Pulmonary Artery Hypertension Incidence in the Postoperative Course in Lung Cancer Surgery and the Influence of Pulmonary Artery Hypertension on the Postoperative Course and Long-term Survival

Inauguraldissertation

zur Erlangung des Grades eines Doktors der Medizin

des Fachbereichs Medizin

der Justus-Liebig-Universität Gießen

Vorgelegt von

Ibrahim Alkoudmani

aus Damaskus/Syrien

Gießen 2023

Aus dem Fachbereich Medizin der Justus-Liebig-Universität Gießen

Betreuerin: Frau PD Dr. Witte, Biruta

Klinik für Allgemein-, Viszeral-, Thorax-, Transplantations- und Kinderchirurgie.

Gutachterin: Frau. Prof. Dr. Pullamsetti, Soni

Prüfungsvorsitz: Prof. Dr. Bräuninger, Andreas

Prüfungsmitglied: Frau Prof. Dr. Schänzer, Anne

Dekan: Prof. Dr. Weidner, Wolfgang

17.01.2024

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PAH Incidence in the Postoperative Course in Lung Cancer Surgery and the Influence of PAH on the Postoperative Course and Long-term Survival

Abstract

Objectives: Pulmonary artery hypertension (PAH) is one of the serious complications of advanced lung cancer, as well as lung cancer surgical therapy. PAH is also related to high morbidity and mortality in postoperative lung cancer survivors. This study aims to determine the postoperative incidence of PAH in lung cancer surgery in stage II & III lung cancer patients, and the influence of PAH on the postoperative course and long-term survival.

Methods: A retrospective cohort study included 241 lung cancer patients who underwent curative resection for non-small cell lung cancer NSCLC (stage II, III) at Giessen Lung Cancer Centre in Hessen Germany between 2010 and 2019. Pulmonary artery diameter/Aorta diameter (PA/A) ratio derived from chest computed tomography (CT) scan was used as a predictor for pulmonary hypertension before and after lung surgery. Techniques, complications, Long-term survival and outcomes were analyzed using IBM SSPS.

Results: Mean PA & A diameters and PA/A ratio were 27.2 mm, 34.1 mm and 0.81 respectively. Postoperative PAH incidence at 6, 12, 18 months was 5.9%, 9.4%, and 15% respectively. Complications after lung resection occurred in 117 (48.5%) patients; respiratory complications were the most common. However, patients with postoperative atrial fibrillation were at a high risk to develop PAH in each follow-up ($p<0.01$), mostly at 18 months (odds ratio, 9.9; 95% CI, 2.5 to 295; $p= 0.006$). Mean hospitalization period in patients with postoperative PAH at 6, 12, 18 months was 12.6, 14.8, and 12.6 days respectively, mean survival years for those patients was (2.6 ± 2.79), (3.2 ± 3.05), (4.3 ± 2.94) respectively ($p>0.05$). Mortality was related to pulmonary comorbidities with a detected 118-fold risk for those patients ($p=0.02$), complicated cases were also at a higher risk for death compared to patients without postoperative complications (non-adjusted hazard ratio, 2.1; 95% CI, 1.2 to 3.5; $p=0.006$). Pulmonary artery hypertension as a predictor of death was of weak sensitivity and specificity (< 70%).

Conclusion: Pulmonary artery hypertension is one of the possible lung cancer comorbidities. However, new onset PAH after lung resection is often detected, with tendency to occur late. Therefore, investigations for increased pulmonary artery pressure should -at least- continue for 18 months after surgery. Atrial fibrillation in particular should arise suspicion for PAH.

Keywords: pulmonary hypertension, lung cancer, lobectomy, pneumonectomy.

INTRODUCTION

Lung cancer is considered the fatal cancer number one around the world, it was responsible for about 1.8 million deaths in 2020 [1]. The median age at diagnosis is 70 years [2], but geographic and gender-specific rates are variable. However, equal new cases are noticed in men and women, and about half of lung cancer deaths occur in females [3]. Lung cancer is tightly related to tobacco smoking which increases morbidity and mortality. The median overall 5-year survival rate is low. However, development of screening and treatment methods improved survival rates [4].

Lung cancer can follow the exposure to carcinogens, genetic predisposition, and the altered microenvironment. It is histologically classified into two main types; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) which approximately comprise 95 percent of all lung cancer. while other cell types comprise about 5 percent of malignancies arising in the lung [5]. The most common histologic subtypes among NSCLC are adenocarcinoma (40%), squamous cell carcinoma (25%-30%), and large cell carcinomas (10%-15%) [6]. SCLC accounts for about 13 percent of all lung cancer, and it has a strong correlation to tobacco smoking [7]. The risk of lung cancer among non-smokers increases in the presence of underlying pulmonary disease or exposure to radiation therapy [8].

Clinical presentation

Cough is almost the most common symptom, occurring in about 50 to 75 percent of patients [9]. Actually, new onset of cough in a smoker or former smoker must arise suspicion for lung cancer. Other possible symptoms are dyspnea, chest pain, weight loss, hemoptysis, and hoarseness. Extrathoracic symptoms may be noticed when metastases are already existed, paraneoplastic syndromes (e.g., hypercalcemia, Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion SIADH) may also occur, especially with SCLC [10].

Diagnosis

Early diagnosis of lung cancer is now possible due to the screening computerized tomography (CT) scan in high-risk population; persons between 55 to 74 years of age with 30-pack-year smoking history whether they are smokers or have quit within past 15 years [11]. Diagnostic and staging tools for lung cancer include sputum cytologic studies, bronchoscopy, positron emission tomography (PET) scan, magnetic resonance (MRI) and bone scintigraphy [12]. NSCLC stage is determined according to primarily tumor size, metastases, and affected regional lymph nodes. However, tumor size is particularly an important prognostic factor where the 5-year survival and prognosis worsen for each centimeter increase in tumor size [13]. Table 1 shows the eighth edition TNM staging system from the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) [14].

Table 1. TNM classification/staging for non-small cell lung cancer	
T (Primary tumor)	
TX	Primary tumor cannot be assessed, or the presence of malignant cells in sputum/bronchial washing but not seen by bronchoscopy.
T0	No tumor
Tis	Carcinoma in situ.
T1	Tumor ≤3 cm.
T1(mi)	Minimally invasive adenocarcinoma.
T1a	Superficial spreading tumor in central airways.
T1a	Tumor ≤1 cm.
T1b	Tumor >1 but ≤2 cm.
T1c	Tumor >2 but ≤3 cm.
T2	Tumor >3 but ≤5 cm or tumor involves visceral pleura, main bronchus (Not carina), atelectasis to hilum.
T2a	Tumor >3 but ≤4 cm.
T2b	Tumor >4 but ≤5 cm
T3	Tumor >5 but ≤7 cm or invades chest wall, pericardium, phrenic nerve, or separate tumor nodule(s) in the same lobe.
T4	Tumor >7 cm, or tumor invades: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine or tumor nodule(s) in a different ipsilateral lobe.
N (REGIONAL LYMPH NODES)	
NX	Regional hymph nodes cannot be assessed.
N0	No regional node affected.
N1	Metastasis in ipsilateral pulmonary or hilar nodes.
N2	Metastasis in ipsilateral mediastinal/ subcarinal nodes.
N3	Metastasis in contralateral mediastinal hilar or supraclavicular nodes.
M (DISTANT METASTASIS)	
M0	No metastasis.
M1a	Malignant pleural/pericardial effusion or nodules, or separate tumor nodule(s) in a contralateral lobe.
M1b	Single extrathoracic metastasis.
M1c	Multiple extrathoracic metastases (1 or >1 organ).
Stage	
0	Tis-N0-M0
IA1	T1mi-N0-M0 / T1a-N0-M0
IA2	T1b-N0-M0
IA3	T1c-N0-M0
IB	T2a-N0-M0
IIA	T2b-N0-M0
IIB	T1a-N1-M0 / T1b-N1-M0 / T1c-N1-M0 / T2a-N1-M0 / T2b-N1-M0 T3-N0-M0.
IIIA	T1a-N2-M0 / T1b-N2-M0 / T1c-N2-M0 / T2a-N2-M0 / T2b-N2-M0 T3-N1-M0 / T4-N0-M0 / T4-N1-M0.
IIIB	T1a-N3-M0 / T1b-N3-M0 / T1c-N3-M0 / T2a-N3-M0 / T2b-N3-M0 T3-N2-M0 / T4-N2-M0.
IIIC	T3-N3-M0 / T4-N3-M0
IVA	T any-N any-M1a / T any-N any-M1b
IVB	T any-N any-M1c

Lung cancer comorbidity

Lung cancer comorbidity means conditions and diseases which exist before cancer diagnosis and are not adverse effects of cancer treatment. This has always been an important issue that may influence prognosis in lung cancer as well as complicate its treatment. Comorbidity is related to age and life style (e.g., smoking, obesity…etc.), and both age and smoking are strongly associated with lung cancer. A co-existing pulmonary disease may delay lung cancer diagnosis; the most common pulmonary comorbidity associated with lung cancer is chronic obstructive pulmonary disease COPD (36%), followed by pneumonia (3%), residual tuberculosis (3%), silicosis and others (1%) [15]. On the other hand, the presence of another health problem has an essential role in treatment decision. Some patients, for example, might not be able to undergo surgery, others may need the neoadjuvante chemotherapy to be downstaged. Also, several health issues such as hypertension, cardiovascular disease, cerebrovascular disease, COPD, and diabetes mellitus (DM) have a serious influence on the survival of cancer patients [16].

