients who were discharged from the hospital after surgery with data from those who died postoperatively. This approach allows for a more precise assessment of the criteria determining patient operability.

7.2. Analysis of Postoperative Outcomes in Terms of Cardiovascular Risk in Patients with Bronchopulmonary Cancer and Advanced Anesthetic-Surgical Risk

Cardiovascular comorbidities present a specific risk profile during the perioperative period for patients undergoing surgical treatment. In this study, these comorbidities were evaluated in a prospective cohort of patients concerning postoperative mortality. Among the 95 lung cancer patients, 21 (22.1%) had heart failure. Of these, 2 out of 11 patients (18.2%) died postoperatively, representing a mortality rate that was 6.6% higher than the overall mortality rate of 11.6%. However, this difference was not statistically significant ($\chi2=0.11$; p=0.7387).

Preoperative arrhythmias (all types combined) were found in 6 out of 95 patients (6.3%), with 1 out of these 6 patients (16.7%) dying postoperatively ($\chi2=0.16$; p=0.6874). The presence of arrhythmias did not significantly influence postoperative mortality. However, additional focused studies are necessary to assess the role of atrial fibrillation in postoperative mortality. Our calculations indicated a relative risk (RR) of 1.48 (odds ratio

[OR] = 1.58) in this context, though this did not reach statistical significance, likely due to the small sample size.Furthermore, investigating the role of chronic atrial fibrillation in the incidence of various cancer types, including lung cancer, could be an interesting research direction. This is particularly important given that atrial fibrillation is often associated with chronic heart failure.

Preoperative pulmonary hypertension serves as a significant prognostic factor for postoperative outcomes. In this study, patients with a pulmonary artery pressure of 30 mmHg or higher experienced a markedly increased risk of mortality, with a death rate of approximately 50%. This condition was associated with a relative risk (RR) of 6.8 and an odds ratio (OR) of 15.4 ($\chi2$=12.1; p=0.0005).

7.3. Analysis of Differences in Laboratory Parameter Values Between Lung Cancer Patients Who Died and Those Who Survived After Surgical Treatment

In oncologic thoracic surgery, specific laboratory parameters—such as blood glucose, hemoglobin, fibrinogen, and leukocytes—can act as prognostic biomarkers when they exceed certain thresholds. These markers may help predict complications, postoperative mortality, or reduced life expectancy in the medium to long term. This analysis evaluates various laboratory parameters in this context (see Tables 10, 11, 12).

Table 10. **Comparison of Hematological Parameters in Surviving Patients Versus Deceased Patients After Surgical Intervention**

Parameter	**Discharged (n=84)**	**Deceased (n=11)**	**t**	**p**
Hemoglobin, g/L	133,6 (129,7 – 137,6)	128,8 (113,1 – 144,6)	0,7929	0,4299
Erythrocytes, T/L	4,4 (4,3 – 4,5)	4,4 (3,9 – 4,8)	0,1475	0,8830
Hematocrit, %	38,9 (37,3 – 40,5)	37,0 (28,3 – 45,7)	0,7497	0,4554
Platelets, G/L	293,4 (232,7 – 354,0)	321,8 (212,7 – 430,8)	0,3331	0,7398
Leukocytes, $\times 10^9$ /L	12,5 (6,2 – 18,9)	10,6 (7,0 – 14,2)	0,1970	0,8442

Note: Statistical test applied – Unpaired two-tailed t-Student test.

At first glance, the hematological indicators in patients who died postoperatively, compared to those who survived, do not show statistically significant or clinically important differences (see Table 10). However, when viewed in terms of threshold values, the informational content changes substantially. The calculation of postoperative mortality risk based on different leukocyte threshold values yielded the following results:

- Risk of death for leukocyte count above 11,000: OR = 1.7; RR = 1.6; $\chi2$ = 0.65; p = 0.4209.
- Risk of death for leukocyte count above 12,000: OR = 2.0; RR = 1.8; $\chi2$ = 1.0; p = 0.3169.
- Risk of death for leukocyte count above 15,000: OR = 2.6; RR = 3.1; $\chi2$ = 2.4; p = 0.1201.

In deceased patients, fibrinogen levels were significantly elevated from a clinical standpoint, approaching statistical significance given the number of patients enrolled in the study (see Table 11).

The risk of postoperative mortality for patients with preoperative fibrinogen levels exceeding 4.5 g/L was found to have a relative risk (RR) of 2.14 (odds ratio [OR] = 2.43); $\chi2$ = 1.75; p = 0.1853. This indicates that elevated fibrinogen is an independent risk factor for postoperative mortality in patients with lung cancer, particularly those in stage IIIA. Furthermore, the significance of increased fibrinogen levels extends beyond the immediate postoperative period, suggesting a reduced life expectancy for lung cancer patients compared to those with fibrinogen levels within normal limits.

Table 11. **Comparison of Hemostatic Parameters in Surviving Patients Versus Deceased Patients After Surgical Intervention**

Parameter	Discharged (n=84)	Deceased (n=11)	t	p
INR	2,34 (0,05 – 4,6)	1,15 (1,0 – 1,2)	0,3647	0,7162
aPTT, sec	34,0 (27,0-41,1)	29,9 (23,4 – 36,3)	0,4198	0,6758
Fibrinogen, g/L	4,5 (3,67 – 5,34)	7,35 (0,8 −13,8)	1,854	0,0673
Intraoperative Hemorrhage,mL	418,6 (320,7 – 516,5)	931,8 (439,0 – 1425)	3,332	0,0013
Postoperative Dtainage in 24 Hours, mL	352,1 (265,4 – 438,9)	600,0 (179,8 – 1020)	1,851	0,0679

Note: Statistical test applied – Unpaired two-tailed t-Student test.

