Università degli Studi di Padova

Corso di Laurea in Medicina e Chirurgia

Dipartimento di Scienze Cardio-Toraco-Vascolari e Sanità Pubblica

Direttore: Prof. Federico Rea

U.O. Chirurgia Toracica

Responsabile: Prof. Federico Rea

TESI DI LAUREA

Role of pleural invasion in non-small cell lung cancer: therapeutic implications and long-term prognosis

Relatore: Prof. Andrea dell'Amore

Correlatore: Dott. Alessandro Bonis

Laureanda: Alessandra Moro

Anno Accademico: 2024/2025

INDEX

ABSTRACT

Assumptions

In the scenario of treatment of clinical stage I Not Small Cells Lung Cancer of the last decades, surgery has been the gold standard of treatment, with the emerging of two different techniques (segmentectomy, both anatomical, both wedge resection, and lobectomy) as main approaches.

Purpose of the study

Since the outcomes after the applying of these two techniques have been inconstant in terms of oncological and post-surgical outcomes, this retrospective cohort study, concerning patients treated for clinical stage 1 (a, b, or c) NSCLC between 2016 and 2021 in AOPD, Azienda Ospedaliera di Padova, aims to explore the outcomes (in terms of overall survival, recurrence free survival, 5-years-survival and other indicators) after receiving the two different surgical approaches, segmentectomy and lobectomy.

Materials and methods

The study is conducted analyzing 55 patients receiving segmentectomy and 212 lobectomy, stratifying them according to prognostically-relevant histological (such as tumors' visceral pleural invasion status, as determined by pathological analysis of the surgical specimen) and radiological characteristics, such as the diameter of the lesion or the CT mean value in Hounsfield units.

Results

Even if a correlation between VPI and Overall Survival could not be statistically determined (p-value= 0.665), a tendency of VPI to correlate with recurrence of disease was evidenced (with a p-value= 0.07). Regarding the segmentectomy and lobectomy techniques employed, they had comparable Overall Survival (p-value of the HR= 0.854) and 5-years RFS (p-value= 0.64) were obtained.

Conclusions

Aligning to the previous studies on the topic, VPI shows to correlate with recurrence of disease, whereas this association can not be highlighted in terms of OS. Moreover, showing comparable results to lobectomy, segmentectomy is a viable surgical technique for early stage NSCLC.

RIASSUNTO

Scenario

Nel panorama del trattamento dello stadio clinico I del Tumore polmonare non a piccole cellule degli ultimi decenni, la chirurgia ha svolto un ruolo chiave nella terapia, con l'emergere di due diverse tecniche (segmentectomia, sia anatomica, che resezione apicale, e lobectomia) come approcci principali.

Scopo dello studio

Dal momento che gli outcomes dopo l'applicazione di queste due tecniche sono stati incostanti in termini di risultati oncologici e post-operatori, questo studio retrospettivo di coorte, che riguarda pazienti trattati per stadio clinico I (a, b, o c) di NSCLC fra il 2016 e il 2021 in AOPD, Azienda Ospedaliera di Padova, si propone di esplorare gli outcomes (in termini di sopravvivenza totale, sopravvivenza libera da recidiva, 5-anni di sopravvivenza, e altri indicatori) dopo essere stati sottoposti a due diversi approcci chirurgici, segmentectomia e lobectomia.

Materiali e metodi

Lo studio è stato condotto analizzando 55 pazienti che hanno ricevuto la segmentectomia e la lobectomia, stratificandoli in base a istologie prognosticamente-rilevanti (come lo status di di invasione della pleura viscerale da parte del tumore, come determinato dalle analisi anatomopatologiche del pezzo operatorio) e caratteristiche radiologiche, come il diametro della lesione o il valore medio in unità Hounsfield alla TC.

Risultati

Sebbene non sia stato possibile determinare statisticamente una correlazione tra VPI e sopravvivenza globale (OS) (p-value= 0.665), è stata evidenziata una tendenza di VPI a correlarsi con la recidiva di malattia (p-value= 0.07). Per quanto riguarda le tecniche di segmentectomia e lobectomia impiegate, sono stati ottenuti valori di sopravvivenza globale (p-value= 0.854) e RFS a 5 anni (p-value=0.64) comparabili.

Conclusioni

In linea con gli studi precedenti sull'argomento, VPI mostra una correlazione con la recidiva di malattia, mentre questa associazione non può essere evidenziata in termini di OS. Inoltre, mostrando risultati comparabili alla lobectomia, la segmentectomia è una tecnica chirurgica valida per il NSCLC in stadio iniziale.

1. INTRODUCTION

1.1. Epidemiology and risk factors for NSCLC

Lung cancer is the leading cause of death and this statistic will increase in 2025 (of a 3.2% exclusively due to the population composition and not to a change of the risk of death from this cancer). The incidence is comparable to mortality, with 43.808 new diagnoses of lung cancer in Italy in 2022 (1).

With regard to the disparity between the two sexes, males demonstrate the highest incidence and mortality rates. In Italy, in 2023, the male-to-female ratio was more than one-fourth of all tumour-related deaths (and more than one in ten for women) (2), becoming the most frequent cause of death from cancer in men and the second most common in women (even if this statistic is now declining due to anti-smoking campaigns and decreased tobacco use (3)).

The most well-known risk factor for NSCLC is inhaled tobacco use, which is reported to be the cause of approximately 90% of all lung cancers. In addition, risk factors may be related with other risks increasing the overall likelihood. For example, asbestos exposure, alcohol use, environmental exposure to secondhand smoke, radon, arsenic, chromium, nickel, ionizing radiation, polycyclic aromatic hydrocarbons (4), pulmonary fibrosis (5), radiation therapy (used for the treatment of breast cancer or LH) (6,7) and HIV (independently from antiretroviral therapy use) (8,9) are well-recognized risk factors for lung cancer (10).

1.2. Symptoms and physical examination

Lung cancer often does not produce symptoms until the disease is advanced, resulting in 55% of patients with distant spread, 25% with regional metastasis at diagnosis, 20% have localized disease, and 7-10% of cases being an occasional chest opacity on radiography. Signs and symptoms of lung cancers can be due to the primary tumor, locoregional spread, metastatic disease, or ectopic hormone production. Among them, cough is the most common, but also dyspnea, chest pain (especially for peripheral tumors), shortness of breath and hemoptysis (especially in central tumors), are described

(11,12). Other symptoms of primitiveness can be wheezing and post-obstructive pneumonia for central tumors, and pleural effusion for more peripheral ones.

Locoregional compressive or infiltrative symptoms include superior vena cava obstruction, recurrent laryngeal nerve palsy and hoarseness, phrenic nerve palsy (with elevated hemidiaphragm and worsening dyspnea), brachial nerve root compression (Horner syndrome), esophageal compression and dysphagia, airways compression and dyspnea.

Metastatic spread can cause brain metastasis especially in adenocarcinoma (which can be present with headache, vomiting, visual field deficit, seizures or focal neurologic deficits (13)), spinal cord compression (11,12), bony destruction and back pain (in 20% of patients at presentation (14), liver metastasis and hepatomegaly (11,12).

Initial evaluation after history and physical exam should include a complete blood count and metabolic panel (for hematologic and ionic complicance, such as hypercalcemia or elevated ALP from bony metastasis. Imaging should begin with a chest radiograph, followed by CT scan and tissue biopsy (for histopathologic and IHC diagnosis). Once the diagnosis is made, a CT of chest and upper abdomen (with adrenals included), brain MRI and a PET scan should be performed to stage the tumor and research metastatic disease.

1.3. NSCLC classification

Among pulmonary lesions, it is important to differentiate between not-neoplastic and neoplastic ones, which can be further divided into benign and malignant. Amid malignant lesions, as visible in the below Figure 1, the first big classification of primitive lesions can be done, based on histological findings, in Small Cells Lung Cancer and Non-Small Cells Lung Cancer. NSCLC is the most common type, amounting to 85% of total lung cancers. According to C. Ho et al., more than 60% of NSCLC are adenocarcinoma, more than 15% are SCC (more frequently starting from the origin of the tracheobronchial tree (15)) and the 20% left include heterogeneous categories and broad

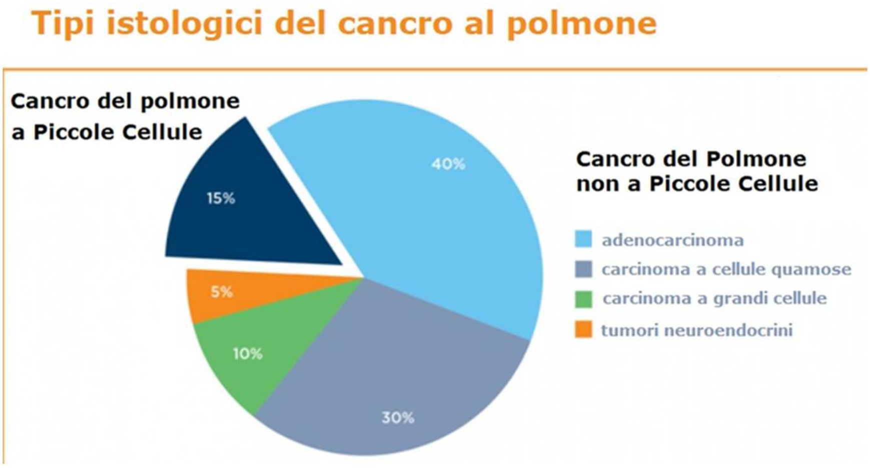

Figure 1 Types of Lung cancer

terminologies such as adenosquamous carcinoma, sarcomatoid carcinoma, bronchoalveolar carcinoma, large-cell carcinoma and other types (16).