Management

Histological differentiation between NSCLC and SCLC helps in the treatment decision. While combination of chemotherapy and radiation therapy is the standard of SCLC management, surgical resection is one of the long-term survival factors in resectable NSCLC [17]. Surgery is the treatment of choice for stage I, stage II, and stage IIIa NSCLC [18]. The decision of the surgical procedure is based on the extent of disease, age, cardiopulmonary reserve, performance status, and comorbid risk factors.

Understanding surgery techniques helps in predicting of increased pulmonary pressure after resection. First of all, there are two main surgical procedures; open thoracotomy and video-assisted thoracoscopic surgery (VATS). Thoracoscopic surgery is performed using a thoracoscope, which is inserted through a small incision between the ribs. This procedure has less complications, less pain, and shorter hospital stay, pulmonary functions are also preserved [19, 20]. However, minimal invasive surgery has some limits, and patients selected for this type typically have smaller and more peripheral tumors.

Lung cancer surgery can be used as lobectomy, pneumonectomy, sublobar resections (segmentectomy, bisegmentectomey..), or wedge resection. Anatomically speaking, the right lung consists of three lobes, the left one consists of two lobes; the right lung has 10 segments, while the left lung has 9 segments: the upper lobes contain 3 segments, the middle lobe / lingula 2, and the lower lobe on the right side has 5 segments, while the lower lobe on the left side has 4 segments. Each segment has its own pulmonary arterial branch and bronchus; thus, each segment is functionally and anatomically discrete allowing a single segment to be surgically resected [21].

Lobectomy surgery means the removal of one entire lobe; about 15-30% of total lung volume. Lobectomy with complete tumor mass removal has become the standard surgical choice for resectable NSCLC patients, with less mortality and better outcomes specially when performed through Thoracoscopic surgery [22]. A VATS lobectomy is commonly performed for peripherally located T1 or T2 tumors, it can also be performed in most cases, even in the presence of comorbidities, but it is contraindicated when tumor is > 8 cm; T4 tumors; and possible vascular or bronchial sleeve resection [23]. When performing lobectomy, the hilum is dissected anatomically and the vessels and bronchus are stapled using an endo-stapler [24].

Bilobectomy technique stands for the resection of two lobes, usually the upper or lower lobe with the middle in the right lung, it is usually indicated when tumor extends across the fissure, invades the vessels, or involves the lobar bronchus carina. Sometimes, bilobectomy may associate with bronchial and/or vascular plasty and requires bronchial and/or arterial anastomosis [25].

Sleeve resection is indicated when tumor invades the bronchus but not the lymph nodes, so that the* affected lobe with a portion of the bronchi is removed instead of complete removal of the lung, then the remaining bronchus is anastomosed to the proximal airway. Sleeve lobectomy is more challenging than pneumonectomy, but long-term outcomes and cost-effective measures favor sleeve surgery [26].

Pneumonectomy, which refers to the removal of one entire lung is used for patients with central lesions that cannot be completely resected otherwise. This procedure carries higher risk for postoperative complications and mortality.

Wedge resection surgery removes the tumor, as well as a wedge-shaped section of the lung around the tumor, without any vascular intervention. Wedge resections are chosen in patients with small peripheral tumors without nodal affected with poor cardiopulmonary reserve [22]. The increased risk for local recurrence limits the use of this procedure [27].

Sublobar anatomic resections can be used for small peripheral Tumors, can be performed safely by an open thoracotomy or VATS approach. It can provide the same overall survival compared with lobectomy on patients without lymph node involvement [28].

In general, postoperative mor tality accounts for about 6.3%, and complications occur in 48% of lung cancer patients with the risk factors of male gender, advanced age, previous stroke, renal disease, congestive heart failure, and pneumonectomy [29].

Complete resection describes: (a) free resection margins confirmed microscopically, (b) a lobe-specific systematic nodal dissection, (c) no extracapsular tumor extension in the removed nodes, and (d) negative highest mediastinal removed nodes [30], this matches R0 category of Residual Tumor Classification which also includes [31]: (RX) the presence of residual tumor cannot be assessed; (R1) microscopic residual tumor; and (R2) macroscopic residual tumor.

Complications

Most of lung cancer complications are related to the reduced respiratory space due to tumor mass and invasion as well as the loss of pulmonary parenchyma after resection. Pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, atelectasis, bronchopleural empyema, prolonged air leakage, and pneumothorax are relatively common postoperative pulmonary complications [32].

Pulmonary artery hypertension (PAH) is also one of the serious complications of lung cancer, it might not be early detected because the exertional dyspnea could commonly be a symptom of decreased respiratory volume after the resection. PH is defined as a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest [33]. The underlying cause of preoperative pulmonary hypertension in lung cancer patients may be due to vascular remodeling and perivascular inflammatory cell accumulation, or due to the increased cardiopulmonary comorbidities [34]. PAH may also develop when the large tumor mass increases pulmonary vascular resistance through mechanical obstruction [35]. After lung cancer surgery, especially pneumonectomy or bilobectomy, acute increasing in pulmonary artery pressure has been reported, because the entire blood volume is directed through the remaining lung tissue [36, 37]. Pulmonary vascular pressure changes due to angioplasty and vascular anastomoses may also cause late onset PH.

Pulmonary hypertension is generally classified into five groups; Group (1): Pulmonary arterial hypertension (PAH) (Idiopathic, heritable, associated with drugs, toxins, connective tissue disease, HIV infection, or portal hypertension). Group (2): PH associated with left heart disease (heart failure, valvular heart disease, cardiovascular conditions leading to post-capillary PH). Group (3): PH associated with lung diseases and/or hypoxia (chronic obstructive pulmonary disease COPD, interstitial lung disease, obstructive sleep apnea). Group (4): PH associated with pulmonary artery obstructions. Group (5): PH with multifactorial mechanisms (e.g., Hematological, systemic or metabolic disorders) [38].

Lung disease, especially COPD, is the second most common cause of PH after the left heart disease [38], the prevalence of PH in patients with COPD ranges from 25 to 90 percent [39]. Therefore, during the routine evaluation of chronic lung disease, patients should undergo imaging with chest radiography and/or computed tomography, pulmonary function test, lung volumes, and diffusing capacity.

The right heart catheterization (RHC) is the golden standard in the diagnosis of pulmonary hypertension because it enables direct measurement of pulmonary pressures, resistance, and cardiac output. However, it is invasive, requires exposure to ionizing radiation, and does not provide morphologic information [38]. Other adjunctive methods are pulmonary artery: Aorta ratio (PA/A ratio) derived by CT scan, chest X-ray, echocardiography, Ventilation-perfusion (V/Q) scintigraphy, pulmonary function test with lung diffusion capacity for carbon monoxide (DLCO), and arterial blood gases (ABG).

Computed tomography (CT) scan is routinely performed in patients with lung cancer as a part of their diagnostic work-up and follow-up. It helps measuring the main pulmonary artery diameter (mPAD) and PA/A ratio which have been shown to be useful parameters for detection of PH; a PA diameter ≥ 28 mm or PA/A ratio ≥ 1 are highly predictive of PH [38]. This method is non-invasive, reliable for PH detection with a sensitivity and specificity of 74% and 81% respectively [40].

We sought to evaluate pulmonary hypertension (PH) in patients with stage II and stage III lung cancer in this retrospective cohort study.

METHODS :

Study population

A number of 316 lung cancer patients who underwent curative lung resection at Giessen Lung Cancer Centre in Hessen/Germany were enclosed in a retrospective cohort study between January 2010 and December 2019. The study included patients with NSCLC stage (II, III) as they are most likely treated surgically. Patients with NSCLC stage (IV) (n=4) and those with missing data (n= 71) were excluded, thus a total number of 241 patients were included in the final analysis. Eligible patients underwent a serial of chest computed tomography (CT) scans before and after the surgery. Data was collected out of participants' medical records at our institution, CT images were analyzed for detection of pulmonary hypertension. Ethical approval for this analysis of imaging techniques and routinely collected data was given by our institutional review board.

Objectives

pulmonary hypertension (PH) has been described as a frequent tumor-associated comorbidity and is associated with an unfavorable prognosis. This finding confronts the thoracic surgeon with questions about the PAH incidence in the postoperative course in lung cancer surgery, and the influence of PAH on the postoperative course and long-term survival, so the co-primary objectives of this study were to clarify these questions.

Intervention

Clinical manifestations, including age at surgery, smoking status, comorbidities, tumor histology, pathologic stage, tumor size and location, and type of surgery were obtained from patients' medical records. Tumor was staged according to the 8th edition of the TNM classification [14]. The routine preoperative evaluation included spirometry and CT scan. Chest CT scans were analyzed for size and lobar location of the tumor, interstitial lung abnormalities, and ratio of main pulmonary artery-to-ascending aorta diameter (PA/A ratio). Pulmonary hypertension was defined as PA/A ratio ≥ 1 or a PA diameter ≥ 28 mm on chest CT scan [38]. Pulmonary functions were also studied in order to detect pulmonary comorbidity and to differentiate between pulmonary and non-

pulmonary causes of PH. In particular, diffusing capacity of the lungs for carbon monoxide (DLCO) and forced expiratory volume in the first second (FEV1) were measured in this study. DLCO ≤ 75% of predicted (for height, age, sex) and FEV1 ≤ 79% of predicted (for height, age, sex) were considered predictors of underlying lung disease (e.g., COPD) [42]. Data after surgery about complications, hospitalization period, mortality and survival rate were collected, radiographic analysis of CT scans was performed to detect signs of postoperative PAH, we excluded patients with preoperative PAH in order to study the incidence of PAH after resection in each follow-up time; (1) after 6 months, (2) after 12 months, and (3) after 18 months. Survival rate in this study was defined as the percentage of patients who are still alive for 18 months after lung cancer surgery.

Measurement points:
Primary endpoint was; PAH incidence in the postoperative course. Secondary endpoints were the postoperative course and overall survival during the follow-up.