The following set of parameters examined relates to hydro-electrolytic balance and renal function, both of which are directly associated with postoperative mortality rates. Table 12 compares the values of key parameters regarding hydro-electrolytic balance between the groups of patients who died and those who were discharged after surgical intervention.

Table 12. **Comparison of Fluid Balance Parameters in Surviving Patients Versus Deceased Patients After Surgery**

Parameter	Discharged (n=84)	Deceased (n=11)	t	p
Urea, mmol/L	5,7 (5,2 – 6,2)	6,7 (4,0 – 9,3)	1,215	0,2276
Creatinine, µmol/L	86,0 (78,3 – 93,8)	92,3 (37,6 – 147,0)	0,4552	0,6501
Intraoperator Fluid Volume, mL	2738 (2480 – 2996)	2827 (2045 – 3609)	0,2338	0,8156
Postoperative Fluid Volume, mL	2249 (2101 – 2397)	2387 (1725 – 3048)	0,5645	0,5739
Intraoperative Urine Output, mL	343,4 (308,9 – 377,9)	386,4 (288,9 – 483,8)	0,8585	0,3929
Postoperative Urine Output, mL	2105 (1931 – 2279)	1189 (593,9 – 1784)	3,316	**0,0013**

Note: Statistical test applied – Unpaired two-tailed t-test.

In this study, 10% of patients had elevated urea levels, with 3% classified as clinically significant. Among the 11 patients who died, 2 (18.2%) had urea levels above 9.0 mmol/L, while 5 out of 84 survivors (6.0%) also had elevated urea levels. However, this does not indicate a significant association with postoperative mortality ($\chi2$=2.13; p=0.1443). In any case, further multicenter studies are needed to investigate the relationship between urea, blood urea nitrogen, albumin, and total protein with postoperative mortality and life expectancy after surgical treatment, considering various covariates, in order to draw a definitive conclusion.

In this study, 5 out of 84 survivors (6%) had a serum creatinine level below 60 µmol/L, while among the deceased patients, 4 out of 11 (36.4%) had similarly low levels ($\chi2$=10.5; p=0.0012). This finding is one of the major conclusions of the research, as it was observed that a plasma creatinine level below 60 µmol/L is associated with a risk ratio (RR) of 6.11 (odds ratio, OR=9.03) for postoperative death compared to patients with normal creatinine levels.

The data indicate that perioperative fluid loading did not significantly differ between patients with bronchopulmonary cancer who died and those who survived after surgery (Table 12). However, research suggests that a restrictive fluid repletion strategy is linked to improved survival rates after lung surgery in patients with acute (e.g., ARDS, pneumonia) or chronic (e.g., COPD) lung conditions. Consequently, it is advisable to maintain a minimum fluid intake both during and after surgery, transitioning as early as possible from intravenous to oral fluids.

In contrast, reduced urine output during the postoperative period was linked to increased mortality. Specifically, a urine volume of less than 1000 mL within the first 24 hours after surgery significantly raised the risk of death (RR=4.7; OR=7.5; $\chi 2=7.2$; p=0.0072). This finding underscores that even with comprehensive preoperative assessments and careful risk stratification, certain risks can still materialize within a day after surgery, emphasizing the importance of continuously refining predictive models.

7.4. Analysis of Postoperative Outcomes in Patients with Bronchopulmonary Cancer and Advanced Anesthetic-Surgical Risk Based on Disease Stage and Charlson Comorbidity Index

Since patient comorbidities play a critical role in determining operability after evaluating tumor resectability criteria, it is important to examine postoperative outcomes using the Charlson Comorbidity Index (CCI). This index can be divided into two major clinical categories: 1. Comorbidities with minimal impact on overall health (CCI=0-4 points).2. Comorbidities with significant impact on overall health (CCI≥5 points). In this study, we focus on patients with a CCI of 5-12 points, which indicates severe comorbidities that can affect surgical outcomes. Table 13 provides a comparative analysis of postoperative results based on disease stage, Charlson score, Th-RCRI score, and MET.

Table 13. **Comparative Results Based on Disease Stage and Charlson Comorbidity Index versus Age, Gender, MET, and Th-RCRI Class**

Comparison Parameters	**Stage I-II CCI 0-4 p. (n=38)**	**Stage I-II CCI 5≤ p. (n=17)**	**Stage IIIA CCI 0-4 p. (n=22)**	**Stage IIIA CCI 5≤ p. (n=17)**	**p**
Age, years	57,0 (52,0 – 62,0)	62,7 (59,7 – 65,6)	58,7 (54,2 – 63,2)	61,6 (56,6 – 66,7)	0,0001
Gender distribution	B: 15 (39,5%) F: 23 (60,5%)	B: 13 (76,5%) F: 5 (23,5%)	B: 18 (81,8%) F: 4 (18,2%)	B: 12 (70,6%) F: 5 (29,4%)	0,0045
Metabolic Equivalent MET 4-6 MET 7-10	21 (55,2%) 17 (44,8%)	14 (82,4%) 3 (17,6%)	20 (90,9%) 2 (9,1%)	12 (70,6%) 5 (29,4%)	0,0192
Th RCRI Score class A class B	22 (57,9%) 16 (42,1%)	17 (100,0%) 0 (0,0%)	0 (0,0%) 22 (100,0%)	17 (100,0%) 0 (0,0%)	0,0001

Note: Statistical test applied – Mantel-Haenszel for linear trends.