Adenocarcinoma requires evidence of neoplastic gland formation, pneumocyte marker expression of TTF-1 with or without napsin, or intracytoplasmic mucin. The majority of neoplastic gland formation includes acinar, papillary, micropapillary, lepidic, or solid growth patterns (17).

Instead, SCC is individuated by the presence of keratin production by tumor cells, intercellular desmosomes, or expression at IHC of p40, p63, CK5, or desmoglein (18).

Large cell carcinoma is a diagnosis of exclusion which can have squamous, glandular, or neuroendocrine differentiation (in 90% of cases), whereas if it is poorly differentiated, it is defined as large cell carcinoma only in case of absence of other IHC markers.

Apart from malignant bronchogenic carcinoma, a potential differential diagnosis can include metastasis, such as from the breast, extranodal lymphoma, benign neoplasms (f. e. fibroma, lipoma, angioma), vascular phenomena, cyst, inflammatory findings (such as sarcoidosis, rheumatoid nodule, granulomatosis with polyangiitis), infectious granuloma (coccidioidomycosis, tuberculosis, atypical mycobacteria, cryptococcus) and bacterial abscess.

1.4. Radiological assessment

Actually the most used exams for the staging of the malignancy are total-body CT scan and 18FDG-PET scan. CT can play a role in preoperative biopsy, but, since it has limitations in evaluating the tumor invasion into adjacent structures such as brachial plexus or spinal canal, MRI is used. 18FDG-

PET scan is useful to assess the glucose uptake of nodal stations and any other uptake elsewhere, indicating the suspect of further metabolic active regions that need to be investigated. Since staging accuracy is imperfect with radiological scans, pathologic confirmation is recommended, whenever possible (19).

Regarding lymph nodes, CT criteria of involvement theoretically include morphology such as nodal attenuation and margination, but, in practice, nodal enlargement (>1 cm in short axis diameter) is the only currently useful diagnostic criterion, even with poor sensitivity (positive lymph nodes without enlargement) and low specificity (for instance, bigger lymph nodes in post obstructive pneumonitis). On the other hand, 18FDG-PET is superior to CT in terms of sensitivity (80%, especially for larger lymph nodes, resulting in more false positive) and specificity (90%, especially for smaller lymph nodes, which can go under the limit of spatial resolution, thus increasing the number of false negative), and the combination of CT-PET is even better (19). Then, each suspected lymph node should be biopsied (19), to differentiate it from sarcoidosis, tuberculosis (20) and to discriminate any suspicion of cancer-involved nodal stations.

Regarding systemic disease, instrumental tests differentiate it from benign disease, but in doubt cases a biopsy confirmation is required. Moreover, 18FDG-PET can detect unsuspected distant metastases especially in the abdomen (even if false positives on GI tract, muscles and fat can occur, as well as false negative), and also exclude malignancy from suspicious areas in the CT. The addition of 18FDG-PET to CT has been reported to change management in 20-30% of patients, mostly by upstaging the disease (21), but also reducing the number of unindicated thoracotomies of one half (21).

1.5. Biopsy: CT or US guided or endoscopic evaluation

Biopsy involves sampling a piece of tissue from a node or tumor for examination, in order to determine type and (if adequately obtained) genetic modifications of the radiological suspected lesion. A biopsy can be done with a fine and core needle biopsy guided by CT or US imaging or through trans bronchial bronchoscopy (with a bronchoscope introduced with microscopic lens), Wang needle biopsy, EBUS, Endobronchial ultrasound with biopsy, navigational bronchoscopy, mediastinoscopy (22) for biopsying suspected lymph nodes (20), VATS or surgery (22). There is a discussion on the necessity of preoperative biopsy (23), since the long-term outcomes compared to diagnostic segmentectomy are more explored with the increasing use of this technique. According to the ESMO, a pathologic diagnosis is recommended before any curative treatment unless the risk of biopsy is deemed unacceptable by a multidisciplinary team. In case of lesions unsuitable for preoperative diagnosis, a high glucose uptake and an irregular radiological shape are elements of suspicion deserving further evaluations.

1.6. cTNM staging: preoperative assessment of resectability

cTNM assesses the local and systemic extension of the neoplasia, thus determining the treatment and the prognosis of the patient (19): for instance, individuals with stage IA lung cancer are most commonly treated with surgery (24), as well as for those with a localized disease or a locally advanced stage after neoadjuvant therapy. Radiation therapy may be used in cases that involve chest wall, the mediastinum in case of combined treatment (chemo-radiation) or those medically unfit for surgery (palliative intent). Systemic treatments usually are adopted for diffused disease (metastatic or locally advanced unsuitable for neoadjuvant therapy (19). Surgery can be adopted in combination with surgery in limited cases. Since the prognosis decreases for the upper stages, diagnosing lung cancer at an early stage can thus contribute to improving the prognosis (24).

NSCLC is staged using the TNM system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). In particular, right now, the 9th TNM classification for lung cancer is taking place instead of the 8th, which is in use right now.

1.6.1. T stage

The 8th TNM classification, which is from here on analyzed:

- T1 tumors are small (≤3 cm) and they do not involve the visceral pleura. These lesions may affect a lobar or more peripheral bronchus, but they cannot involve a main bronchus (because in this case they are upstaged). T1 can be both in stage IA, whether tumor size is ≤1 cm (even in those patients exhibiting clinical stage IA disease, lobectomy with mediastinal lymph node dissection can be an alternative in some cases, such as in case of VPI, to merely undergoing segmentectomy (24), both in the IB, when it is >1-2 cm, both in IC, which is > 2–3 cm.

- T2 tumors are larger than 3 cm in diameter or they involve a distal main bronchus (>2 cm from the carina) and/or they invade the visceral pleura (19). In this last case, it is recommended, by the 8th edition of the TNM system, that they are staged from IA to 1B, highlighting the difference in prognosis (24). However, we will go into detail about this point in the paragraph of this work called "Discussion". T2 lesions may have post-obstructive atelectasis or pneumonia that involve less than an entire lung. They are split into IIA, >3–4 cm, and IIB, which is between 4 and 5 cm (19).

- T3 includes tumor between 5 and 7 cm in diameter, or, according to the previous classification, lesions of any size if they directly invade one among chest wall (including superior sulcus), diaphragm, mediastinal pleura, parietal pericardium, or proximal main bronchus (at less than 2 cm from the carina). Also the presence of at least one satellite nodule in the same lobe of the lung as the primary tumor falls in this category.
- T4 tumors are more than 7 cm, and they may be of any size if they directly invade one between the mediastinum, with the heart, the great vessels, trachea, esophagus, carina or the vertebral bodies. This category also includes those tumors with one or more satellite tumor nodules within a different, ipsilateral, lobe.

Table I Staging of NSCLC according to the TNM system

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1-3	N2	M0
Stage IIIB	T3-4	N2	M0
	T1-2	N3	M0
Stage IV	Any T	Any N	M1

1.6.2. N stage

- N0: No regional lymph nodal metastasis;
- N1: Metastasis in ipsilateral peribronchial and/or hilar lymph nodes (10 to 14 ipsilateral), and intrapulmonary nodes involved by direct extension from the primary tumor;
- N2: Ipsilateral mediastinal and/or subcarinal lymph nodes (2, 3a, 4, 8, 9 ipsilateral, and/or 3p and 7, which are considered ipsilateral for both the sides);

- N3: Contralateral mediastinal and/or hilar (2, 3a, 4, 8, 9, 10 to 14 contralateral), as well as any (ipsilateral or contralateral) supraclavicular and also the scalene lymph nodes, and 5 and 6 station whether the neoplasia is in the right lung.

The presence of metastatic disease in hilar lymph nodes (N1 disease) affects patient prognosis (as visible in Tables I and II), but does not generally affect resectability, because it is not related to mediastinal lymph node involvement. Tumors with metastatic disease to ipsilateral mediastinal nodes (N2 disease, which include N2a1, N2a2 and N2b) are potentially resectable, generally after neoadjuvant chemotherapy and/or radiotherapy, as long as the nodes are not numerous and/or bulky (19), whereas N3 are not resectable (19,21).

1.6.3. Nomenclature of lymph nodes stations

The grouping organization of the lymph node stations in the 8th edition of the TNM is based on retrospective survival analyses of international databases, according to the American Thoracic Society (21), thus being classified in the ATS atlas, which is helpful also in directing preoperative lymph node sampling (19) as following and visible in Figure 2:

Table II Staging NSCLC according to TNM

T/M	Label	N0	N1	N2	N3
T1	T1a ≤1	IA1	IIB	IIIA	IIIB
	T1b >1-2	IA2	IIB	IIIA	IIIB
	T1c >2-3	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

- Supraclavicular nodes
  - 1. Low cervical, supraclavicular and sternal notch nodes, which are N3 because they are considered extra thoracic nodes, whereas nodes of the stations 2 and 3 are N2. The

lower border of level 1 is the clavicles bilaterally and, in the midline, the upper border of the manubrium.