Measurment method:

On chest CT scan we measured PA and A on an axial CT image at the level of the PA main bifurcation at the widest diameter vertical to its long axis and of the adjacent Aorta diameter. Emphysema (none, mild, moderate, severe), coronary artery calcifications, and chronic lung disease, which included honeycombing, interstitial, and small airways disease, were further confirmed CT abnormalities.

Statistical analysis

Data was collected and organized in an EXCEL spreadsheet, then statistical analysis was performed using IBM SPSS software version 26. The evaluation of the endpoints was exploratory. All data were summarized with descriptive statistics, including mean ± standard deviation (SD) for continuous measures and counts with percentages for categorical measures. The Chi-square test was used in order to assess the correlation between some categorical variables. Univariate logistic regression was used to determine the association of postoperative PAH with complications and tumor recurrence. Risk analysis and odds ratio estimation for patients with PAH was conducted with backward elimination multivariate logistic regression analysis. The prognosis of PH for predicting the study outcomes was estimated by the Kaplan–Meier analysis and Cox regression. In multivariate Cox models, we included all variables that are important to our study. The models also included those considered confounders factors. Hazard ratios estimation for patients with PAH who died and had recurrence were conducted. The cut-off PA/A ratio most likely to predict the occurrence of postoperative PAH was detected by the receiver operating characteristic (ROC) curve. Survival time of our study was defined as the interval between the date of diagnosing lung cancer and the date of death, or end of follow-up. Repeated measures ANOVA were studied in order to evaluate the differences in arteries diameters. A value of $p< 0.05$ was considered to indicate statistical significance.

RESULTS

Patients

Analysis of records of patients who presented with NSCLC stage (II, III) in 2010-2019 revealed that 175 of 241 patients were men, the median age and SD of population was (66 ± 9) years. An increased incidence of lung cancer was observed among young people; about 61% of patients were younger than 70 years old. Smokers formed 85.8% of population. Only 63 of 241 patients didn't have co-morbidities, while about 73.9% had one or more health problem in association with lung cancer (Table 2). The common comorbidities were pulmonary disease (COPD 74.1%, emphysema 16.2%, sleep apnea 6.1%, asthma 1.6%, and others), cardiac disease 34.8% (coronary disease 23%, atrial fibrillation 10%, dilated cardiomyopathy 1.6%), increased blood pressure (HTN) 62.3%, diabetes mellitus 21.9%, obesity 23%, history of other cancer 3.3%, hyperthyroidism 7.3%, chronic renal failure 2.8 %, deep vein thrombosis DVT 2.8%, and hypothyroidism 1.6%.

Table 2. Baseline characteristics at study enrolment.

	Count (Total 241)	**%**
Age, yr		
< 70	147	61
≥ 70	94	39
Sex		
Male	175	72.6
Female	66	27.4
Smoking status		
Smoker	207	85.8
Nonsmoker	4	1.6
Missing data	30	12.4
Comorbidity		
Total	178	73.8
Pulmonary disease		
COPD	132	74.1
Emphysema	29	16.2
Sleep apnea	11	6.1
Asthma	3	1.6
Cardiac disease	62	34.8
Coronary disease	41	23
Atrial fibrillation	18	10.1
Dilated cardiomyopathy	3	1.6
Hypertension	111	62.3
Diabetes mellitus	39	21.9
Obesity	41	23
Other cancer	6	3.3
Hyperthyroidism	13	7.3
Chronic renal failure	5	2.8
DVT	5	2.8
Hypothyroidism	3	1.6

Lung function and CT findings

About 31% of patients had an underlying lung disease before surgery, COPD was the most common. FEV1 mean was 73.5% of predicted value, and DLCO mean was 62.7% of predicted value, measurements in postoperative follow-up were variable (Table 3).

Both of pulmonary artery and descending aorta diameters on CT scans were measured for patients before the surgery and during the 1st, 2nd, and 3rd postoperative follow up, and then PA/A ratio was calculated to predict of pulmonary artery hypertension (PAH). In addition, we calculated the mean systolic pulmonary artery pressure (SPAP) of 48 patients in whom echocardiographic data were available. Measurements of mean and standard deviations are shown in table 3.

Table 3. Lung function/ pulmonary artery & aorta diameter measurements on CT scan before and after surgery.

		Mean	Standard deviation
Initial	FEV1 %	73.5	19.6
	DLCO %	62.7	17.7
	PA (mm)	27.3	4.5
	A (mm)	34.1	4.2
Preoperative SPAP (mmHg)		26	13
Postoperative SPAP (mmHg)		30	12
1st follow-up	FEV1 %	76.1	19.2
	DLCO %	65.1	17.8
	PA (mm)	28.4	5.1
	A (mm)	34.5	4.4
2nd follow-up	FEV1 %	75.5	20.7
	DLCO %	65.7	16.9
	PA (mm)	28.5	5.2
	A (mm)	34.5	4.5
3rd follow-up	FEV1 %	75.1	21.4
	DLCO %	65.8	18.0
	PA (mm)	28.9	5.2
	A (mm)	34.3	4.6

CT scan records were also studied with the aim of identifying tumor location, size, nodes, metastases and subsequently tumor stagging. As shown in Table 4; the most common location of lung cancer was in the upper lobes; in the right lung (53.1%, 56% respectively), the mean diameter and SD of the tumor was (5.08 ± 2.41), lung cancer stage IIIA was the most common category (44.4%) according to the eighth edition TNM staging system from the Union for International Cancer Control (UICC) [14]. The histological study of lung biopsies showed an equal prevalence of adenocarcinoma and squamous cell carcinoma (43.2%). It's commonly known that lung adenocarcinoma is the most common cell subtype in females (smokers or non-smokers) and in non-smoking males, but it is less common in Europe [43]. Therefore, an increase in the incidence of squamous cell carcinoma in our study could be geographically explained.

Table 4. Tumor characteristics and stagging.			
		count (total 241)	%
Tumor location	*Right lung*	135	56
	Left lung	106	44
	Upper lobe	128	53.1
	Middle lobe	9	3.7
	Lower lobe	94	39
	Multi-focal	10	4.1
Pathology	*Adenocarcinoma*	104	43.2
	Squamous cell carcinoma	104	43.2
	Large cell carcinoma	21	8.7
	Adenosquamous carcinoma	5	2.1
	Others	7	2.9
TNM	*T1a*	4	1.7
	T1b	13	5.4
	T1c	12	5
	T2a	33	13.7
	T2b	37	15.4
	T3	82	34
	T4	60	24.9
	N0	100	41.5
	N1	76	31.5
	N2	61	25.3
	N3	3	1.2
	Nx	1	0.4
	M0	236	97.9
	M1a	1	0.4
	M1b	1	0.4
	M1c	2	0.8
	Mx	1	0.4
UICC stagging	*IIA*	20	7.7
	IIB	84	36.5
	IIIA	106	42.9
	IIIB	24	10.3
	IIIC	1	1.0
	IVA	2	1.0
	IVB	2	0.6

Surgical techniques and tumor resection

Most patients underwent thoracotomy (61.4%) for lung cancer resection. Video-assisted thoracoscopic surgery (VATS) was done in 90 patients (37.3%), while some patients needed open surgery after uncompleted VATS (1.2%). Surgery technique depended on tumor location; lobectomy with complete tumor mass removal was the most common

used technique (49%), followed by sleeve lobectomy (22.8%). However, more aggressive resection (bilobectomy or pneumonectomy) was also used in a number of patients with bronchogenic carcinoma (Table 5). Residual tumor classification was used to verify the complete resection from microscopic and macroscopic residual tumor [31]; R0 was the most common category (85.1%), which means that most patients had successful surgery with complete resection of the tumor. However, tumor recurrence was noticed in 33 of 241 patients after surgery, the mean time of recurrence was (1.89 ± 1.93) year. Local recurrence of the tumor -rather than metastases and lymph nodes recurrence- occurred in 13 patients (39.3%), those patients were included in the analysis of postoperative possible causes of PAH.

Table 5. Surgical related characteristics

		count (total 241)	%
Surgical approach	Thoracotomy	148	61.4
	VATS	90	37.3
	Both	3	1.2
Surgical technique	Lobectomy	118	49
	Sleeve lobectomy	55	22.8
	Bilobectomy	20	8.3
	Sleeve bilobectomy	4	1.7
	Pneumonectomy	26	10.8
	Wedge resection	9	3.7
	Segment resection	9	3.7
Residual tumor classification	R0	205	85.1
	R1	23	9.5
	R2	0	0
	Rx	13	5.4
Tumor recurrence	Total	33	13.7
	Local	11	33.3
	Lymph nodes	10	30.3
	Metastases	10	30.3
	Local & lymph node	2	6.1

Postoperative complications and survival

The mean and SD of hospitalization was 14.55 ±10.58 days. 64 deaths were observed during the follow-up period (26.6% of the population). Death was mainly due to the tumor (recurrence) (40.6%), followed by multiple organ dysfunction (15.6%) and cardiopulmonary comorbidities (9.4%). The median survival was (2.69 ± 2.58) years. 117 of 241 patients suffered postoperative complications, which was primarily acute respiratory problems after pneumonectomy and bilobectomy.