The survival duration (in months) from the time of diagnosis was compared between two groups: a prospective cohort treated surgically using an innovative approach and a retrospective cohort treated with a traditional method. The results are as follows:

- Patients with lung cancer in stages I-II and CCI 0-4 points: 34.1 ± 7.2 months (innovative approach) vs. 26.0 ± 17.4 months (traditional method), p = 0.0256.
- Patients with lung cancer in stages I-II and CCI over 5 points: 33.9 ± 10.1 months (innovative approach) vs. 26 months (one case, traditional method).
- Patients with lung cancer in stage IIIA and CCI 0-4 points: 21.0 ± 4.3 months (innovative approach) vs. 15.9 ± 8.9 months (traditional method), p = 0.0235.
- Patients with lung cancer in stage IIIA and CCI over 5 points: 17.0 ± 6.4 months (innovative approach) vs. 16.2 ± 6.1 months (traditional method), p = 0.8583.

As a result, surgical treatment performed with an innovative multimodal perioperative approach significantly enhances the survival duration of patients compared to those who did not undergo surgery, specifically in stages I-IIIA and with a Charlson Comorbidity Index ranging from 0 to 12 points. However, this advantage does not extend to patients with stage IIIA and a Charlson Comorbidity Index of 5 to 12 points.

GENERAL CONCLUSIONS

1. In recent decades, the morbidity of bronchopulmonary cancer has increased significantly and has become younger, with 16.6% of cases occurring in individuals under 50 years of age. Mortality rates remain consistently high, ranking first among all cancer types. In the age group of 30-34 years, the incidence has increased fivefold (from 0.8 to 4.6 cases per 100,000 population); in the 35-39 age group, it has tripled (from 4.4 to 12.5 per 100,000); and in the 40-44 age group, it has doubled. Contributing factors include not only smoking but also environmental pollution, radon exposure, and asbestos particles. A staggering 75-94% of patients are diagnosed at advanced stages (stage IIIA or later), and the five-year survival rate at this point is extremely low (3-10%). For various reasons, 45-75% of patients receive no treatment for bronchopulmonary cancer, and only 3-15% undergo surgical intervention.
2. Data from our own research on the retrospective cohort (n=200), which employed a traditional therapeutic approach (81.5% men, average age 67.2±8.8 years, with 94% diagnosed at stage III), show that only 17% of patients would have qualified for surgical treatment based on the current operability criteria. Over 80% of these patients exhibited typical clinical symptoms of bronchopulmonary cancer, including asthenia, hemoptysis, dry cough, and chest pain. Additionally, 57% had associated pulmonary conditions, such as pleurisy, atelectasis, and endobronchitis. Approximately 90% of the patients had comorbidities, with 25.5% experiencing a moderate impact on their overall health and 16.0% suffering from severe comorbidities. Patients with untreated natural progression of the cancer (58.5%), as well as those treated with radiotherapy (10%), chemotherapy (31.5%), or a combination of these therapies, but without surgical intervention, had a two-year survival rate ranging from 35.0% to 42.9%. Their median survival was between 12.0 and 17.6 months, depending on the disease stage at the time of diagnosis.
3. The analysis of the prospective cohort (n=95), who underwent surgical treatment based on the proposed innovative approach, showed that 74.7% were men with an ave-

rage age of 59.5±10.9 years, and 41% were diagnosed at stage III. Among these patients, 95% exhibited characteristic clinical symptoms of lung cancer, while 48.9% had associated pulmonary conditions. Additionally, comorbidities were identified in 65.3% of patients, with 9.2% having a moderate impact on their overall health and 36.7% experiencing severe comorbidities.