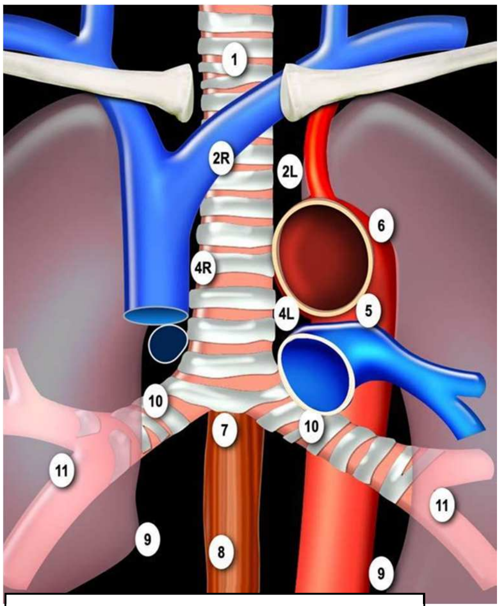

Figure 2 Lymph nodal stations

- Superior mediastinal nodes

● 2. Upper Paratracheal: above the aortic arch, but below the clavicles;

● 3A. Pre-vascular: nodes not adjacent to the trachea like the nodes in station 2, but anterior to the vessels;

● 3P. Prevertebral/retro-tracheal: nodes not adjacent to the trachea, but behind the esophagus, which is prevertebral (3P).

- Inferior Mediastinal nodes

● 4. Lower Paratracheal (including Azygos Nodes): below upper margin of aortic arch down to level of main bronchus. The boundary between level 4R and 4L is the left lateral border of the trachea, and not the anatomic midline.

- Aortic nodes

● 5. Subaortic (A-P window): nodes lateral to ligamentum arteriosum. These nodes are not located between the aorta and the pulmonary trunk, but lateral to these vessels.

● 6. Para-aortic (ascending aorta or phrenic): nodes lying anterior and lateral to the ascending aorta and the aortic arch.

- Subcarinal nodes

● 7. Subcarinal.

- Inferior Mediastinal nodes
  - 8. Paraesophageal (below carina).
  - 9. Pulmonary Ligament: nodes lying within the pulmonary ligaments.
- Pulmonary nodes
  - 10-14. N1-nodes: these are located outside of the mediastinum. The boundary between level 10 and level 4 is on the right the lower border of the azygos vein and on the left the upper border of the pulmonary artery (N1 vs. N2).

Paracardial, internal mammarian, diaphragmatic, axillary and intercostal lymph nodes are not described in the IASLC lymph node map, but since occasionally they can occur, it was proposed in to regard them as metastatic disease in the 8th TNM edition (19,25,26).

1.6.4. M status

- M0: there aren't distant metastasis;
- M1: there are distant metastasis (including separate metastatic tumor nodule(s) in the ipsilateral non-primary tumor lobe of the lung). The M category has been subdivided into M1a and M1b: M1a includes patients with distant metastatic disease confined to the lung and pleura, such as malignant pleural nodules, malignant pleural or pericardial effusion, or separate tumor nodule(s) in a contralateral lobe. The M1b category includes distant metastases outside of the lung and pleura.

Approximately 18–36% of patients with a new diagnosis of NSCLC are M1, with adenocarcinoma having a greater risk of metastasis than the SCC, and brain, bone, liver, and adrenal glands as the most common sites involved.

1.7. Chest wall and mediastinal invasion: focusing on the wall to parenchymal layer

Before the pathological stage can be assessed, especially when visceral pleural invasion risk factors are present (such as elderly age, adenocarcinoma and poor tumor differentiation), CT has a role in detecting chest wall invasion, with a sensitivity of 38-87% and a specificity of 40 to 90%. Signs of invasion may include pleural thickening, loss of the extrapleural fat plane, obtuse angle between mass and chest wall, and contact between mass and chest wall greater than 3 cm (19). Other features could be pleural retraction, pleural tags, small distance of the tumor from the pleura and pleural indentation (24,27). The exact diagnostic accuracy of these features, however, reportedly ranges from 62.7 to 72.3% (24), so the only reliable criteria for diagnosis of chest wall invasion with routine CT, actually, is bone destruction. Induced pneumothorax CT and the lack of relative movement between the chest wall and adjacent tumor during the respiration (at inspiratory/expiratory CT and US) have been employed for trying to detect chest wall invasion, but they resulted in augmented false positives. Although mediastinal invasion falls into T4 staging, minimal invasion of fat only is generally considered resettable by many surgeons. On the other hand, gross invasions of the mediastinal main organs is surely non resectable. Since in many cases it's difficult to differentiate between tumor abutment of a structure and actual invasion by CT, exams such as mediastinoscopy, trans-tracheal Wang needle biopsy and bronchoscopy might be used in doubt cases.

MR has the same limitations in evaluating mediastinal invasion, while transesophageal echocardiography could have a role in evaluating aortic invasion.

1.8. Pleural effusion: meanings and state of the art

Pleural effusion (PE) may be differentiated into benign and malignant pleural effusion. The benign pleural effusion should be infectious derived or not, and the difference between the transudate and exudate is defined by the Light criteria (serum LDH > 200UI/L, pleural fluid LDH/serum LDH > 0.6, pleural fluid proteins/serum protein > 0.5 for the exudate) (28).

Otherwise, malignant pleural effusion (MPE) is defined as detection of malignant cells in pleural exudate plus eventually in the parietal pleura, and its most common cause (40%) is lung cancer, which is also the cause of the shortest survival in MPE. However, a MPE in a patient with LC could be both cancer-derived or not malignant (such as a post obstructive pneumonia or postoperative effusion) (29). MPE is usually symptomatic, whereas the most frequent symptoms are shortness of breath (71%), cough (57%) and chest pain (53%), for the involvement of visceral pleura and other intercostal structures (28). Chest RX or CT are usually the first exams detecting the fluid accumulation, then a thoracentesis is performed for the cytology, and additional tests such as pleural biopsy and biomarkers can be performed to confirm the diagnosis (29). The treatment of MPE associated with LC (therapeutic thoracentesis, permanent pleural catheter and pleurodesis) is done in order to control symptoms and improve the quality of life. The treatment of stage IV LC (considered, by the 7th TNM edition, as a M1a descriptor) relies upon palliative chemotherapy (level of evidence IA if there is a sufficient performance status) plus radiotherapy (28).

Median survival time after the diagnosis of MPE from lung cancer ranges from 3 to 12 months, depending on the tumor's stage and the patient's performance score. Others prognostic factors are patient's age (> 65 years old or not), with discordance about its weight, the MPE coming out during only at the progression of the disease (better prognosis), or the luck of distant metastasis associated to MPE (better prognosis), or decreased serum LDH, decreased WBC count and other seric indicators (28).

1.9.Tumor microenvironment

Since they affect the prognosis and some of them can be used also for monitoring the response in case of neoadjuvant chemotherapy, some pathological variables are routinely assessed in NSCLC: the histological type of the tumor, invasiveness in case of adenocarcinoma (such as an in situ tumor), histological subtypes, the involvement of visceral pleura, the STAS, Spread Through Air Space, the lymphovascular invasion, the neuroendocrine differentiation (NE) and others (30). Moreover, the most common mutations are searched in order to identify the tumors benefiting from targeted therapy and immunotherapy, such as EGFR and its exons (18, 19, 20 and 21), kRAS, ALK and ROS1, for which crizotinib is employed, PD-L1 and PD-1, targetable by their inhibitors, Met, Ret, ROS1, BRAF, especially the V600E, leading to an activation of the MAPK pathway, TMB (Tumor Mutational Burden), microsatellite instability and MMR, Mismatch Repair-deficiency (with the last three identified by pathologists' reflex-testing) (31). According to the CAP/IASLC/AMP, the "must-test" genes are EGFR, ALK and ROS1, and if adequate quantity of tissue is available, an expanded panel (including BRAF, MET, ERBB2 HER2, KRAS and Ret) should be included. NCCN suggested to test all the advanced adenocarcinoma of the lung for EGFR, ALK, ROS1, and BRAF mutations, along with PD-L1 expression level; a strong recommendation is also put on the testing of MET, RET, ERBB2 and TMB, even if for this last one there is not a clear consensus on how to effectively measure it (31). A ctDNA assay can be used to identify EGFR mutations when the biopsied tissue is limited (according to CAP/IASLC/AMP and ASCO) or in case of medical unfitness for invasive biopsy (by the NCCN) (31). These molecular mutations could be both tested with the use of NGS Next Generation Sequencing (giving the precise sequence of base of the genome as an output) when tumor nuclei are at least 20% of the total number, or IHC immunohistochemistry array staining (uplighting a pre-defined specific sequence recognized by tailor-made anticorps, which, on turns, light up through a macroscopic chemical reaction). However, NCCN does not endorse specific testing modalities or techniques for biomarker tests (31).

Among microscopical variables, pleural invasion deserves particular attention.

The pleura is a serous membrane (mesothelium, made up of squamous cells supported by connective tissue) that folds back on itself to form a two-layered membranous pleural sac, with the outer layer named "parietal pleura" which is attached to the chest wall, the inner layer called "visceral pleura" closely related to the surface of lung parenchyma (apart for two recesses), and the pleural serous fluid between the two layers allowing the sliding of the two membranes during inflation and the surface tension for the expansion (20). Visceral pleura covers the outer surface of the lungs, and extends into the interlobar fissures, through which the lymph is drained (32), whereas it is continuous with the parietal pleura at the hilum of each lung (33), as visibile in Figure 3. There is no anatomical connection between the right and left pleural cavities, and the central compartment called mediastinum. The pleura is histologically composed of continuous elastic fibers, thin layers of fibrous tissue rich in lymphatic networks, and mesenchymal cells located in the basement membrane (34).