In our study, a combination of more than one complication was seen in many patients, the most common complication was pneumonia (34.1%), followed by emphysema (14.5%), hemothorax (13.6%), respiratory failure (11.9%) Prolonged air leak (11.1%),

and atelectasis (6.8%). Cardiac complications were detected in few patients; atrial fibrillation (13.6%), elevated cardiac enzymes (9.4%) and non-ST elevation myocardial infarction non-STEMI (0.8%). Other complications included recurrent laryngeal nerve paralysis (7.6%), and bleeding (1.7%). (Table 6)

Table 6. postoperative outcomes			
		count (total 241)	%
Death		64	26.6
Survival		177	73.4
Cause of death	Tumor	26	40.6
	Multiple organ dysfunction	10	15.6
	Comorbidities	6	9.4
	Respiratory failure	5	7.8
	sepsis	1	1.6
	Pneumonia	2	3.1
	Renal failure	1	1.6
	Cardiac failure	1	1.6
	Unknown	12	18.8
Complications	Yes	(117)	48.5
	Pneumonia	40	34.1
	Emphysema	17	14.5
	Hemothorax	16	13.6
	Respiratory failure	14	11.9
	Prolonged air leak	13	11.1
	Plural empyema	9	7.6
	Atelectasis	8	6.8
	Pleural effusion	6	5.1
	Mediastinal emphysema	1	0.8
	Pulmonary embolism	1	0.8
	Pulmonary edema	1	0.8
	Pulmonary artery stenosis	1	0.8
	Subcutaneous emphysema	13	11.1
	Non-STEMI	1	0.8
	Atrial fibrillation	16	13.6
	Cardiac enzymes elevation	11	9.4
	Bleeding	2	1.7
	Recurrent laryngeal nerve paralysis	9	7.6

The incidence of PAH after surgery

A number of 18 patients who were known to have initial PAH were excluded in this study. The incidence of postoperative PAH was studied in patients at the first follow up after 6 months of the surgical intervention. Those with new incidence of PAH were also excluded from 2nd follow-up population after 12 months, and the same protocol was done

for the 3rd follow-up after 18 months in order to study the incidence of PAH in each follow-up. Some participants failed to review, so we also excluded patients with missing data from the final analysis. As mentioned before, the predictor test of PAH used in this study was measuring pulmonary artery and aorta diameters on CT scan records, calculating PA/A ratio, and considering PA/A ratio ≥ 1 strongly suggests pulmonary hypertension [38]. 9 of 152 patients at the first follow-up showed signs of new-onset postoperative PAH. New PAH development was noticed in 11 of 117 patients at the second follow-up, and 15 of 100 patients at the third follow-up. Table 8; shows the cumulative 6-month / 12-month / 18-month incidence (CI) of postoperative PAH, and it is clear that late-onset postoperative pulmonary hypertension was the most common in our study (15%).

Table 8. postoperative pulmonary hypertension incidence

	Total	Patients with PAH	Patients without PAH	Cumulative incidence
1st follow-up	152	9	143	5.9%
2nd follow-up	117	11	106	9.4%
3rd follow-up	100	15	85	15%

The relationship of postoperative PAH incidence with age, gender, and smoking

We observed that the number of patient younger than 70 years with PAH was slightly more than older ones. Males were noticed to have PAH more than women in our study, and smokers developed PAH more than non-smokers. However, no statistical significance between the variants was approved. (Table 9)

Table 10. Difference in postoperative pulmonary hypertension according to age, gender, and smoking (Chi-square's test)

	Pulmonary Hypertension 1st follow-up					Pulmonary Hypertension 2nd follow-up					Pulmonary Hypertension 3rd follow-up				
	Don't have		Have		P value	Don't have		Have		P value	Don't have		Have		P value
	N	%	N	%		N	%	N	%		N	%	N	%	
Age Youth Elders	93 50	61.2 32.9	6 3	3.9 2	.92 1	71 35	60.7 29.9	7 4	6 3.4	.82 3	57 28	57 28	10 5	10 5	.976
Gender Males Females	104 39	68.4 25.7	7 2	4.6 1.3	.74 1	78 28	66.7 23.9	8 3	6.8 2.6	.95 1	63 22	63 22	12 3	12 3	.629
Smoking Non-smoking	123 3	91.8 2.2	7 1	5.2 0.7	.14 7	93 2	88.6 1.9	10 0	9.5 0	.58 8	75 1	84.3 1.1	13 0	14.6 0	.999

The relationship of postoperative PAH incidence with surgical technique

The pattern of resection in lung cancer usually affects pulmonary artery pressure. However, analysis data in our study showed negative relationship between the type of resection and the development of pulmonary hypertension (p-value > 0.05). Besides, we noticed that the number of patients with PAH following lobectomy was more than pneumonectomy (4 patients *vs* 1 at 2nd follow-up, 7 patients *vs* 5 at 3rd follow-up respectively), but it could be statistically explained by small number of the specimen (Table 9). Postoperative pulmonary hypertension was less common in patients underwent video-assisted thoracoscopic surgery (VATS) rather than thoracotomy (1.3% *vs* 4.6% at 1st follow-up, 1.7% *vs* 7.75% at 2nd follow-up, 3% *vs* 12% at 3rd follow-up respectively). However, p-value was of no statistical significance, indicating no relationship between surgical approach and the development of PAH. (Table 10,11)

Table 10. postoperative pulmonary hypertension incidence according to surgical approach and resection type

Surgical approach & resection type	Pulmonary Hypertension 1st follow-up				Pulmonary Hypertension 2nd follow-up				Pulmonary Hypertension 3rd follow-up			
	Don't have		Have		Don't have		Have		Don't have		Have	
	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Thoracotomy	87	57.2 %	7	4.6 %	66	56.4 %	9	7.7 %	54	54%	12	12%
VATS	55	36.25	2	1.3 %	38	32.5 %	2	1.7 %	30	30%	3	3%
Both	1	0.7%	0	0	2	1.7%	0	0	1	1%	0	0
Lobectomy	71	46.7 %	1	0.7 %	46	39.3 %	4	3.4 %	37	37.0 %	7	7.0 %
sleeve lobectomy	31	20.4 %	2	1.3 %	26	22.2 %	3	2.6 %	23	23.0 %	2	2.0 %
Bilobectomy	12	7.9%	2	1.3 %	10	8.5%	2	1.7 %	7	7.0%	1	1.0 %
sleeve Bilobectomy	2	1.3%	0	0.0 %	1	0.9%	0	0.0 %	1	1.0%	0	0.0 %
Pneumectomy	16	10.5 %	2	1.3 %	13	11.1 %	1	0.9 %	10	10.0 %	5	5.0 %
Wedge resection	5	3.3%	1	0.7 %	4	3.4%	0	0.0 %	2	2.0%	0	0.0 %
Segment resection	6	3.9%	1	0.7 %	6	5.1%	1	0.9 %	5	5.0%	0	0.0 %

Table 11. Binary logistic regression for postoperative pulmonary hypertension based on surgical approach and resection type										
PAH		VATS	Thoracotomy	Lobectomy	Sleeve Lobectomy	Bilobectomy	Sleeve Bilobectomy	Pneumo ne-ctomy	Wedge resection	Segment resection
1st follow-up	Count	2	7	1	2	2	0	2	1	1
	%	1.3%	4.6 %	0.7%	1.3%	1.3%	0	1.3%	0.7 %	0.7%
	p-value	.333	.626	.508	.221	.051	.999	.082	.075	.094
	Non-adjusted OR	.452	-	-	4.581	11.833	.000	8.875	14.200	11.833
	Lower	.091	-	-	.400	.994	.000	.757	.769	.655
	Upper	2.255	-	-	52.41	140.907	.000	103.981	.655	231.849
2nd follow-up	Count	2	9	4	3	2	0	1	0	1
	%	1.7%	7.7 %	3.4%	2.6%	1.7%	0	0.9%	0	0.9%
	P-value	.239	.499	.983	.724	.372	.999	.916	.999	.588
	Non-adjusted OR	.386	-	-	1.327	2.300	.000	.885	.000	1.917
	Lower	.079	-	-	.275	.369	.000	.091	.000	.183
	Upper	1.880	-	-	6.393	14.337	.000	8.615	.000	20.111
3rd follow-up	Count	3	12	7	2	1	0	5	0	0
	%	3%	12%	7%	2%	1%	0	5%	0	0
	p-value	.243	.506	.660	.357	.806	.999	.156	.999	.999
	Non-adjusted OR	.450	-	-	.460	.755	.000	2.643	.000	.000
	Lower	.118	-	-	.088	.080	.000	.690	.000	.000
	Upper	1.721	-	-	2.406	7.133	.000	10.129	.000	.000

Comorbidities and complications' effects on postoperative PAH

In general, preoperative comorbidities in our study had no relationship with the incidence of PAH after lung cancer surgery (p>0.05). (Table 12)

However, patients who suffered cardiac arrythmias, particularly atrial fibrillation, after lung resection showed a high risk for PAH in each follow-up at 6 months, 12 months, and 18 months (OR, 9.9; 95% CI, 1.5 to 62.5; p=0.017), (OR, 27.3; 95% CI, 3.6 to 202; p=0.001) and (OR, 27.3; 95% CI, 2.5 to 295; p=0.006) respectively. We also noticed that pleural effusion increased risk of PAH about 11-fold at 12 months (OR, 11.2; 95% CI, 1.39 to 90.8; p=0.023). (Table 13)

Table 12. Binary logistic regression for postoperative pulmonary hypertension based on preoperative comorbidities