4. A comprehensive analysis of over 200 unique parameters identified several factors associated with an increased risk for surgical treatment of lung cancer. Based on this analysis, specific criteria for inoperability in lung cancer (stages I, II, IIIA) were established. These criteria include a forced expiratory volume in one second (FEV1) of less than or equal to 1.7 L, a predicted postoperative FEV1 (ppoFEV1) of less than or equal to 1.4 L for patients classified as class B in the Th-RCRI score, and a ppoFEV1 of less than or equal to 1.0 L for those classified as class A. Additionally, a pulmonary artery pressure (PAP) greater than 30 mmHg in stage IIIA lung cancer indicates inoperability, as does being in stage IIIA with a Charlson Comorbidity Index (CCI) score of 5 or lower.The analysis also highlighted certain preoperative biochemical markers that are linked to a significantly reduced postoperative life expectancy. These markers include fibrinogen levels greater than 4.5 g/L and leukocytosis exceeding 11 G/L. Furthermore, several negative prognostic factors were identified during the postoperative period. These include diuresis of less than or equal to 1000 mL in the first 24 hours, intraoperative blood loss exceeding 1000 mL, postoperative drainage bleeding over 500 mL in the first 24 hours, and readmission to the intensive care unit. Notably, patients who ultimately died had between 3 and 8 of these preoperative risk criteria present, underscoring the importance of thorough preoperative assessment in this patient population.
5. In this study, ultrasound-guided interfascial thoracic blocks (PECS 1 and PECS 2, anterior serratus) did not significantly alter postoperative ventilatory and hemodynamic parameters, nor did they affect the duration of hospitalization or the rate of postoperative complications when compared to patients who did not receive these blocks. However, a slight reduction in the total hospital stay was observed, decreasing from an average of 15.6 days (range: 13.0 – 18.25) to 12.9 days (range: 10.4 – 15.35) ($t=1.388$; $p=0.1686$).These results are inconsistent with findings in existing literature, which may be attributed to the use of lidocaine in a single injection, resulting in a short duration of action. This differs from the application of long-acting local anesthetics, such as ropivacaine, which are administered over an extended period. The choice of anesthetic may have influenced the pharmacological effects that typically facilitate postoperative extubation.
6. The study found that the intraoperative use of tranexamic acid to reduce postoperative fibrinolysis did not significantly affect hematological parameters, standard coagulation tests, intra- and postoperative bleeding volumes, or duration-related metrics (such as hospital stay, intensive care unit admission, and mechanical ventilation). This discrepancy with existing literature may be due to the non-randomized assignment of patients receiving tranexamic acid and the greater severity of their conditions compared to those who did not receive the drug.
7. The analysis identified three important duration-related parameters for treating lung cancer patients: total length of hospital stay (LOS), time spent in the intensive care

unit (ICU), and duration of mechanical ventilation after surgery (VAP). These parameters showed significant differences in cases where patients died.For predicting increases in these durations before surgery, the Th-RCRI score (class A vs. B) was useful for both ICU (p=0.0025) and VAP (p=0.0001). The Charlson Comorbidity Index also correlated with LOS, especially at a score of 5 or more points (p=0.0536). However, basic spirometric tests (FEV1, ppoFEV1, FVC), hemodynamic measures, and lab tests did not show significant associations with these duration parameters.

8. The most effective method for preoperatively assessing patient operability involved evaluating three key factors: the stage of the disease (ranging from I to IIIA), the Charlson Comorbidity Index (divided into two categories: 0-4 points and 5-12 points), and the Th-RCRI score (class A and B). This stratification successfully identified patients at increased risk of postoperative mortality and was significantly associated with several important outcomes, including the duration of mechanical ventilation (VAP) (p=0.0113), length of hospital stay (LOS) (p=0.0001), the likelihood of postoperative complications (p=0.0149), intraoperative blood loss (p=0.0169), and rates of postoperative mortality (p=0.0147 and p=0.0028), particularly when compared to patients in stages I-II and those with a Charlson Comorbidity Index of 0-4 points.
9. The main finding of this research, along with the proposed innovative approach to surgical treatment and perioperative management, is that surgical intervention based on expanded operability criteria is feasible for patients in stage IIIA with a Charlson Comorbidity Index (CCI) of 0-4 points. This approach significantly increases survival duration—by up to 6 months (p=0.0235)—and improves the 2-year survival rate. However, the feasibility of surgical treatment does not apply to patients in stage IIIA with a Th-RCRI score of class B and/or a CCI of 5 or more points.
10. The key findings of this research suggest that surgical treatment for lung cancer is suitable for patients with disease stages up to IIIA, provided that established criteria for inoperability are adhered to and that factors associated with reduced postoperative survival are taken into account.Adopting an Enhanced Recovery After Surgery (ERAS) protocol—encompassing prehabilitation programs, ultrasound-guided interfascial blocks, and the intraoperative use of tranexamic acid—may expand the pool of patients eligible for surgical intervention. However, further studies are needed to clarify these approaches.Additionally, future research should investigate the effects of non-diabetic hyperglycemia, anemia, leukocytosis, and preoperative fibrinogen levels on survival outcomes, considering various covariates.

PRACTICAL RECOMMENDATIONS

1. The trends in epidemiological data over recent decades indicate a pressing need to revise smoking cessation policies, improve environmental conditions (such as reducing aerosols, suspended microparticles, microplastics, and radon exposure), and enhance public education on both primary and secondary prevention of cancer, with a specific focus on bronchopulmonary cancer.
2. The most effective way to significantly increase the proportion of patients with bronchopulmonary cancer who can benefit from surgical treatment is to establish a screening system aimed at identifying the disease in stages I and II. This early detection allows for maximal impact from treatments (including radiotherapy and chemotherapy) on life expectancy following diagnosis.