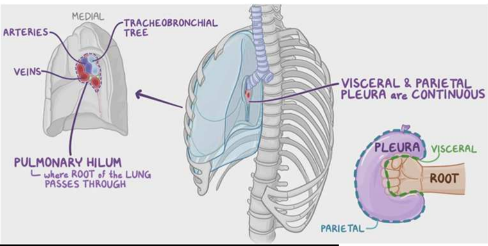

Figure 3 Pleural reflexion

Table III Upstaging of VPI T1 to T2 in the 8th and 9th TNM edition

TNM 9th edition			
Tx	Tumor in sputum/bronchial washings not assessed in imaging/scopy	Nx	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
Tis	Carcinoma in situ	N1	• Ipsilateral peribronchial and/or • Ipsilateral hilar and/or • Intrapulmonary lymph nodes, including involvement by direct extension
T1	• ≤ 3 cm, surround by lung/visceral pleura, or in lobar or peripheral bronchus • T1mi Minimally invasive adenocarcinoma • T1a ≤ 1 cm • T1b >1 cm but ≤ 2 cm • T1c >2 cm but ≤ 3 cm	N2	• Metastasis in ipsilateral mediastinal /subcarinal nodes • N2a Single N2 station involvement • N2b Multiple N2 station involvement
T2	• T2a > 3cm but ≤ 4cm • or invasion of main bronchus without carina or invasion visceral pleura, transgression fissure, invading adjacent lobe • Atelectasis or obstructive pneumonitis extending to the hilum • T2b >4 cm but ≤ 5 cm	N3	Contralateral mediastinal/hilar, ipsilateral/contralateral scalene or supraclavicular
T3	• >5 cm but ≤ 7 cm • or invasion parietal pleura, chest wall, pericardium, phrenic nerve, azygos vein, thoracic nerve roots (T1, T2) or stellate ganglion • or separate nodules in same lobe	M0	No distant metastasis
T4	• > 7 cm • or invasion mediastinum, thymus, trachea, carina, recurrent laryngeal nerve, vagus nerve, esophagus, diaphragm • or invasion heart, great vessels, intrapericardial pulmonary arteries/veins, supra-aortic arteries, brachiocephalic veins, subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, brachial plexus. • or separate nodules in different ipsilateral lobe	M1	• Distant metastasis • M1a Pleural or pericardial nodules or malignant pleural or pericardial effusions Separate tumor nodule(s) in contralateral lobe • M1b Single extrathoracic metastasis in a single organ system • M1c1 Multiple extrathoracic metastases in a single organ • M1c2 Multiple extrathoracic metastases in multiple organs

The degree of visceral pleural invasion (VPI) in lung cancer has been divided into PL0, PL1 and PL2, with PL0 defined by the IASLC as tumor growth till an incomplete penetration of the elastic layer, PL1 as invasion beyond the elastic layer and PL2 on the pleural surface (34). As it will be subsequently discussed in the present study, positivity for visceral pleura invasion causes the staging upgrading of a tumor of <3 cm (otherwise staged as T1) to T2 with the evolution from the 7th to the 8th edition of TNM (as visible in Table III).

1.10. Treatment

Treatment varies based on the patient's functional status, comorbidities, tumor stage, and molecular characteristics of the disease. Patients who have stage I, II, or III NSCLC are treated with surgery (generally lobectomy) first, and then a combined modality with chemotherapy or radiation therapy can be chosen after the pathologic staging.

The wall invasion does not preclude surgical resection (19) because an en bloc resection can be associated with chest wall reconstruction, at the condition there are no mediastinal lymph nodes metastasis (19,20). For this reason, in case of pathologic stage from IIB, adjuvant chemotherapy is indicated. In case of findings of positive margins, postoperative radiation or re- resection followed by adjuvant chemotherapy may be required.

If the patient is a clinical-stage I or II and deemed not a surgical candidate, then treatment would focus on stereotactic body radiation therapy (SBRT) or definitive RT.

Clinical stage III would indicate a multidisciplinary approach to treatment that would include consultation with medical oncology, radiation oncology, and thoracic surgery to decide on the optimal combined approach to the disease process.

It is important for tissue biopsy to be analyzed for targetable mutations, which can aid in the treatment of patients with stage IV NSCLC, so when systemic therapy is necessary (which is the case of stage 4 or when distant metastasis are present). For example, if EGFR is positive, TKI such as osimertinib, erlotinib, gefitinib, or afatinib can be utilized in treatment. If the tumor contains ALK fusion oncogene, treatment with an ALK TKI is preferred, which can include alectinib, ceritinib, or brigatinib (35).

A variety of targetable mutations can also be found, as well as the level of PD-L1 expression should be quantified, and if greater than 50 percent, then pembrolizumab or atezolizumab may be utilized in the treatment plan (which sometimes include it singularly) (35).

1.11. Prognosis

The prognosis of NSCLC depends on the performance status/comorbidities of the patient (in particular patients with poor performance status have a shortened survival) and on the TNM staging, giving a 5-years OS of 6% in stage IV and 82% in IA, for instance (24).

Poor appetite, weight loss, LVI, metabolic activity on PET are also poor prognostic signs (35–38). On the contrary, patients with actionable mutations have been shown to have a better prognosis, both because they can be targeted, both because they are associated with more genetic and less environmental risk factors. For example, activating EGFR mutations are found in adenocarcinoma associated with never smokers, women, and/or Asian ethnicity and generally have a significantly better prognosis (35–39).

Recurrence after complete resection has been cited at 41 percent, with the median time to recurrence at 11.5 months and median survival of 8.1 months after it. Shorter survival depends on performance status, disease-free interval, the involvement of distant metastases, and prior use of neoadjuvant CT or adjuvant RT (35–40).

2. AIMS OF THE STUDY

The purpose of this study is to evaluate the role of visceral pleural invasion in a single cohort of patients resected with clinically determined stage I lung adenocarcinomas receiving either anatomical segmentectomy or lobectomy.

In particular, the aim of the study is to answer the following questions:

- Do visceral pleural invasion and its grades somehow affect oncological outcomes (overall survival or recurrence)?
- Has segmentectomy lower survival or recurrence (presence, DFS, localisation) than lobectomy?

3. MATERIALS AND METHODS

3.1. Study design

This is a monocentric retrospective cohort study on patients who underwent anatomical segmentectomy or lobectomy for NSCLC in the UOC of Thoracic surgery of the Azienda Ospedaliera Università di Padova between 2016 and 2021. The data analyzed come from paper and digital medical records searched with the software Galileo e-Health solutions, and, in case the data were missing, the field of the dataset collecting all the data was left empty. Moreover, if follow up were partial, having data till a certain period, the fields concerning free OS were left empty, thus counting into the total counting of months of live, only the months in which the patient was certainly alive (because after he/she has been at a medical visit). Basically, missing or incomplete columns were considered as if the patient was dead.

The inclusion criteria were:

4. NSCLC adenocarcinoma;
5. Patients undergoing lobectomy or segmentectomy in the considered timeline;
6. With clinical stage IA, IB, IIA and IIB (T size)
7. Lymph node dissection must be performed in a systematic or lobe-specific dissection way.

The exclusion criteria were:

8. Types of surgeries not being anatomical segmentectomy or lobectomy (such as wedge resections, sleeve resections- in which the two ends of the bronchus are rejoined after removing of the tumor- bi-lobectomy and pneumonectomy);
9. Tumors not having the lung primitiveness (metastasis) or being Small Cells Lung Cancers;
10. Tumors with N- status strictly bigger than 0 (so N1 and N2), with M status of 1 (presence of metastasis);
11. Patients having, at the time they are admitted to hospital staying, obstructive pneumonia, atelectasis, or infringement of adjacent structures or organs.

Included patients entered a spreadsheet in Microsoft Office Excel. The data collected were part of different fields which could be ascribed to one of the following categories: Personal data, Clinical data of the tumor, Data of the surgery, Data of the hospital staying and postoperative complications, Pathological and molecular data, and Oncological and survival data.

3.1.1. Personal data

In the preoperative category of data, anagraphical and clinical data of the patients have been considered. Some variables, such as height, weight, BMI, years of smoke, cigarettes per day, pack/year have been considered as continuous, whereas the nominal discrete ones were considered to have a qualitative and not sortable number of options, such as sex, smoking history and number and type of comorbidities. The last one, more deeply, were sex (male or female), and smoking history, whether they had never smoked (which means they have smoked less than 100 cigarettes in their lives), if they were previous smokers (which means that they had stopped the smoking activity from at least six months) or if they were current smokers. Through the collected data, it was possible to calculate the CCI, Charlson Comorbidity Index, with the online calculator MDCalc available at the URL https://www.mdcalc.com/charlson-comorbidity-index-cci, obtaining as results ordinal qualitative variables.

3.1.2. Clinical data of the tumor

Patients also underwent imaging exams, such as CT scan and PET or PET-CT, in order to assess the eventual presence of distant metastasis and the involvement of lymph nodes in the hilar and mediastinal stations of the lung.