PAH		COPD	Emphysema	Sleep apnea	Asthma	Coronary heart disease	Atrial fibrillation	Hypertension (HTN)	Diabetes mellitus	Obesity
1st follow-up	Count	4	8	0	0	1	0	5	2	1
	%	2.6%	0.7%	0%	0%	0.7%	0%	3.3%	1.3%	0.7%
	p-value	.793	.994	.999	.999	.566	.999	.701	.632	.730
	Non-adjusted OR	.834	.992	.000	.000	.537	.000	1.304	1.491	.688
	Lower	.251	.116	.000	.000	.064	.000	.336	.291	.082
	Upper	3.234	8.457	.000	.000	4.477	.000	5.054	7.635	5.773
2nd follow-up	Count	4	1	0	0	3	1	3	3	2
	%	3.4%	0.9%	0%	0%	2.6%	0.9%	2.6%	2.6%	1.7%
	P-value	.461	.894	.999	.999	.262	.757	.164	.262	.649
	Non-adjusted OR	.616	.864	.000	.000	2.275	1.414	.375	2.275	1.460
	Lower	.170	.101	.000	.000	.542	.158	.094	.542	.286
	Upper	2.230	7.402	.000	.000	9.553	12.686	1.419	9.553	7.469
3rd follow-up	Count	7	0	0	0	2	1	5	4	4
	%	7%	0%	0%	0%	2.0%	1%	5%	4%	4%
	p-value	.716	.999	.999	.999	.547	.733	.256	.180	.230
	Non-adjusted OR	.815	.000	.000	.000	.615	.688	.512	2.446	2.212
	Lower	.271	.000	.000	.000	.127	.080	.161	.661	.605
	Upper	2.449	.000	.000	.000	2.990	5.934	1.624	9.048	8.093

Table 13. Binary logistic regression for postoperative pulmonary hypertension based on complications										
PAH		Pneumonia	Emphysema	hemothorax	Respiratory failure	Bronchopleural fistula	Pleural effusion	Pleuritis	Atrial fibrillation	bleeding
1st follow-up	Count	3	0	0	1	0	0	0	2	0
	%	2%	0%	0%	0.7%	0%	0%	0%	1.3%	0%
	p-value	.168	.999	.999	.145	.999	.999	.999	.017	.999
	Non-adjusted OR	2.800	.000	.000	5.833	.000	.000	.000	9.917	.000
	Lower	.647	.000	.000	.544	.000	.000	.000	1.505	.000
	Upper	12.12	.000	.000	62.56	.000	.000	.000	62.56	.000
2nd follow-up	Count	1	2	0	0	1	2	0	3	0
	%	0.9%	1.7%	0%	0%	0.9%	1.7%	0%	2.6%	0%
	P-value	.761	.111	.999	.999	.277	.023	.999	.001	.999
	Non-adjusted OR	.717	4.300	.000	.000	3.684	11.250	.000	27.300	.000
	Lower	.083	.716	.000	.000	.355	1.393	.000	3.684	.000
	Upper	6.125	25.825	.000	.000	37.342	90.873	.000	202.31	.000
3rd follow-up	Count	1	1	1	0	1	2	0	3	0
	%	1%	1%	1%	0%	1%	2%	0%	3%	0%
	p-value	.248	.858	.172	.999	.359	.999	-	.006	.999
	Non-adjusted OR	.290	1.231	7.300	.000	.460	.000	-	27.375	.000
	Lower	.035	.127	.422	.000	.088	.000	-	2.539	.000
	Upper	2.372	11.925	126.139	.000	2.406	.000	-	295.185	.000

The influence of PAH on postoperative course and long-term survival

Mean hospitalization in patients with postoperative PAH at 6, 12, 18 months was 12.6, 14.8, and 12.6 days respectively, but p-value was of no statistically significance ($p>0.05$). Mean survival years for those patients was (2.6 ± 2.79), (3.2 ± 3.05), (4.3 ± 2.94) respectively, and p-value was of no statistically significance ($p>0.05$). furthermore, no relationship was detected between postoperative PAH and tumor recurrence or lung functions (FEV1 and DLCO). (Table 14)

Kaplan-Meier curve illustrating tumor recurrence based on PAH at each follow-up is shown below (Figures 1,2,3).

Table 14. Binary logistic regression for postoperative PAH based on hospitalization, lung functions, tumor recurrence, and survival

	Pulmonary Hypertension 1 follow-up							
	Don't have		Have				95% CI	
	Mean	Standard Deviation	Mean	Standard Deviation	P-value	Non-adjusted OR	Lower	Upper
Hospitalization (days)	14.54	10.36	12.67	5.63	.589	.975	.889	1.069
Diameter	5.01	2.48	6.63	2.94	.071	1.229	.983	1.536
Time of recurrence (Year)	2.142	1.930	1.545	1.260	.366	.809	.511	1.281
Survive (year)	3.243	2.782	2.653	2.791	.538	.918	.699	1.206
FEV1 %	76.1	19.2	61.9	33.1	.061	.968	.937	1.001
DLCO	65.1	17.8	59.2	11.0	.466	.979	.925	1.036
	Pulmonary Hypertension 2 follow-up							
	Don't have		Have				95% CI	
	Mean	Standard Deviation	Mean	Standard Deviation	P-value	Non-adjusted OR	Lower	Upper
Hospitalization (days)	14.05	10.76	14.89	6.49	.817	1.007	.949	1.068
Diameter	4.77	2.46	5.27	2.63	.519	1.079	.856	1.360
Time of recurrence (Year)	2.505	1.998	1.969	1.941	.398	.853	.591	1.232
Survive (year)	3.667	2.775	3.245	3.059	.633	.944	.745	1.196
FEV1 %	75.5	20.7	76.6	30.7	.870	1.002	.974	1.032
DLCO	65.7	16.9	70.1	25.2	.521	1.014	.972	1.058
	Pulmonary Hypertension 3 follow-up							
	Don't have		Have				95% CI	
	Mean	Standard Deviation	Mean	Standard Deviation	P-value	Non-adjusted OR	Lower	Upper
Hospitalization (days)	14.10	9.62	12.64	5.93	.583	.978	.904	1.059
Diameter	4.73	2.49	5.75	2.49	.159	1.154	.945	1.408
Time of recurrence (Year)	2.651	2.051	2.641	1.713	.985	.997	.756	1.316
Survive (year)	3.872	2.830	4.371	2.945	.530	1.062	.881	1.280
FEV1 %	75.1	21.4	73.9	19.5	.845	.997	.971	1.025
DLCO	65.8	18.0	71.0	22.2	.434	1.015	.978	1.053

Figure.1: Kaplan-Meier curve of tumor recurrence based on PAH at 1st follow-up

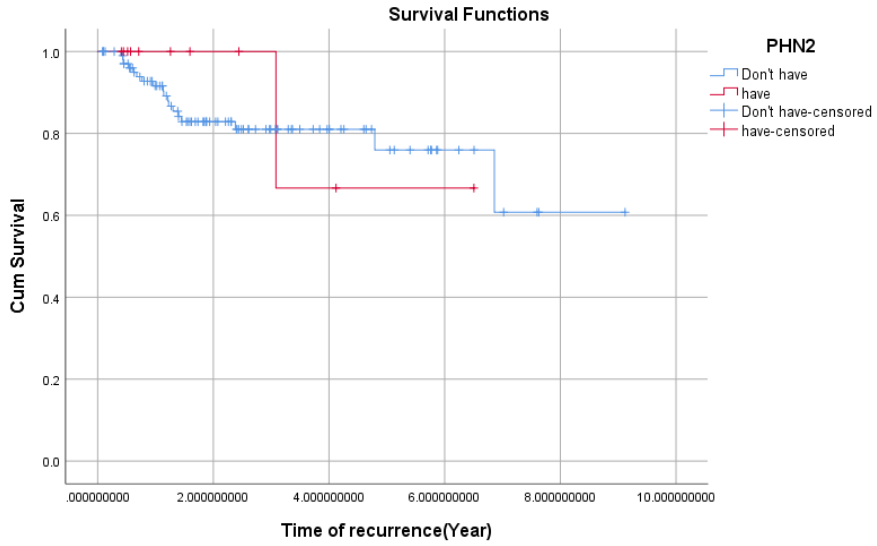

Figure.2: Kaplan-Meier curve of tumor recurrence based on PAH at 2nd follow-up

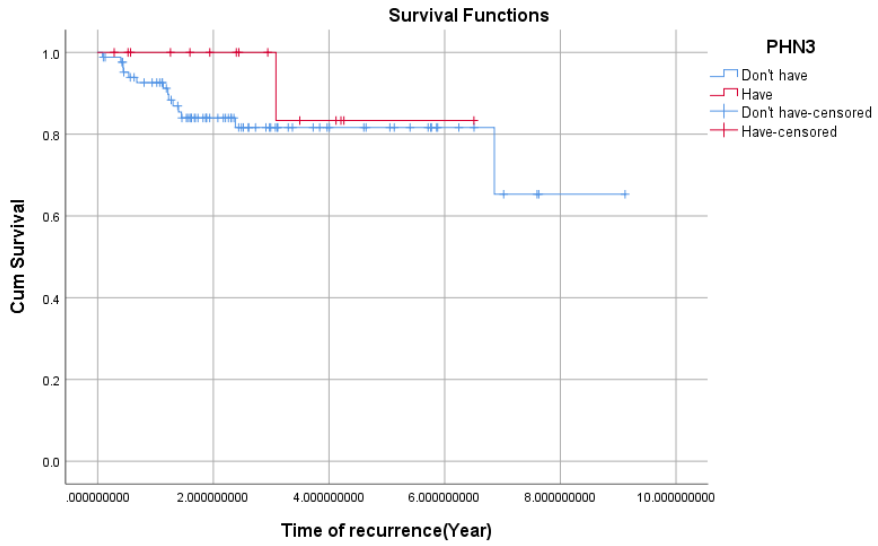

Figure.3: Kaplan-Meier curve of tumor recurrence based on PAH at 3rd follow-up

Using Kaplan-Meier curve, we also illustrated survival rate related to PAH at 1st, 2nd, and 3rd follow-up. As (Figure.4) shows, a 1.5-year survival rate in patients without pulmonary artery hypertension at 6 months was about 80%, but it decreased to about 55% in patients affected with PAH. However, we detected no significant statistical influence of increased pulmonary pressure on mortality and survival rate after lung resection. (Figures 4,5,6)