3. Surgical treatment for bronchopulmonary cancer will be indicated after staging the disease and meeting the criteria for tumor resectability. These criteria include non-small cell cancer, a primary pulmonary neoplasm with a surgically accessible location, solitary brain metastasis, absence of invasion in the upper mediastinal lymph nodes, and solitary adrenal metastasis.
4. The following conditions are considered non-resectable due to tumor-related factors: small cell lung cancer; infiltration of the vertebral body by the lung tumor; location in the right upper lobe with involvement of the lateral wall of the trachea; involvement of the superior vena cava; and metastases (including seemingly solitary ones) in the bones, liver, or lungs. Angiography can help determine the resectability of tumors located in the left pulmonary hilum, the right upper mediastinum, and the lobar arteries.
5. For bronchoplasty, it is recommended to use a refined sealing suture technique.
6. Once the resectability criteria are met, the following factors related to the patient's general condition are considered indicators of inoperability:
   - Age over 75 years if the disease is staged IIIA or higher;
   - Staging IIIA with a Charlson score of 5 or higher;
   - Preoperative FEV1 $\leq$ 1.7 L;
   - ppoFEV1 $\leq$ 1.4 L (for Th-RCRI class B) and ppoFEV1 $\leq$ 1.0 L (for Th-RCRI class A);
   - PAP > 30 mmHg in stage IIIA of bronchopulmonary cancer
7. Patients are considered operable if they meet the following criteria (after tumor resectability is confirmed): age up to 80 years, with stage I-II of the disease and a Charlson Comorbidity Index (CCI) score of less than 4 points (pneumonectomy excluded).
8. For a more accurate estimation of the postoperative mortality risk in patients operated on for stage IIIA disease, it is recommended to use the custom nomogram developed for this purpose.
9. Reserved prognostic factors after pulmonary resection include:
   - Diuresis $\leq$1000 mL/24 hours postoperatively
   - Readmission to the Intensive Care Unit (ICU)
   - Intraoperative bleeding >1000 mL
   - Drainage bleeding >500 mL/24 hours postoperatively.
10. Preoperative factors associated with reduced life expectancy (regardless of surgical treatment) include:

    - Persistent hyperglycemia (6.2 mmol/L) in the absence of diabetes
    - Leukocytosis without associated bacterial or viral infection exceeding 11.0 g/L
    - Preoperative fibrinogen levels above 4.5 g/L
    - Walking capacity of less than 250 meters or a decrease in SpO2 of 4% or more during the test.
11. Perioperative Management Guidelines:

    Preoperative Assessment:

• Evaluate the patient’s nutritional status, and consider prescribing nutritional supplements if necessary.
• Assess for the presence of anemia, which may require injectable iron therapy.

Prehabilitation Program:

• For patients with borderline pulmonary function tests or reduced physical endurance, implement a prehabilitation program that includes respiratory exercises, physiotherapy, and physical activity for 2-3 weeks before surgery.
• If there is no improvement in spirometry or endurance tests (e.g., the ability to walk 250 meters), the patient’s operability should be reevaluated.

Anesthesia Preparation:

• Prior to anesthetic induction, perform an ultrasound-guided fascial plane block using 0.2% lidocaine (15-25 mL), choosing the appropriate block type (serratus anterior, PECS 1, PECS 2, or paravertebral) based on the location of the surgical incision.

Intraoperative and Postoperative Management:

• Employ a restrictive fluid replacement strategy during and after the surgery, using balanced solutions like Ringer’s lactate or acetate to maintain euvolemia. Transition from intravenous fluids to oral intake as soon as the patient is able to take fluids orally.

Postoperative Care:

• Implement respiratory physiotherapy and encourage patient mobilization within the first 24 hours postoperatively, following extubation.

SELECTIVE BIBLIOGRAPHY

1. Salati M., Brunelli A. Risk stratification in lung resection. *Curr. Surg. Rep.*, 2016; 4: 37.
2. Taylor M., Hashmi Charloux A., Brunelli A., Bolliger C. *et al*. European Respiratory Society and European Society . of Thoracic Surgeons Joint Task Force on Fitness for Radical Therapy. Lung function evaluation before surgery in lung cancer patients: how are recent advances put into practice? A survey among members of the European Society of Thoracic Surgeons (ESTS) and of the Thoracic Oncology Section of the European Respiratory Society (ERS). *Interactive Cardiovascular and Thoracic Surgery*, 2009; 9: 925-931.
3. S., Martin G. *et al.* A systematic review of risk prediction models for perioperative mortality after thoracic surgery. *Interact. Cardiovasc. Thorac. Surg*., 2021; 32: 333-342.
4. Devereaux PJ, Goldman L, Cook DJ, et al: Perioperative cardiac events in patients undergoing noncardiac surgery: A review of the magnitude of the problem, the path-ophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005;173(6):627–634.
5. FleisherLA,FleischmannKE,AuerbachAD,etal.2014ACC/ AHA guideline on periop-erative cardiovascular evaluation and management of patients undergoing noncardiac sur- gery: a report of the American College of Cardiology/ American Heart Associa-tion Task Force on Practice Guide- lines. J Am Coll Cardiol 2014;64:e77–137.
6. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physi- ologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and man-age- ment of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e166S–90S
7. Brunelli A, Varela G, Salati M, et al. Recalibration of the revised cardiac risk index in lung resection candidates. Ann Thorac Surg 2010;90:199–203
8. Brunelli A, Ferguson MK, Salati M, Vigneswaran WT, Jimenez MF, Varela G. Tho-racic Revised Cardiac Risk Index Is Associated With Prognosis After Resection for Stage I Lung Cancer. Ann Thorac Surg. 2015 Jul;100(1):195-200.
9. Lockwood P. The principle of predicting the risk of post-thoracotomy function-re-lated complications in bronchial carcinoma. Respiration, 1973; 30: 329-344.