The collected data, useful also for the clinical TNM assignment (so the stadiation) and the planning of the surgical operation, were the presence of multiple primary lesions (and which lobes and segments were affected), whether the main lesion included, within it, GGO components (so not solid, ground-glass opacities) for more than 50% of the diameter, the maximum diameter of the total size and of the solid component of the main lesion (in mm), the mean value of density (in H.U.) at enhanced CT scan. Moreover, a confirmation field that brain CT (or MRI) and PET scan of the whole body were checked, and, in case of positivity, whether metastasis were present, and the value of maximum SUV of the main lesion at the PET scan (which refers to the biological activity of the cancer). After that, the clinical T, N and M stages were defined, with the cN and cM stages evidently equal to zero (in order to consent the inclusion of the patients in the study), whereas the T could vary from T1a to T3, thus being one of the main criteria to decide which treatment had to be assigned to that specific patient. As a consequence, according to the T status, the staging was ranked from IA to IIB, passing for IB and IIA, as already mentioned.

Instead, they were not considered, in this part of the database, histological data coming from the pre-surgical biopsy, thus not influencing the decision for which type of surgery was the best option.

3.1.3. Intraoperative data

Collected intraoperative data were whether the intention of the surgery was intentional or compromised, the date of the intervention and the surgical approach, which was, of first intention, VATS technique (whereas RATS, Robot-Assisted, and thoracotomy were not used in first intention). Collected statistics were also on the duration of the surgery, whether there was a conversion to open thoracotomy or from segmentectomy to lobectomy, and which of the last two techniques was used. It was also specified whether the patient was dead within 30 and 90 days and whether the patient was re-operated. Data on the number of segments removed, or the type of segmentectomy (anatomical versus wedge resection), the laterality of the intervention, the localization of the neoplasia (if peripheral or central) were not collected instead.

3.1.4. Data of the hospital staying and postoperative complications

Variables about post-operative complications were analyzed, referring to their presence and number during hospital stay: some examples were diuresis restriction, hypokalemia, FA, BBDx, pneumothorax, dyspnea, respiratory failure, dysphonia and air leakage in spontaneous breath. Perioperative complications were evaluated too, and some examples were the most frequent types of arrhythmia (such as atrial fibrillation, atrial flutter, ventricular arrhythmia), myocardial ischemia/infarction, bronchopleural fistula, respiratory failure, atelectasis, pulmonary air leakage (defined as prolonged air loss for more than 5 days from the thoracic drainage), phrenic nerve paralysis (marked by diaphragm elevation), thrombosis or embolism and others were considered. The necessity for poly transfusions, the length of the hospital stay, the duration and total volume of chest drainage and whether there was a reinsertion of a second chest drainage (and, in case of positive response, the reason) were evaluated too. Moreover, among the variables extracted from the medical records, they have not been analyzed whether there was necessity for oxygen administration and if the thoracic pain was still present at the demission, and the Ottawa score, which is a score made for evaluating the risk of recurrence of venous thromboembolism associated with cancer in the first six months after the intervention, in order to correctly empower anticoagulant therapy (for example, Aurélien Delluc, Sébastien Miranda et All. suggested that in case of low risk, oral anticoagulants could be useful (41)).

In conclusion, complications have been evaluated throughout medical records and ambulatory controls, of which the long term ones follow the NCCN guidelines (so the second follow-up at 3 months from the intervention, then after 6 months for the first two years and then annually for 3 years).

3.1.5. Pathological and molecular data

For each patient, they were collected the histology type of the tumor (which should have been adenocarcinoma), its invasiveness (among invasive adenocarcinoma, AAH, AIS and MIA, resulting in an intraoperative confirmation of eligibility) and, in case of the presence of more than one subtype, the second more frequent histology (between lepidic, papillary, acinar, micropapillary, solid, mucinous and other to be specified) and the maximum tumor diameter. Other prognostically valuable information were the involvement of visceral pleura, (between p0, p1 and p2) and the presence of "Spread through air space" STAS or not. STAS (Spread Through Air Space) is a pathological microscopic variable which has been characterized as micropapillary clusters, solid networks, or single cells extending into the air spaces beyond the tumor edge (with singular cells or more histologic types). From 2015 this parameter is considered to be prognostically valuable, thus being recently investigated by Padova group (42) in terms of its prognosis as survival and DFS. From this work, it came out that it does not significantly change the prognosis of localised tumors (both as OS and DFS) when turning from negative to positive. On the contrary, a related variable, vascular invasion VI, which is the crossing of the muscular middle tunic of the arteries, worsens the prognosis, even if with differences according to the intra or extra tumoral location of the vessels (42). For this reason, the presence of lymphovascular invasion was traced to, as well as the number of lymph nodes dissected or biopsied and the number of stations from which they came (both for mediastinal N2, and for hilar/lobar/intrapulmonary N1). The pathologic stage in terms of T (between Ia, Ib, Ic, IIa and IIb), N and M was assessed too, with the N stage that, in case of majority to 0, was reported with the number of the lymph nodal station (starting from 14 from the intralobar stations and going up along the bronchial tree). Other prognostically relevant specifications were evaluated, such as the "R" (which stands for the degree of invasion of the surgical margins of the specimen, between R0, R1, R2 and uncertain), beyond the minimum distance from the parenchymal margin and from the hilar margin. Mutations such as EGFR (and which exons are affected between 18, 19, 20, 21), kRAS, ALK, PD-L1, Met, Ret and ROS1 were detected, and the assignment of adjuvant therapies was checked out too.

3.1.6. Oncological and survival data

Oncological and survival data regarded the presence of a recurrence or not, and, in the affirmative case, in which site (local, mediastinal lymph nodes, systemic, or at the thorax plus systemic), after how much time (DFS) and which treatment was administered for it. In case the patient had not a recurrence, they were indicated the months in which it was sure a recurrence had not occurred. Moreover, the date of death, which was the cause and the time passed from the surgery were specified (whether known). The last field is the overall survival (in months). In case it was not known the date of death, in this field it was inserted the number of months in which it was sure the patient was still alive, for instance for the presence of a medical ambulatory visit within the Azienda Ospedaliera Università di Padova, even if for other reasons than the lung cancer. Other variables were the follow-up, in months, and, as a consequence, the 1, 3, and 5 years of survival.

It must be noted that, for the last field of years of survival, for the data of the last patients undergoing surgery, so that ones of the 2021, and almost all the patients operated in 2020, the 5 years survival could not be reached, since less than 5 years have passed from the date of the intervention till now. For this reason, for these patients the last column was left empty. The same happened for the patients who did not do a medical visit before five years after the intervention, thus not giving the certitude of their viability at the 5-years follow-up. In this specific case, so in case of doubt between effective death or simply not presentation to any of the following follow-up, or absence of any other disease justifying the return to the hospital, or, as an example, change of residency, the next boxes in the line (regarding the years of follow-up) were left empty.

3.2. Statistical analysis

Continuous variables were described using the median and interquartile range, while the absolute number and percentage frequency were reported for categorical variables. Statistical comparisons between groups were performed using the Wilcoxon rank sum test, Pearson $\chi 2$ test and Fisher's exact test, where appropriate. Survival analysis for overall survival (OS) was conducted using the Kaplan-Meier estimator. The Log-rank test was used to compare survival curves. In addition, the relationship between the variables and OS was examined using the univariable Cox model. The level of statistical significance was set at $p \leq 0.05$.

The disease recurrence has been calculated with the cumulative incidence function.

The analysis has been performed using R Statistical Software.

4. RESULTS

4.1. Personal data

In total, 55 patients (20.60% of the total) underwent segmentectomy, whereas 212 (79.40%) underwent lobectomy; females were slightly more than male patients (53.56%), the average BMI was 25.7, so slightly on overweight, with the I and III IQ of 22.7 and 28.2. Regarding the smoking history, almost 55% of the patients were current smokers at the time of surgery, 17% were previous smokers and 28% had never smoked, with the average amount of 10 cigarettes, for 29 years on average. Of the total number of patients, none had ever been operated on at the chest, whereas, on the contrary, only one had no comorbidities. Also the number of comorbidities per person was pretty high, with 230 (out of 267 patients) having at least two comorbidities (in which they were counted also familiar and personal history for cancers and lung cancers, and surgical treatments received during the life), and 160 having at least five comorbidities. The CCI was 4 on average (QI: 3, 5), of the 252 patients with collected preoperative FEV1, the average value was 2.29 (QI: 1.78, 2.85), for FVC 2.86 (QI: 2.34, 3.60), and that of DLCO, collected for 246 patients, 13 (QI: 6, 20).

Regarding data stratified according to the type of treatment, it must be noted that, among the years from 2016 to 2021, those considered in this study, the tendency was an increase in the use of segmentectomy, more than lobectomy. According to the sex, 18% of the males received segmentectomy, against 22% of the females. Among segmentectomy, there were more currently smoking patients than in the lobectomy group (72.73% against 50.00%, respectively), whereas similar percentages of patients who had never smoked were found between the two groups. In the segmentectomy group were included patients having smoked the same amount of cigarettes but for more years (32 vs 25), thus resulting in an higher pack/year (25 vs 13). The CCI was higher among segmentectomies (5 vs 4), whereas functional preoperative volumes were slightly inferior in the segmentectomy group, even though with high p-values, as visible in Tables IV and V.