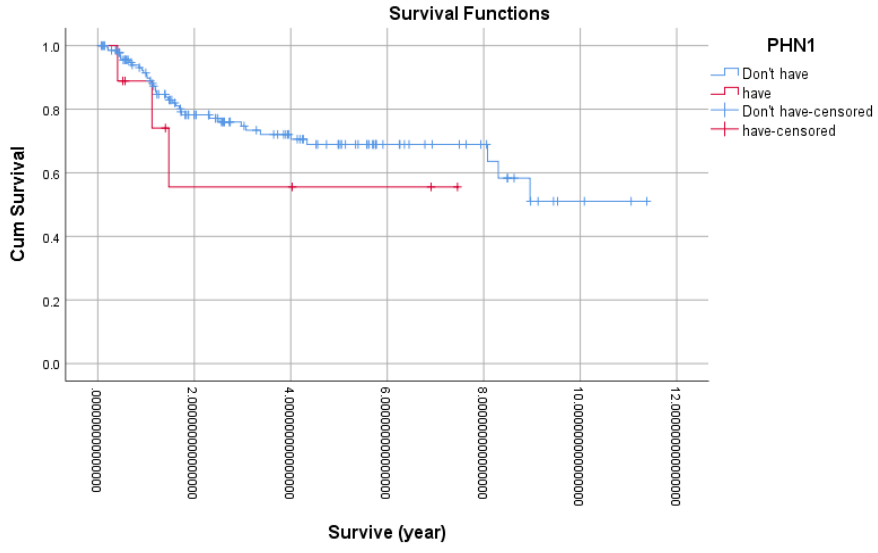

Figure.4: Kaplan-Meier curve of overall survival based on PAH at 1st follow-up

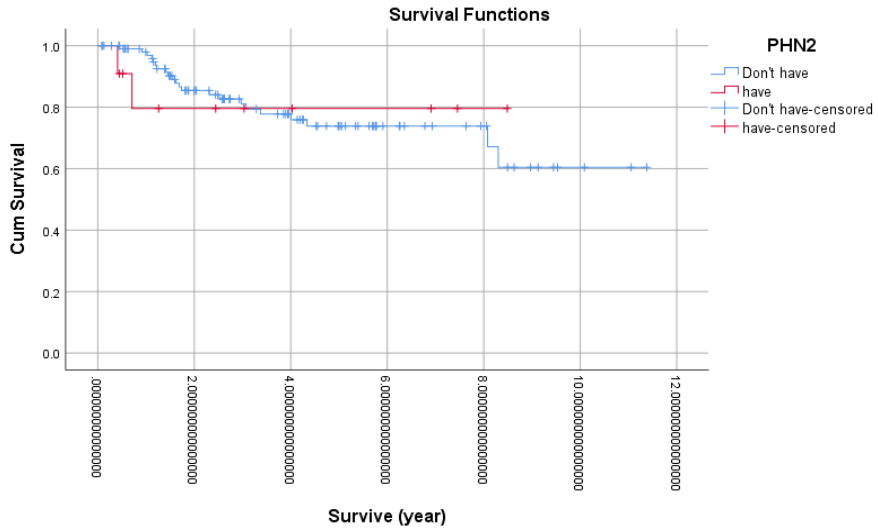

Figure.5: Kaplan-Meier curve of overall survival based on PAH at 2nd follow-up

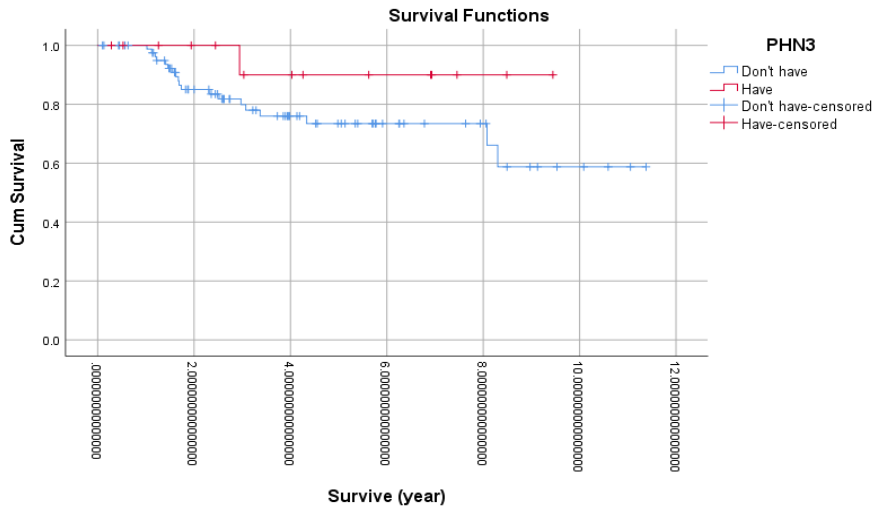

Figure.6: Kaplan-Meier curve of overall survival based on PAH at 3rd follow-up

Using pearson correlation coefficient, we found a weak correlation between PAH incidence at 1st and 3rd follow-up (correlation coefficient, 0.373; p= 0.000), a medium correlation between PAH incidence at 2nd and 1st follow-up (58%; p= 0.000), and a strong correlation between PAH incidence at 3rd and 2nd follow-up (70%; p= 0.000), as shown in (Table 15)

Table 15. Person's Correlation of recorded pulmonary artery hypertension throughout the postoperative period				
		PAH (1st)	**PAH (2nd)**	**PAH (3rd)**
PAH (1st)	Correlation Coefficient	1.000		
	p-value			
PAH (2nd)	Correlation Coefficient	.588**	1.000	
	p-value	.000	.	
PAH (3rd)	Correlation Coefficient	.373**	.707**	1.000
	p-value	.000	.000	.

Trying to identify postoperative PAH a prognostic marker of patients' mortality, we used receiver operating characteristic curve (ROC curve) analysis, which showed a weak sensitivity and specificity for preoperative and postoperative PAH at 6, 12,
and 18 months with regard to mortality, and all measurements were not statistically significant, as depicted in Figure 7 and Table 16.

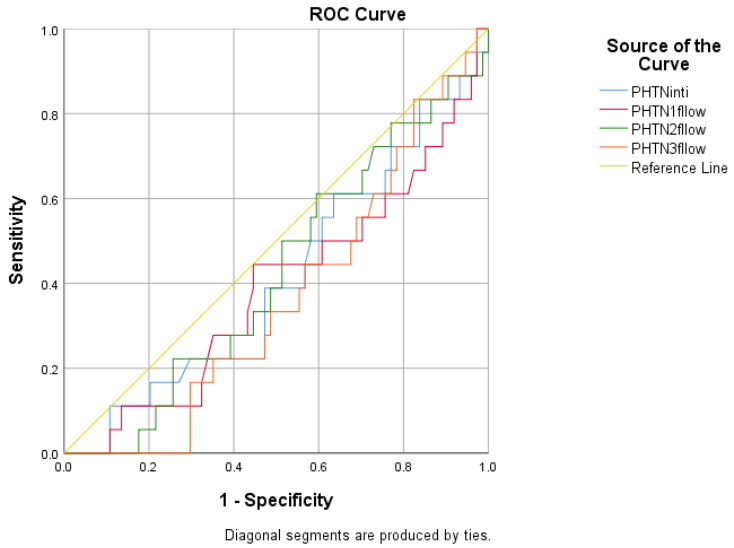

Figure 7. Receiver operating characteristic (ROC) curve analysis of the prognostic value of pulmonary artery hypertension pressure with mortality

Table 16. specificity and sensitivity of PAH as a predictor of mortality					
Test Result Variable(s)	Area under the carve (AUC)	Optimal cutting point	P-value	Sensitivity	Specificity
Initial PAH	.410	0.7825	.240	38.9%	52.7%
PAH 1ST follow-up	.388	0.8222	.143	44.4%	55.4%
PAH 2nd follow-up	.423	0.8022	.313	50%	48.6%
PAH 3rd follow-up	.365	0.8045	.077	44.4%	43.2%

Analyzing data, using adjusted Hazard ratio, showed that patients with pulmonary comorbidities -in addition to hospitalization period, tumor pathology & diameter, resection type, and pulmonary artery hypertension at 1st & 3rd follow-up- were at a 118-fold higher risk for death compared with those who didn't have pulmonary comorbidities (adjusted hazard ration, 118; 95% CI, 1.714 to 8247; p= 0.027). Patients with postoperative complications were also at a higher risk for death compared with

uncomplicated cases (non-adjusted HR, 2.112; 95% CI, 1.24 to 3.59; p= 0.006). Finally, we noticed that the more DLCO was high the more mortality risk was low (non-adjusted HR, 0.967; 95% CI, 0.944 to 0.991; p= 0.006). (Table 17)

Table 17. Cox regression to estimate adjusted and non-adjusted hazard ratio of mortality among resected lung cancer patients