LIST OF PUBLICATIONS AND PARTICIPATIONS IN SCIENTIFIC FORUMS

1. Specialized Books

1.1. Single-author Specialized Books

1.1.1. MAXIM, I. Surgery for Advanced Lung Cancer: Challenges and Solutions. Chișinău: Print-Caro Publishing House, 2021. 152 pages. ISBN 978-9975-56-880-7.

2. Articles in Scientific Journals

2.1. Articles in Recognized Foreign Journals

2.1.1. MAXIM, I., BELÎI, A., ROJNOVEANU Gh. Current Multidisciplinary Treatment Options in Advanced Lung Cancer. In: Journal of Surgery, 2023; 19(2): 136-142. DOI: 10.7438/JSURG.2023.02.05.

2.1.2. MAXIM, I., BURLACU, I., GUȚU, S., CABAC-POGOREVICI, I. The Role of Pulmonary Hypertension in the Postoperative Evolution of Lung Cancer Patients. In: Journal of Surgery, 2023; 19(1): 25-35. DOI: 10.7438/JSURG.2023.01.04.

2.1.3. MAXIM, I. Prehabilitation of the Oncological Patient: Achievements and Perspectives. In: Health Policies, Chișinău, 2022, no. 3, pp. 56-57. ISSN 2501-2576.

2.1.4. MAXIM, I. The Concept of Prehabilitation and Its Impact in Surgery: A Systematic Literature Review. In: Clinical Anesthesiology and Intensive Therapy, 2021, no. 2, pp. 34-51. ISSN 2616-5945. https://doi.org/10.31379/2411.2616.18.2.5.

2.1.5. MAXIM, I. The Concept of Prehabilitation in Thoracic Surgery: A Systematic Literature Review. In: Clinical Anesthesiology and Intensive Therapy, 2021, no. 2, pp. 16-33. ISSN 2616-5945. https://doi.org/10.31379/2411.2616.18.2.4.

2.1.6. MAXIM, I. Perioperative Evaluation of Patients with Bronchopulmonary Cancer from the Tertiary Prevention Group: Literature Review. In: Journal of Surgery, 2021, 17(3), pp. 6-13. ISSN 1584–9341.

2.2. Articles in the National Registry of Specialized Journals (Category B)

2.2.1. MAXIM, I., GUTU, S., BURLACU, I. Cardiovascular Risk in Patients with Non-Small-Cell Lung Cancer. In: Arta Medica, 2024, no. 1(90), pp. 10-21. https://doi.org/10.5281/zenodo.11106488.

2.2.2. MAXIM, I., GUTU, S., BURLACU, I. Outcome Analysis of Traditional Therapeutic Approach in Patients with Bronchopulmonary Cancer and Advanced Anesthetic-Surgical Risk. In: Modovan Journal of Health Sciences, 2024, vol. 2, no. 11, pp. 8-16. https://doi.org/10.52645/MJHS.2024.2.02.

2.2.3. MAXIM, I. Advanced Lung Cancer Complicated by a Medical-Surgical Emergency in a Patient with Comorbidities: Clinical Case. In: Bulletin of the Academy of Sciences of Moldova. Medical Sciences, 2020, vol. 68, no. 4, pp. 126-129. ISSN 1857-0011. https://ibn.idsi.md/vizualizare_articol/132190.

3. Theses in Scientific Collections

3.1. In the Proceedings of International Scientific Conferences

3.1.1. MAXIM, I., BURLACU, I., GUTU, S. Results of Surgical Treatment in Patients with Lung Cancer Undergoing a Cardiovascular Prehabilitation Program. In: National Congress of Oncology, October 12-14, 2023. Poiana Brașov, Romania, 2023. DOI: 10.26416/OnHe.64.3.2023.

3.1.2. MAXIM, I., BURLACU, I., GUTU, S. Pulmonary Hypertension as a Predictive Factor for Postoperative Complications after Resections in NSCLC. In: XIV Congress of the "Nicolae Anestiadi" Surgeons Association of the Republic of Moldova and IV Congress of the “V.M. Guțu” Society of Endoscopy, Minimally Invasive Surgery, and Ultrasound of the Republic of Moldova, September 21-23, 2023. Chișinău, 2023, pp. 58-59. ISSN 1810-1852.

3.1.3. MAXIM, I., et al. Cardiopulmonary Outcomes of Patients with Pulmonary Hypertension Undergoing Lung Resection for Lung Cancer. In: The 37th Balkan Medical Week Abstract Book, June 7-9, 2023, Chișinău, 2023, pp. 29. ISSN 1584-9244.

3.1.4. MAXIM, I., GUTU, S., BURLACU, I. Normocellular Lung Cancer Associated with Cardiovascular Pathologies – Analysis of Postoperative Complications. In: National Congress of Surgery Abstract Book, May 24-27, 2023. Eforie-Nord, Romania, 2023, pp. 173-174. ISSN 1221-9118.

3.1.5. MAXIM, I., GUTU, S., BURLACU, I. Impact of Pulmonary Hypertension on Major Pulmonary Resection Outcomes for Normocellular Lung Cancer – A Series of Clinical Cases. In: National Congress of Surgery Abstract Book, May 24-27, 2023. Eforie-Nord, Romania, 2023, pp. 174-175. ISSN 1221-9118.