Table IV Statistical explorative analysis on the clinics

Characteristics	Values	N	Value
Grouping	Segmentectomy	55	55 (20.60%)
	Lobectomy	212	212 (79.40%)
Year of the surgery	2016	37	37 (13.86%)
	2017	47	47 (17.60%)
	2018	38	38 (14.23%)
	2019	46	46 (17.23%)
	2020	50	50 (18.73%)
	2021	49	49 (18.35%)
Gender	Female	143	143 (53.56%)
	Male	124	124 (46.44%)
Height		267	166 (160, 172)
Weight		267	70 (61, 80)
BMI		267	25.7 (22.7, 28.2)
Smoking history	never	75	75 (28.09%)
	previous smoker (stopped for more than 1 year)	46	46 (17.23%)
	Current smoker	146	146 (54.68%)
Cigarettes per day		231	10 (0, 20)
	Unknown	36	
Years of smoking		248	29 (0, 45)
	Unknown	19	
Smoking amount (pack/year)		224	14 (0, 40)
	Unknown	43	
Comorbidities	Yes	265	265 (99.62%)
	No	1	1 (0.38%)
	Unknown	1	
Number of comorbidities	At least 1	265	
	At least 2	261	
	At least 3	246	
	At least 4	230	
	At least 5	191	
Charlson comorbidity index cci		267	4.00 (3.00, 5.00)
FEV1	measured value	252	2.29 (1.78, 2.85)
	Unknown	15	
Measured FEV1 on predicted FEV1		71	100 (86, 112)
	Unknown	196	
FVC	measured value	251	2.86 (2.34, 3.60)
	Unknown	16	
		73	100 (92, 116)

Measured FVC on predicted FVC	Unknown	194	
DLCO	measured value	246	13 (6, 20)
	Unknown	21	
Measured DLCO on predicted DLCO (%)		71	79 (69, 93)
	Unknown	196	

Table V Inferential statistics on the clinics and general information

Characteristics	Values	N	Segmentectomy (N=55)	Lobectomy (N=212)	p-value
Year of the surgery	2016	267	5 (9.09%)	32 (15.09%)	<0.001
	2017		1 (1.82%)	46 (21.70%)	
	2018		7 (12.73%)	31 (14.62%)	
	2019		9 (16.36%)	37 (17.45%)	
	2020		18 (32.73%)	32 (15.09%)	
	2021		15 (27.27%)	34 (16.04%)	
Gender	Female	267	32 (58.18%)	111 (52.36%)	0.4
	Male		23 (41.82%)	101 (47.64%)	
Height		267	166 (161, 172)	166 (159, 172)	0.8
Weight		267	70 (61, 80)	70 (61, 80)	0.7
BMI		267	24.8 (22.8, 28.0)	25.7 (22.6, 28.1)	0.5
Smoking History	Never	267	14 (25.45%)	61 (28.77%)	<0.001
	Previous smoker (stopped for more than 1 year)		1 (1.82%)	45 (21.23%)	
	Current smoker		40 (72.73%)	106 (50.00%)	
Cigarettes per day		231	10 (0, 20)	10 (0, 20)	0.8
	Unknown	36	6	30	
Years of smoking		248	32 (0, 47)	25 (0, 44)	0.5
	Unknown	19	2	17	
Smocking amount (pack/year)		224	25 (0, 46)	13 (0, 38)	0.5
	Unknown	43	7	36	
Previous chest surgery		267	0 (0.00%)	0 (0.00%)	>0.9
Comorbidities	No comorbidities	1	1 (1.82%)	0 (0.00%)	0.2
	Comorbidities	265	54 (98.18%)	211 (100.00%)	
	Unknown	1	0	1	
Number of comorbidities	At least 1	261			
	At least 2	246			

	At least 3	230			
	At least 4	191			
	At least 5	156			
Charlson comorbidity index CCI		267	5.00 (4.00, 6.00)	4.00 (3.00, 5.00)	<0.001
FEV1	measured value	252	2.16 (1.89, 2.92)	2.29 (1.76, 2.83)	0.5
	Unknown	15	0	15	
Measured FEV1 on predicted FEV1		71	103 (96, 113)	99 (86, 110)	0.5
	Unknown	196	36	160	
FVC	measured value	251	2.83 (2.46, 3.80)	2.88 (2.28, 3.55)	0.2
	Unknown	16	1	15	
Measured FVC on predicted FVC		73	104 (90, 117)	99 (92, 114)	0.6
	Unknown	194	35	159	
DLCO	measured value	246	18 (15, 22)	9 (5, 18)	<0.001
	Unknown	21	1	20	
Measured DLCO on predicted DLCO (%)		71	85 (77, 95)	77 (65, 89)	0.14
	Unknown	196	35	161	

4.2. Clinical data of the tumor

For what it concerns the clinical data, almost 10% of the patients had multiple primary lesions, especially in the segmentectomy group (more than 18% of the segmentectomies, against 7% of the lobectomies); the lobes mostly interested were the upper lobes (left and right), and tumors especially had no GGO components (almost 68%), without significant differences among the two treatment groups and a p=0.7. The maximum radiological size was 20 cm (QI: 15, 25) and with bigger dimensions in the lobectomy group (16 vs 20 cm, with a statistically significant p-value <0.001), with the majority of the patients being 1b and 1c (the 1c especially for lobectomies), and staged IB (more than 40%) and IA2 (29%), without differences of prognostic stage between the two methods and a p-value=0.008. The mean CT value in HU was 71 (QI: 39, 99), being slightly inferior in segmentectomy than in lobectomy, whereas, at the PET, no tumor had metastasis (nor at MRI in the brain, nor in the whole body), and the maximum SUV was in median of 3.9 (QI: 2.4, 6.4), even with statistically significant differences among the two groups of 4.2 vs 2.9 (p-value <0.001).

4.3. Intraoperative data

As visible in Table VI, the surgery was mainly intentional (in almost 92%) rather than compromised, and the VATS was the unique used approach. The average time of an operation is 120 minutes, with 115 minutes for a segmentectomy and 125 for the other approach; the conversion to open thoracotomy was done only twice, due to fibrosis, and conversion on a segmentectomy to lobectomy never occurred. The segmental plane methods were always a combination of stapler and energy devices, the measures for air-leakage prevention were always unattended, the number of drainage tubes was always one, and lymph nodes were always dissected systematically.

Table VI Preoperative data and perioperative complications

cT stage	1a	24	24 (8.99%)
	1b	120	120 (44.94%)
	1c	123	123 (46.07%)
cN stage	0	267	267 (100.00%)
cM stage	0	267	267 (100.00%)
Clinical staging	IA1	49	49 (18.99%)
	IA2	74	74 (28.68%)
	IA3	16	16 (6.20%)
	IB	104	104 (40.31%)
	IIA	3	3 (1.16%)
	IIB	12	12 (4.65%)
	Unknown	7	
Intention of surgery	Intentional	245	245 (91.76%)
	Compromised	22	22 (8.24%)
Surgery approach	VATS	267	267 (100.00%)
Operation time		265	120 (90, 150)
	Unknown	2	
Conversion to open thoracotomy	Yes	2	2 (0.75%)
	No	265	265 (99.25%)
Conversion from segmentectomy to lobectomy	Yes	0	0 (0.00%)
	No	267	267 (100.00%)

Mortality 30 day	Yes	266	266 (99.63%)
	No	1	1 (0.37%)
Mortality 90 day	Yes	2	2 (0.75%)
	No	265	265 (99.25%)
Unplanned reoperation after surgery	Yes	1	1 (0.37%)
	No	266	266 (99.63%)
Re admission	Yes	4	4 (1.50%)
	No	263	263 (98.50%)
Length of hospital stays		266	7.0 (5.3, 9.0)
	Unknown	1	
Duration of chest drain		265	3.00 (2.00, 4.00)
	Unknown	2	
Total volume of chest drainage		264	750 (350, 1,200)
	Unknown	3	
Reinsertion of chestdrain	Yes	8	8 (3.02%)
	No	257	257 (96.98%)
	Unknown	2	
Reason	apical left pneumothorax	1	1 (12.50%)
	depositioning of TD	1	1 (12.50%)
	heavy loss	1	1 (12.50%)
	idrothorax right base	1	1 (12.50%)
	malfunction	1	1 (12.50%)
	pneumothorax	3	3 (37.50%)
Complications	No	162	162 (60.90%)
	Yes	104	104 (39.10%)
	Unknown	1	
Number of complications	0	161	161 (60.30%)
	1	64	64 (23.97%)
	2	24	24 (8.99%)
	3	10	10 (3.75%)
	4	2	2 (0.75%)
	5	4	4 (1.50%)
	6	2	2 (0.75%)

Perioperative complications	Any arrhythmia	24	24 (9.02%)
	Atrial fibrillation	21	21 (7.89%)
	Atrial flutter	1	1 (0.38%)
	Atrial tachycardia paroxysous atrial tachycardia	4	4 (1.50%)
	Sinus bradycardia	1	1 (0.38%)
	Ventricular arrhythmia	3	3 (1.13%)
	Pulmonary air leakage	17	17 (6.39%)
	Recurrent laryngeal nerve palsy	3	3 (1.13%)

4.4. Data of the hospital staying and postoperative complications

The median length of hospital stay was 7 days (QI: 5.3, 9.0) on average, but of 6 days for segmentectomy, with 3 days in which the chest drainage was held, a total evacuated volume of 750 ml (with higher volumes in lobectomy) and its reinsertion in 8 cases (all in lobectomy group), due mainly to pneumothorax. Perioperative complications occurred in 40% of the patients, with higher percentages and higher numbers of complications in the lobectomy group (in 86 patients receiving lobectomy, thus 40.57% of the patients receiving this treatment, versus 18 patients, 33.33%, of those receiving segmentectomy, p-value =0.3). Complications were mainly cardiovascular and respiratory (17 patients with air leakage, 24 with arrhythmia, of which 21 with atrial fibrillation).