		P-value	Adjusted HR	95.0% CI		P-value	Non-adjusted HR	95.0% CI	
				Lower	Upper			Lower	Upper
Hospitalization		.098	.782	.584	1.046	.100	1.016	.997	1.035
Pathology	Squamous cell carcinoma	.689				.435			
	Adenocarcinoma	.133	.081	.003	2.152	.605	.862	.492	1.511
	Large cell carcinoma	.971	.000	.000	.000	.358	.635	.241	1.673
	Adenosquamous carcinoma	.995	.000	.000	.000	.975	.000	.000	.000.
	Others	.994	.000	.000	.000	.150	2.176	.755	6.269
Resection	Lobectomy	.766				.991			
	Manchette lobectomy	.114	11.159	.561	221.810	.861	1.058	.562	1.992
	Bilobectomy	.971	.000	.000	.000	.496	1.361	.560	3.305
	Manchette Bilobectomy	.997	.018	.000	.000	.976	.000	.000	.
	Pneumectomy	.784	.555	.008	37.198	.632	.791	.304	2.060
	Wedge resection	.781	1.730	.036	82.764	.943	1.044	.316	3.447
	Segment resection	.200	11.171	.279	446.525	.899	1.098	.260	4.634
co-morbidities	Don't have								
	Have	.323	.198	.008	4.913	.943	1.022	.559	1.868
FEV1 %		.486	1.028	.952	1.109	.906	.999	.985	1.013
DLCO		.113	.892	.774	1.027	.006	.967	.944	.991
Pulmonary co-morbidities	Don't have								
	Have	.027	118.881	1.714	8247.409	.031	1.911	1.062	3.441
Complications	Don't have								
	Have	.118	12.134	.530	277.952	.006	2.112	1.240	3.599
Diameter		.691	1.123	.634	1.991	.340	1.051	.949	1.163
Pulmonary hypertension 1 follow-up	Don't have								
	Have	.994	.013	.000	.000.	.341	1.777	.544	5.803
Pulmonary hypertension 3 follow-up	Don't have								
	Have	.971	.000	.000	.000	.207	.274	.037	2.046

The model was adjusted for Hospitalization time, Pathology, Resection, co-morbidities, FEV1 %, DLCO Diameter, Pulmonary hypertension 1 follow-up and 3 follow-up.

Risk factors of tumor recurrence after lung cancer resection

We studied hospitalization period, tumor pathology & diameter, resection type, preoperative comorbidities and postoperative complications including PAH at 1st & 2nd follow-up as possible risk factors for cancer recurrence, but we found no statistically significance of p-value (p> 0.05). (Table 18)

Table 18. Cox regression to estimate adjusted and non-adjusted hazard ratio of tumor recurrence among resected lung cancer patients

		P-value	Adjusted HR	95.0% CI		P-value	Non-adjusted HR	95.0% CI	
				Lower	Upper			Lower	Upper
Hospitalization		.483	.973	.901	1.050	.158	1.019	.993	1.046
Pathology	Squamous cell carcinoma	.721				.997			
	Adenocarcinoma	.179	.072	.002	3.344	.912	.955	.421	2.168
	Large cell carcinoma	.636	.005	.000	.000	.958	.966	.267	3.497
	Adenosquamous carcinoma	.306	.134	.003	6.314	.728	1.441	.185	11.242
	Others	.997	.000	.000	.000.	.979	.000	.000	.000
Resection	Lobectomy	.371				.868			
	Manchette lobectomy	.522	2.251	.188	26.935	.977	1.014	.398	2.579
	Bilobectomy	.630	2.277	.080	64.527	.693	.738	.164	3.322
	Manchette Bilobectomy	.900	.009	.000	.000	.984	.000	.000	.
	Pneumectomy	.925	.366	.000	.000	.463	.566	.124	2.588
	Wedge resection	.902	.010	.000	.000	.782	.750	.098	5.746
	Segment resection	.364	2.396	.362	15.846	.232	2.493	.558	11.144
co-morbidities	Don't have								
	Have	.997	1.004	.076	13.257	.825	1.108	.446	2.754
FEV1 %		.193	1.048	.977	1.124	.643	1.005	.985	1.025
DLCO		.288	.946	.853	1.048	.409	.987	.958	1.018
Pulmonary co-morbidities	Don't have								
	Have	.159	.221	.027	1.801	.746	.882	.412	1.889
Complications	Don't have								
	Have	.994	1.005	.260	3.887	.478	1.316	.616	2.814
Diameter		.291	5.598	.228	137.156	.859	1.015	.862	1.19[4
Pulmonary hypertension 1 follow-up	Don't have								
	Have	.941	.131	.000	.000	.429	1.798	.419	7.709
Pulmonary hypertension 2 follow-up	Don't have								
	Have	.888	.184	.000	.000	.387	.408	.053	3.119

The model was adjusted for Hospitalization time, Pathology, Resection, co-morbidities, FEV1 %, DLCO Diameter, Pulmonary hypertension 1 follow-up and 3 follow-up.

The difference in Pulmonary artery diameters and Aorta diameters:

The difference in pulmonary artery diameters in the three follow-ups were studied, but we found no statistically significance of p-value (p> 0.05). (Table 19). Also, we have studied the difference in Aorta diameter in the three follow-ups. And there is not any statistically significance between the three follow-ups(p> 0.05). (Table 20).

Table 19. Repeated measures ANOVA to estimate the difference in Pulmonary artery					
Pulmonary artery	Mean	Std. Error	95% Confidence Interval		P-value
			Lower Bound	Upper Bound	
First follow-up	28.280	0.500	27.288	29.272	0.067904
Second follow-up	28.420	0.498	27.432	29.408	
Third follow-up	28.905	0.536	27.842	29.968	

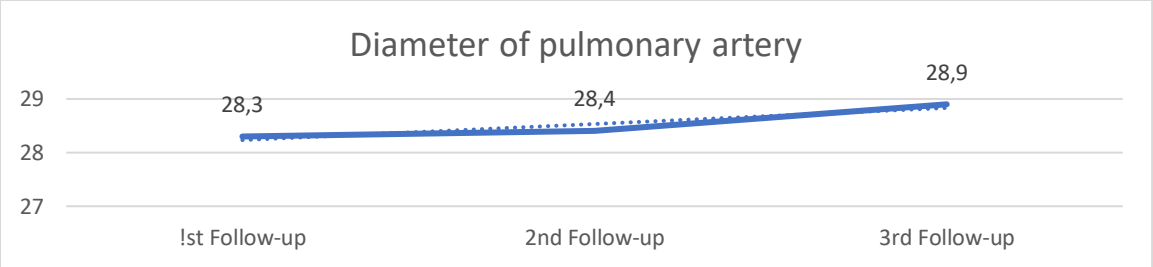

Figure 8. The difference in Pulmonary artery diameters in the three follow-ups.

Table 20. Repeated measures ANOVA to estimate the difference in Aorta diameter.					
Aorta	**Mean**	**Std. Error**	**95% Confidence Interval**		**P-value**
			Lower Bound	Upper Bound	
First follow-up	34.439	0.449	33.549	35.330	0.725696
Second follow-up	34.420	0.468	33.492	35.349	
Third follow-up	34.310	0.463	33.391	35.229	

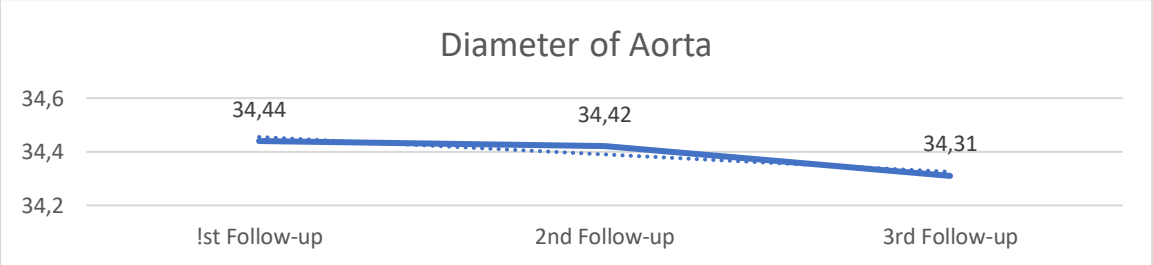

Figure 9. The difference in Aorta diameters in the three follow-ups

DISCUSSION

This project was a retrospective cohort study included 241 lung cancer patients who underwent curative lung resection. The purpose of our study was to focus on a common comorbidity and complication of lung cancer, which is pulmonary artery hypertension.

We know that hypoxia secondary to COPD and smoking has a proven correlation with PAH [45]. In our study, 74.1% of patients had COPD, 85.8% were smokers, and lung functions were consistent with the presence of chronic interstitial lung disease (median FEV1 and DLCO was 73.5%, 62.7% of predicted value, respectively), both COPD and smoking are related to lung cancer, too. Oriana *et al.* [46], in a retrospective review of all cancer patients undergoing right heart catheterization between 2011-2020, stated that about 74% of all patients had PAH, 15.8% of PH was secondary to lung disease.

In our study, about 74% of participants had one or more co-existing disease, and it's well known that comorbidities are seen frequently in patients with lung cancer, as Agata & Adam reviewed in their study [47]. The frequency of these co-existing diseases was 52% in Jiang *et al.* [48] study. The most frequent observed comorbidity in our study was COPD, which is an independent risk factor for lung cancer according to Sekine et al. [49] study, the other common comorbidity seen was increased blood pressure (62.3%), probably due to smoking and advanced age.

We evaluated all tumor characteristics before surgery, finding that the most common location of the cancer was in the right lung, in the upper lobes, and this note is important because upper lung lobes are commonly affected by COPD and emphysema. The histological study of lung biopsies showed an equal prevalence of adenocarcinoma and squamous cell carcinoma (SCC) (43.2%). However, it's commonly known that lung adenocarcinoma is the most common cell subtype in females (smokers or non-smokers) and in non-smoking males, but it is less common in Europe [43]. Therefore, an increase in the incidence of squamous cell carcinoma in our study could be explained geographically, as well as the high percentage of male smokers in the study sample.

The predictor investigation of PAH used in this study was measuring pulmonary artery and aorta diameters on CT scan records, calculating PA/A ratio, and considering PA/A ratio ≥ 1 strongly suggests pulmonary hypertension [40, 41]. The cumulative 6-month / 12-month / 18-month incidence of postoperative PAH in our study was 5.9%, 9.4% and 15% respectively, it was clear that postoperative pulmonary hypertension tended to occur late. We followed up our patients in this study for only 18 months after surgery, probably when follow up for a longer time, more accurate results about the incidence and influence of PAH on morbidity and mortality after lung cancer resection could be obtained.