3.1.6. MAXIM, I., GUTU, S., BURLACU, I., HAREA, A. Pulmonary Artery Hypertension as a Predictor for Postoperative Complications after Resections in NSCLC. In: 30th Annual Congress of the World Society of Cardiovascular and Thoracic Surgeons Abstract Book. St. Petersburg, Russia, 2022, pp. 272. ISSN 2307-6348.

3.1.7. MAXIM, I., et al. Tertiary Prevention: A Sentence for the Bronchopulmonary Cancer Patient? In: National Congress of Surgery Abstract Book, June 8-11, 2022. Sinaia, Romania, 2022, pp. 169-170. ISSN 1221-9118.

3.1.8. MAXIM, I. Perioperative Risks in Pneumonectomy for Patients with Bronchopulmonary Cancer. In: Annual Scientific Conference. Research in Biomedicine and Health: Quality, Excellence, and Performance Abstract Book, October 20-22, 2021. Chișinău, 2021, pp. 274. ISBN 978-9975-82-223-7.

3.1.9. MAXIM, I., GUȚU, S., ROJNOVEANU, Gh. Surgical Priorities in Primary Pulmonary Tumors Associated with Multi-Organ Localization. In: National Surgery Conference. Online Event, June 9-12, 2021, Bucharest, Romania, 2021, vol. 116, S125 pp. 125 (Suppl. 1). ISSN 1221-9118. Link

3.1.10. MAXIM, I., et al. Extension of Indications for Pulmonary Resections in Patients with Lung Cancer. In: Arta Medica, 2019, vol. 72, no. 3, pp. 67-68. ISSN 1810-1852.

3.1.11. GURAU, P., TIRBU, V., MAXIM, I. Adenoid Cystic Carcinoma of the Trachea: Fibroendoscopic Approach with Long-Term Survival (Case Report). In: 4th European Congress for Bronchology & Interventional Pulmonology. Abstract Book, EP-12. Crowne Plaza, Belgrade, Serbia, 2017, pp. 79-84.

3.1.12. GURAU, P., SLIMOVSCHI, C., MAXIM, I. Endoscopic LASER Ablation of Large Lipoma Originating from Lingular Bronchus. In: 4th European Congress for Bronchology & Interventional Pulmonology. Abstract Book, EP-12. Crowne Plaza, Belgrade, Serbia, 2017, pp. 68-70.

4. Patents and Other Intellectual Property Objects (IPO)

4.1. Inventions and Innovations

4.1.1. MAXIM, Igor. Application of Modified Bronchoplasty Technique in the Surgical Treatment of Bronchopulmonary Cancer. Innovator Certificate No. 6185, dated 13.02.2024.

4.1.2. MAXIM, Igor, ROJNOVEANU, Gheorghe, BELÎI, Adrian, BURLACU, Ion. Preoperative Assessment and Stratification of Anesthesia-Surgical Risks in the Perioperative Period for Patients with Bronchopulmonary Cancer. Innovator Certificate No. 6186, dated 13.02.2024.

4.1.3. MAXIM, Igor, ROJNOVEANU, Gheorghe, BELÎI, Adrian. Predictive Models of Postoperative Treatment Outcomes and Justification of Extended Operability Criteria in Patients with Advanced Anesthesia-Surgical Risk in Bronchopulmonary Cancer. Scientific Work Series OȘ, No. 7907, dated 29.03.2024.

4.1.4. MAXIM, Igor, ROJNOVEANU, Gheorghe, BELÎI, Adrian. Identification, Characterization, and Justification of New Predictive Parameters for Negative Postoperative Outcomes in Patients with Advanced Anesthesia-Surgical Risk in Bronchopulmonary Cancer. Scientific Work Series OȘ, No. 7908, dated 29.03.2024.

Oral Communications

1. Results of surgical treatment in patients with lung cancer undergoing a cardiovascular prehabilitation program (poster presentation) at the National Oncology Congress, Poiana Brașov, 2023.
2. Non-small cell lung cancer associated with cardiovascular pathologies – analysis of postoperative complications. In: National Surgery Congress Abstract Book. Eforie-Nord, Romania, May 24-27, 2023.
3. The impact of pulmonary hypertension on the consequences of major lung resections for non-small cell lung cancer – a series of clinical cases. In: National Surgery Congress Abstract Book. Eforie-Nord, Romania, May 24-27, 2023.
4. Pulmonary artery hypertension as a predictor for postoperative complications after resections in NSCLC. In: 30th Annual Congress of the World Society of Cardiovascular and Thoracic Surgeons Abstract Book, September 15-18, 2022. Saint Petersburg, Russia, 2022, p. 272.
5. Tertiary prevention: a sentence for the patient with bronchopulmonary cancer? In: National Surgery Congress Abstract Book, Romania, Sinaia, June 8-11, 2022.
6. Surgery for advanced lung cancer and major anesthetic-surgical risk. Interdisciplinary conference with international participation “Today’s Surgery – The Surgery of the Future: Updates and Perspectives,” 2022.
7. Extension of indications for pulmonary resections in lung cancer patients. In: The 13th Congress of the “Nicolae Anestiadi” Surgeons Association and the 3rd Congress of the Society of Endoscopy, Minimally Invasive Surgery, and Ultrasonography “V. M. Guțu” of the Republic of Moldova, September 18-20, 2019.