Only one patient died within 30 days after surgery, and another one within 90 days (one for pulmonary embolism, while the other for a multi organ failure due to a sepsis, both in the lobectomy group); instead, only one patient was re-operated, due to bleeding, and 4 (1.89%, p-value= 0.6) were readmitted at the hospital, of which one because of atrial fibrillation, and all of them in the lobectomy group, as visible in Table VII.

Table VII Inferential statistics on radiological characteristics and post-operative complications

Characteristics	Values	N	Segmentectomy (N=55)	Lobectomy (N=212)	p-value
Multiple primary lesions	No	238	44 (81.48%)	194 (92.82%)	0.011
	Yes	25	10 (18.52%)	15 (7.18%)	
	Unknown	4	1	3	
Which lobe the main lesion is located	RUL	92	13 (23.64%)	79 (37.26%)	0.002
	RML	18	0 (0.00%)	18 (8.49%)	
	RLL	37	6 (10.91%)	31 (14.62%)	
	LUL	88	23 (41.82%)	65 (30.66%)	
	LLL	32	13 (23.64%)	19 (8.96%)	
Which segment the main lesion is located	1	15	15 (27.27%)	0 (0.00%)	<0.001
	2	36	22 (40.00%)	14 (6.60%)	
	3	79	14 (25.45%)	65 (30.66%)	
	4	23	4 (7.27%)	19 (8.96%)	
	5	114	0 (0.00%)	114 (53.77%)	
Presence of GGO components in the main lesion	No	181	36 (65.45%)	145 (68.40%)	0.7
	Yes	86	19 (34.55%)	67 (31.60%)	
Maximum diameter of the total size of the main lesion		259	16 (12, 21)	20 (16, 25)	<0.001
	Unknown	8	1	7	
Maximum diameter of the solid component size of the main lesion		267	17 (13, 24)	20 (16, 25)	0.013
Mean ct value of the total main lesion at its maximum diameter		175	69 (42, 96)	74 (37, 99)	>0.9
	Unknown	92	12	80	
Brain CT or MRI	no metastasis	267	55 (100.00%)	212 (100.00%)	>0.9
Pet scan of the whole body	no metastasis	267	55 (100.00%)	212 (100.00%)	>0.9
SUVmax of the main lesion on PET scan		248	2.9 (1.3, 4.2)	4.2 (2.7, 7.0)	<0.001
	Unknown	19	0	19	
Clinical T stage	1a	24	11 (20.00%)	13 (6.13%)	0.008
	1b	120	24 (43.64%)	96 (45.28%)	
	1c	123	20 (36.36%)	103 (48.58%)	

Clinical N stage	0	267	55 (100.00%)	212 (100.00%)	
Clinical M stage	0	267	55 (100.00%)	212 (100.00%)	
Clinical staging	IA1	49	10 (18.52%)	39 (19.12%)	>0.9
	IA2	74	16 (29.63%)	58 (28.43%)	
	IA3	16	4 (7.41%)	12 (5.88%)	
	IB	104	22 (40.74%)	82 (40.20%)	
	IIA	3	0 (0.00%)	3 (1.47%)	
	IIB	12	2 (3.70%)	10 (4.90%)	
	Unknown	9	1	8	
Intention of surgery	Intentional	245	51 (92.73%)	194 (91.51%)	>0.9
	Compromised	22	4 (7.27%)	18 (8.49%)	
Operation time		265	115 (85, 149)	125 (95, 155)	0.10
	Unknown	2	1	1	
Conversion to open thoracotomy	No	265	55 (100.00%)	210 (99.06%)	>0.9
	Yes	2	0 (0.00%)	2 (0.94%)	
Mortality 30 day	No	266	55 (100.00%)	211 (99.53%)	>0.9
	Yes	1	0 (0.00%)	1 (0.47%)	
Mortality 90 day	No	265	55 (100.00%)	210 (99.06%)	>0.9
	Yes	2	0 (0.00%)	2 (0.94%)	
Cause of death	Pulmonary Embolism	1	0 (NA%)	1 (50.00%)	>0.9
	Sepsis	1	0 (NA%)	1 (50.00%)	
Unplanned reoperation after surgery	No	266	55 (100.00%)	211 (99.53%)	>0.9
	Yes	1	0 (0.00%)	1 (0.47%)	
Re admission	No	263	55 (100.00%)	208 (98.11%)	0.6
	Yes	4	0 (0.00%)	4 (1.89%)	
Length of hospital stays		266	6.0 (5.0, 9.0)	7.0 (6.0, 9.0)	0.4
	Unknown	1	0	1	
Duration of chest drain		265	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.3
Total volume of chest drainage		264	540 (293, 798)	800 (420, 1,345)	0.002
	Unknown	3	1	2	
Reinsertion of chestdrain	No	257	54 (100.00%)	203 (96.21%)	0.4
	Yes	8	0 (0.00%)	8 (3.79%)	
	Unknown	2	1	1	

Reason of re-insertion of thoracic drainage	apical left pneumothorax	1	0 (NA%)	1 (12.50%)	>0.9
	depositioning of TD	1	0 (NA%)	1 (12.50%)	
	heavy loss	1	0 (NA%)	1 (12.50%)	
	idrothorax right base	1	0 (NA%)	1 (12.50%)	
	malfunction	1	0 (NA%)	1 (12.50%)	
	pneumothorax	3	0 (NA%)	3 (37.50%)	
Complications	No	162	36 (66.67%)	126 (59.43%)	0.3
	Yes	104	18 (33.33%)	86 (40.57%)	
	Unknown	1	1	0	
Number of perioperative complications	0	161	36 (65.45%)	125 (58.96%)	0.4
	1	64	15 (27.27%)	49 (23.11%)	
	2	24	2 (3.64%)	22 (10.38%)	
	3	10	1 (1.82%)	9 (4.25%)	
	4	2	1 (1.82%)	1 (0.47%)	
	5	4	0 (0.00%)	4 (1.89%)	
	6	2	0 (0.00%)	2 (0.94%)	
Perioperative complications	Any arrhythmia	24	2 (3.70%)	22 (10.38%)	0.2
	Atrial fibrillation	21	2 (3.70%)	19 (8.96%)	0.3
	Atrial flutter	1	0 (0.00%)	1 (0.47%)	>0.9
	Atrial tachycardia paroxystic atrial tachycardia	4	1 (1.85%)	3 (1.42%)	>0.9
	Sinus bradycardia	1	0 (0.00%)	1 (0.47%)	>0.9

	Ventricula r arrhythmi a	3	0 (0.00%)	3 (1.42%)	>0.9
	Pulmonary air leakage	17	1 (1.85%)	16 (7.55%)	0.2
	Recurrent laryngeal nerve palsy	3	0 (0.00%)	3 (1.42%)	>0.9
	Unknown	1	1	0	

4.5. Pathological and molecular data

The histological subtype was always that of an invasive adenocarcinoma (IAC), especially acinar or, as a second histological subtype, lepidic, and the diameter was similar to that one found with radiological exams (20, QI: 15, 25). Regarding the visceral pleura invasion, 51.03% of the 243 patients with this field determined were PL1, 43.21% PL0, and 5.76% PL2, but the two degree of pleural invasion, 1 and 2, were joined in the statistical analysis as the new field "PL", which means that there is a certain degree of pleural invasion. In this way, PL positives accomplish 56.79% of the total patients, with a p-value =0.084. Lymphovascular invasion was not present in 76.98% of the 265 patients for whom this feature was determined, whereas in more than 23% there was LVI. Regarding the biopsied/dissected lymph nodes, the mediastinal N2 dissected stations were 4.00 on average (QI: 3.00, 4.00), and the lymph nodes were 5.0 (QI: 3.0, 7.0). Instead, N1 dissected stations were 4.00 on average (QI: 3.00, 5.00), and the lymph nodes were 7.0 (QI: 5.0, 11.0). Of the 261 patients being staged, 39.46% were pT2a, 34.48% pT1b, followed by 18.39% of pT1a, 6.90 of pT1c and 2 patients (0.77%) of pT2b. Instead, unlike the preoperative staging, pN was different from zero (94.01%, 251 patients) for 7 patients being pN1 and 9 patients being pN2; however, the pM was always zero. As a result of the pathological variables and the presence of VPI, with a p-value >0.9, staging was I (Ia or Ib) in 139 patients (52.26%), IIa for 107 patients (40.23%), IIb for 12 patients (4.51%) and IIIa for 8 patients (3.01%). For the resection, only two specimens were R1 (microscopically involved stapled line), whereas all the others were R0; the minimum distance from the parenchymal margin was 10 mm (QI: 2, 25) for the 192 patients with this result in the pathological report, and the distance from the ilar margin was 28 mm (QI: 16, 40).

Concerning the mutations, PDL-1 and EGFR were fairly the principal, as visible in Table VIII and Table IX, with 61 patients presenting a PDL-1 activation (almost 1%), 34 with at least the mutation of one of the exons of EGFR (31% of the specimens for which the mutational status was known), 8 patients with ALK mutation (7.41%), and 5 with that of ROS1 (4.63%). Regarding the type of exons mutated, 12.94% of the 255 patients with the EGFR field completed had a mutation of the exon 19, 9.02% of the exon 21, 4 patients of the exon 18, and 3 of the exon 20.