We studied the techniques of lung resection used in our center to reveal the relationship with postoperative pulmonary hypertension. Theoretically, resection type affects lung volumes and may affect pulmonary vessels when performing vascular anastomoses or plasty, leading to changing in pulmonary artery pressure. The type of resection was determined by the clinical situation and tumor location; lobectomy was performed in

49% patients, sleeve lobectomy in 22.8%, pneumonectomy in 10.8%, bilobectomy in 8.3%, sleeve bilobectomy in 1.7%, wedge or segment resection in 3.7%. In fact, Lobectomy with complete tumor mass removal has become the standard surgical choice for resectable NSCLC patients [22], sleeve lobectomy has also been performing increasingly instead of pneumonectomy. Zhiyuan *et al*. [51], in a meta-analysis of studies published in English between 1996 and 2006, suggested that sleeve lobectomy with or without pulmonary artery reconstruction can be performed safely without increasing the morbidity and mortality as compared to pneumonectomy, and offers better long-term survival.

A clinical trial by Paul *et al*. [52] included 907 patients with T1 N0 non-small cell lung cancer, suggested that cancer recurrences decreased with survival, but new lung cancer occurrences increased, and malignant disease may appear more than 60 months after operation. In our study, most patients had complete resection of the tumor (R0 85.1%). However, tumor recurrence was noticed in 33 of 241 patients, 39.3% of recurrence occurred locally. The median recurrence time was (1.89 ± 1.93) year. We studied hospitalization period, tumor pathology & diameter, resection type, preoperative comorbidities and postoperative complications including PAH at 1^{st} & 2^{nd} follow-up as possible risk factors for cancer recurrence, but we found no statistically significance of p-value ($p > 0.05$).

Analyzing postoperative complications, a combination of more than one complication was seen in many patients, postoperative morbidity was about 48.5%, especially pulmonary complications and arrythmias. Smoking and cancer co-morbidity before surgery were influential factors, we did not study the exact relationship, but the correlation is approved worldwide; for example, Grønkjær *et al*. [58], in a meta-analysis of 107 cohort and case-control studies, preoperative smoking was associated with an increased risk of postoperative complications, including pulmonary complications (RR 1.73, 95% CI 1.35-2.23). Similar complications were described in other studies with variant percentages regarding multiple factors related to each study [32].

Coming to analyze the risk factors of postoperative pulmonary hypertension, we observed that the number of patients younger than 70 years with PAH was slightly more than older ones. Although it is known that advanced age usually associates with increased cardiopulmonary morbidity, but false negative results of PA ratio in diagnosis of PAH may occur in older age, and PA ratio is not useful in the case of aortic dilation [59]. males were noticed to have PAH more than females; and smokers developed PAH more than non-smokers. However, no statistical significance of age, sex, or smoking status was approved.

We noticed that patients with COPD and emphysema associated with lung cancer were more susceptible to develop post-operation PAH; other studies also suggest COPD as a risk factor for PAH [38]. However, preoperative comorbidities in our study had no statistical relationship with the incidence of PAH after lung cancer surgery ($p>0.05$); one suggested explanation is that tumor most common location in our study was in the upper lung lobes, which are commonly affected by COPD and emphysema, in such cases,

resection of the affected lobe improves lung functions after surgery. Another possible explanation is that probably we need more extended research with a bigger specimen.

Whether or not surgical approach affect PAH development. In our study, the majority of patients who developed PAH has undergone thoracotomy rather than VATS, but no statistical significance was found ($p>0.05$).

About resection technique, we hypothesized that the less size of resection -with less needy for anastomoses and vascular overlaps- the lower risk for develop PAH [36.37]. We noticed, 4 and 3 patients with late incidence of postoperative PAH (after a year) were found to have lobectomy and sleeve lobectomy surgery respectively, while only one case had pneumonectomy. This result had no statistical significance but it better be interpreted if we exclude the factor of sample size. Probably, the vascular intervention -including vascular anastomoses, vessels angioplasty, or pulmonary artery reconstruction- affected the vessels diameter and then the pulmonary artery pressure by the time. The number of post-pneumonectomy PAH cases, in our study, has increased after 18 months (5 patients), there was no statistical relationship, but pneumonectomy is generally a strong risk factor of PAH [36, 37]. Wedge and segmental resections have associated with PAH in very few cases, without any statistical significance. It is unusual for minor resection to cause pulmonary hypertension, because the amount of resected lung tissue is usually small and does not include vessels or bronchi. On the other hand, wedge resection carries a high risk of tumor recurrence, which may be a cause of PAH. In one hundred seventy-three patients with non-small-cell lung cancer underwent either a segmental pulmonary resection or lobectomy, the rate of local recurrence was 22.7% after segmental resection versus 4.9% after lobectomy [60]. Anyway, studying tumor recurrence in PAH patients was of no statistical significance.

In order to make more accurate results, we studied the difference in pulmonary artery diameters and aorta diameters in the three follow-ups. We noticed that the mean diameter of the pulmonary artery has increased slightly during the consecutive follow-ups reaching 28.9 mm in the third follow-up, a value close to the upper limit of normal pulmonary artery diameter as determined by Hacking et al; (29-33 mm) indicating dilatation of the main pulmonary artery (mPA) as an indicator of pulmonary hypertension [61]. Mean diameter of the aorta remained almost constant. However, as a statistical relationship, we did not find a significant difference between the three follow-ups for both the mean diameter of the pulmonary artery and the mean diameter of the aorta. The previous observation is consistent with the conclusion that late-onset pulmonary hypertension occurs at a higher rate than early-onset, it also supports the changes in pulmonary vessel diameter as one of the main causes of postoperative pulmonary hypertension, but we need to do more researches to confirm this association statistically.

In our study, we did not find a statistically significant difference for pulmonary hypertension with histopathology and tumor staging ($p>0.05$), but theoretically, it can be said that the larger the size of the tumor, the more it causes compression of the respiratory and vascular structures, and predisposes to an increase in pulmonary pressure. Socinski *et al.*, mentioned

the relationship of smoking with squamous cell carcinoma [62], so a higher incidence of PAH with squamous cell carcinoma is expected.

In general, preoperative comorbidities in our study had no relationship with the incidence of PAH after lung cancer surgery ($p>0.05$). We got the same results for PAH with other postoperative complications. However, patients who suffered cardiac arrythmias, particularly atrial fibrillation (AF), after lung resection showed a high risk for PAH in each follow-up at 6 months, 12 months, and 18 months (OR, 9.9; 95% CI, 1.5 to 62.5; $p=0.017$), (OR, 27.3; 95% CI, 3.6 to 202; $p=0.001$) and (OR, 27.3; 95% CI, 2.5 to 295; $p=0.006$) respectively. A literature review by Shelby et al. [63] stated that postoperative arrhythmia occurs in 10 to 15 percent of lung resections and typically occurs within one to three days postoperatively with a similar incidence for open and minimally invasive approaches. Park *et al*. [64] explained the pathogenesis of postoperative atrial fibrillation to be of autonomic denervation and stress-mediated neurohumoral mechanisms, Krowka *et al*. [65] has also concluded that tachydysrhythmias after lung resection are associated with significant mortality, and occur more frequently with intrapericardial dissection and in patients who develop postoperative interstitial pulmonary edema. According to Rottlaender *et al*., Pulmonary hypertension is associated with increased incidence of atrial fibrillation, which indicates clinical deterioration and advanced disease [66]. The pathology of PAH secondary to AF should be studied more.

We also noticed that pleural effusion increased risk of PAH about 11-fold at 12 months (OR, 11.2; 95% CI, 1.39 to 90.8; $p=0.023$). A prospective study by Wiener-Kronish *et al*. [67] evaluated 37 patients admitted to the coronary care unit with congestive heart failure, 19 of them had pleural effusion, pulmonary artery pressure was higher in this group with a mean value of 38.0 ± 1.5 mmHg versus 30.7 ± 2.1 mmHg ($p < 0.05$) in patients without pleural effusions.

The impact of pulmonary hypertension on postoperative morbidity and mortality remains controversial. Some studies indicate an increased morbidity with poor survival [68, 69]. In contrast, Benjamin *et al*. [70] study on 298 patients, 19 of them have pulmonary hypertension; perioperative mortality (0.0 vs 2.9%; $P= 1.0$) and postoperative complications (57.9 vs 47.7%; $P = 0.48$) were not significantly different between patients with and those without pulmonary hypertension. The presence of PH was either not a predictor of adverse outcomes. Our results were similar to Benjamin et al.; no relationship was detected between postoperative PAH and tumor recurrence or lung functions (FEV1 and DLCO). Also, a 1.5-year survival rate in patients without pulmonary artery hypertension at 6 months was about 80%, but it decreased to about 55% in patients affected with PAH. However, we detected no significant influence of increased pulmonary pressure on mortality and survival rate after lung resection for 1.5-year, postoperative PAH was of no prognostic marker of patients' mortality.

CONCLUSION

Pulmonary artery hypertension is one of the possible lung cancer comorbidities due to the local effect of the tumor and the age-related cardiopulmonary diseases. However, new onset PAH after lung resection is often detected, with tendency to occur late. Therefore, investigations for increased pulmonary artery pressure should -at least- continue for 18 months after surgery. Atrial fibrillation in particular should arise suspicion for PAH, and it should be investigated well after lung surgery. More researches with longer follow up are recommended to study the effect of postoperative PAH on morbidity and mortality.

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