LIST OF ABBREVIATIONS

- ACS – American Cancer Society
- NCI – National Cancer Institute
- ERAS – Enhanced Recovery after Surgery
- ESTS – European Society of Thoracic Surgeons
- ASA – American Society of Anesthesiologists
- MET – Metabolic Equivalent
- RCRI – Revised Cardiac Risk Index
- GLOBOCAN – Global Cancer Observatory
- CCI – Charlson Comorbidity Index
- ST – Overall Survival
- HR – Harm Rate
- VO2 – Oxygen Consumption
- OR – Odds Ratio
- 95%CI – 95% Confidence Interval
- FVC – Forced Vital Capacity
- SpO2 – Oxygen Saturation as measured by Pulse Oximetry
- FEV1 – Forced Expiratory Volume in 1 Second
- COPD – Chronic Obstructive Pulmonary Disease
- ANOVA – Analysis of Variance
- ROC – Receiver Operating Characteristic
- INR – International Normalized Ratio
- aPTT – Activated Partial Thromboplastin Time
- IOP – Intraoperative
- VMC – Continuous Pulmonary Ventilation

ANNOTATION

MAXIM IGOR

SURGICAL TREATMENT OF PATIENTS WITH BRONCHOPULMONARY CANCER AND MAJOR ANESTHETIC-SURGICAL RISK

Thesis of doctor habilitatus in medical sciences, Chisinau, 2024

Thesis structure: The text of the thesis is set out on 203 computer-processed basic text pages, consisting of: list of abbreviations, introduction, 7 chapters, general conclusions, practical recommendations, bibliography from 310 sources and 3 appendices. Illustrative material includes 48 tables and 53 figures. The results are published in 25 scientific papers.

Keywords: Bronchopulmonary cancer, anesthetic-surgical risk, fascial plane echogenic block, prehabilitation, extended operability criteria, accelerated rehabilitation protocols, survival rate.

Field of study: Medical sciences, clinical medicine, surgery (321.13).

Purpose of the research. To develop a multimodal perioperative approach to patients with bronchopulmonary cancer and advanced anesthetic-surgical risk, allowing to extend operability criteria for increasing life expectancy and reducing post-operative complications.

Research objectives: (1) Preoperative evaluation of the patient with bronchopulmonary cancer and advanced anesthetic-surgical risk with individualized prehabilitation program (2) Traditional approach in patients with advanced anesthetic-surgical risk. (3) Usefulness of scores: Charlson, Th-RCRI, ASA and MET in perioperative management and treatment outcomes. (4) Determinants of perioperative mortality: identification, description and analysis for optimizing risk management. (5) Echogenic fascial plane blocks: their role in accelerating postoperative recovery. (6) Intraoperative bleeding reduction strategies: their impact on postoperative recovery. (7) Analysis of postoperative outcomes: development of a rational diagnostic-curative algorithm.

Scientific novelty and originality. It investigated for the first time the surgical approach in patients with lung cancer and advanced anesthetic-surgical risk, a category traditionally considered eligible only for chemotherapy or radiotherapy. It demonstrated the feasibility of surgery in well-defined subgroups of patients, with postoperative outcomes and two-year survival prognosis significantly superior to the traditional approach. Specific risk factors were identified and parameterised to select eligible patients from the high anesthetic-surgical risk group. Predictive models of perioperative mortality based on integrated severity scores were developed and validated. A perioperative management strategy, including prehabilitation, accelerated post-operative rehabilitation, intraoperative antifibrinolysis and anterior serum analgesic block, was successfully implemented, increasing the body's resilience to operative stress and promoting return to homeostasis.

The important scientific-application problem solved. A new conceptual approach to eligibility and perioperative management has expanded the operability criteria for patients with lung cancer and advanced anesthetic-surgical risk previously considered inoperable. Mathematical predictive models of postoperative mortality, based on severity scores (Th-RCRI, Charlson, MET, ASA) and planned lung resection volume, allow individualization of the therapeutic option (surgical vs. non-surgical). Patients operated according to extended criteria and managed perioperatively with prehabilitation and accelerated postoperative rehabilitation show a significant increase in life expectancy compared to the traditional approach.

Theoretical significance, applied value and implementation of scientific results. The paper presents a critical synthesis of the literature on accelerated postoperative rehabilitation in thoracic cancer surgery, with the aim of identifying previously inoperable patients who may benefit from intervention. Theoretical, methodological and practical bases are provided for preoperative assessment, prehabilitation programmes, accelerated postoperative rehabilitation and intra- and postoperative care of the patient with bronchopulmonary cancer and increased anesthetic-surgical risk, with the aim of increasing survival rates. The innovative approach expands operability criteria, allowing more patients to benefit from surgical treatment with significantly better clinical outcomes in terms of survival rate and life expectancy. The results provide practical recommendations for clinicians in risk assessment, prehabilitation and preoperative preparation, with a focus on reducing postoperative pain and accelerating recovery through anterior serratus plane block and tranexamic acid administration.

Implementation of scientific results. The research results were implemented in current clinical practice in the Thoracic Surgery Department of the Institute of Emergency Medicine, Chisinau, Republic of Moldova. The implementation acts are attached in Annex no. 1-2.

MAXIM IGOR

SURGICAL TREATMENT OF PATIENTS WITH BRONCHOPULMONARY CANCER AND MAJOR ANESTHETIC-SURGICAL RISK

321.13 Surgery

Summary of the habilitation thesis in medical sciences

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