Adjuvant therapies were administered in 24 patients, mainly consisting of chemotherapy (33.33%), TKI (25%), and radiotherapy (16.67%).

Table VIII Statistical explorative analysis on the anatomopathological characteristics

Characteristics	Values	N	Value
Histology in case of adenocarcinoma	AHH	0	0 (0.00%)
	AIS	0	0 (0.00%)
	MIA	0	0 (0.00%)
	IAC	267	267 (100.00%)
Predominant histological subtype in case of adenocarcinoma	Lepidic	31	31 (12.11%)
	Papillary	12	12 (4.69%)
	Acinar	197	197 (76.95%)
	Micropapillary	0	0 (0.00%)
	Solid	15	15 (5.86%)
	Mucinous	0	0 (0.00%)
	Others	1	1 (0.39%)
	Unknown	11	11
Other histological subtypes in case of adenocarcinoma	Lepidic	75	75 (39.47%)
	Papillary	31	31 (16.32%)
	Acinar	40	40 (21.05%)
	Micropapillary	12	12 (6.32%)
	Solid	32	32 (16.84%)
	Mucinous	0	0 (0.00%)
	Others (specify)	0	0 (0.00%)
	Unknown	77	77

Involvement of the visceral pleura	p0	105	105 (43.21%)
	p1	124	124 (51.03%)
	p2	14	14 (5.76%)
	Unknown	24	24
Lymphovascular invasion	No	204	204 (76.98%)
	Yes	61	61 (23.02%)
	Unknown	2	2
N2 dissected stations		261	4.00 (3.00, 4.00)
N2 dissected lymph nodes		266	5.0 (3.0, 7.0)
N1 dissected stations		262	4.00 (3.00, 5.00)
N1 dissected lymph nodes		261	7.0 (5.0, 11.0)
pT stage	1a	48	48 (18.39%)
	1b	90	90 (34.48%)
	1c	18	18 (6.90%)
	2a	103	103 (39.46%)
	2b	2	2 (0.77%)
	Unknown	6	6
pN stage	0	251	251 (94.01%)
	1	7	7 (2.62%)
	2	9	9 (3.37%)
pM stage	0	267	267
Pathology staging	Ia or Ib	139	139 (52.26%)
	IIa	107	107 (40.23%)
	IIb	12	12 (4.51%)
	IIIa	8	8 (3.01%)
	Unknown	1	1
R status	r0	265	265 (99.25%)
	r1	2	2 (0.75%)
	r2	0	0 (0.00%)
	r uncertain	0	0 (0.00%)
Parenchimal margin distance minimun		192	10 (2, 25)
	Unknown	75	
Ilar margin distance		188	28 (16, 40)
	Unknown	79	
Mutations	EGFR	34	34 (31.48%)
	EGFR exon 18	4	4 (1.57%)
	EGFR exon 19	33	33 (12.94%)
	EGFR exon 20	3	3 (1.18%)

	EGFR exon 21	23	23 (9.02%)
	k-Ras	0	0 (0.00%)
	ALK	8	8 (7.41%)
	PD-L1	61	61 (56.48%)
	Met	0	0 (0.00%)
	Ret	0	0 (0.00%)
	ROS1	5	5 (4.63%)
	Unknown	159	159

Table IX Inferential statistical analysis on anatomopathological data

Characteristics	Values	N	Segmentectomy (N=55)	Lobectomy (N=212)	p-value
Maximum tumor diameter		242	15 (10, 18)	20 (15, 25)	<0.001
	Unknown	25	6	19	
Histology in case of adenocarcinoma	IAC	267	55 (100.00%)	212 (100.00%)	0.5
Predominant histological subtype in case of adenocarcinoma	Lepidic	31	7 (13.21%)	24 (11.82%)	
	Papillary		2 (3.77%)	10 (4.93%)	
	Acinar	197	41 (77.36%)	156 (76.85%)	
	Solid	15	2 (3.77%)	13 (6.40%)	
	Others (specify)	1	1 (1.89%)	0 (0.00%)	
	Unknown	11	2	9	
Other histological subtypes in case of adenocarcinoma	Lepidic	75	15 (39.47%)	60 (39.47%)	<0.001
	Papillary	31	14 (36.84%)	17 (11.18%)	
	Acinar	40	7 (18.42%)	33 (21.71%)	
	Micropapillary	12	1 (2.63%)	11 (7.24%)	
	Solid	32	1 (2.63%)	31 (20.39%)	
	Unknown	77	17	60	
Involvement of the visceral pleura	0	105	30 (55.56%)	75 (39.68%)	**0.084**
	1	124	23 (42.59%)	101 (53.44%)	
	2	14	1 (1.85%)	13 (6.88%)	
	Unknown	24	1	23	
Lymphovascular invasion	0	204	48 (87.27%)	156 (74.29%)	**0.042**
	1	61	7 (12.73%)	54 (25.71%)	
	Unknown	2	0	2	
Number of N2 dissected stations		261	3.00 (2.00, 4.00)	4.00 (3.00, 5.00)	<0.001

Number of N2 dissected lymph nodes		260	5 (3, 8)	9 (6, 14)	<0.001
Number of N1 dissected stations		262	3.00 (3.00, 5.00)	4.00 (3.00, 5.00)	0.2
Number of N1 dissected lymph nodes		261	6.0 (4.0, 7.0)	8.0 (5.0, 12.0)	<0.001
pT stage	1a	48	10 (18.52%)	38 (18.36%)	0.8
	1b	90	16 (29.63%)	74 (35.75%)	
	1c	18	5 (9.26%)	13 (6.28%)	
	2a	103	23 (42.59%)	80 (38.65%)	
	2b	2	0 (0.00%)	2 (0.97%)	
	Unknown	6	1	5	
pN stage	0	251	53 (96.36%)	198 (93.40%)	0.9
	1	7	1 (1.82%)	6 (2.83%)	
	2	9	1 (1.82%)	8 (3.77%)	
pM stage	0	267	55 (100.00%)	212 (100.00%)	
Pathology staging	Ia or Ib	139	30 (54.55%)	109 (51.66%)	>0.9
	IIa	107	22 (40.00%)	85 (40.28%)	
	IIb	12	2 (3.64%)	10 (4.74%)	
	IIIa	8	1 (1.82%)	7 (3.32%)	
	Unknown	1	0	1	
R status	r0	265	54 (98.18%)	211 (99.53%)	0.4
	r1	2	1 (1.82%)	1 (0.47%)	
	r2	0	0 (0.00%)	0 (0.00%)	
Parenchimal margin distance minimun		192	5 (2, 20)	12 (2, 25)	0.2
	Unknown	75	15	60	
Ilar margin distance		188	20 (15, 40)	30 (20, 40)	**0.026**
	Unknown	79	18	61	
Mutations	EGFR	34	8 (42.11%)	26 (29.21%)	0.7
	ALK	8	1 (5.26%)	7 (7.87%)	
	PD-L1	61	10 (52.63%)	51 (57.30%)	
	ROS1	5	0 (0.00%)	5 (5.62%)	
	Unknown	159	36	123	
EGFR mutations types	EGFR exon 18	4	2 (3.64%)	2 (1.00%)	0.2
	EGFR exon 19	33	10 (18.18%)	23 (11.50%)	0.2
	EGFR exon 20	3	2 (3.64%)	1 (0.50%)	0.12
	EGFR exon 21	23	4 (7.27%)	19 (9.50%)	0.8

4.6. Oncological and survival data

Regarding the recurrence of disease, this happened in 45 patients, thus 18.07% of the 249 patients for whom the data was known (p-value= 0.8), being especially local, with 30 recurrences (66.67% of the total relapses, p-value= 0.6), systemic, for 7 patients (15.56%), and nodal mediastinal, for 4 patients (8.89%), and occurring on average after 25 months (QI: 2, 51), being 16 months (QI: 4, 40) for segmentectomy, and 28 (QI: 2, 53) for lobectomies, with a p-value= 0.3, as visible in Table X and Table XI. This is visible, separately for the two surgical methods, in Figure 4 and Table XII. 41 patients out of 45 (91.11%) received treatment, but 15 died (33.33% of the patients with recurrence). In total, 16 patients died of cancer (including recurrence of the disease), 4 for other causes and 207 (91.19% of the collected data) were still alive. On average, patients died after 41 months from the surgery (QI: 17, 64). Regarding overall survival, at 1 year 6 out of 216 patients followed-up died, 17 out of 172 died within 3 years, and 19 out of 96 within 5 years, with the OS rates in percentage which are visible in Figure 5 and Table XIII after 20, 40 and 60 months from the surgery. The date of death was known only for 15 patients out of 249 (6.02%) for which the data was known, and only 12 patients underwent a second pulmonary resection (4.49%). In Figures 6 and 7 and in Tables XVIII and XIX the overall survival and recurrence rates are presented differentiating the results for VPI+ and VPI- patients. They have

Table XII Cumulative incidence of recurrence of disease after 20, 40 and 60 months from the surgery.

Group	Time (months)	Cuminc	Lower IC	Upper IC
Segmentectomy	20	0.1556	0.0290	0.282
Segmentectomy	40	0.1930	0.0524	0.334
Segmentectomy	60	0.1930	0.0524	0.334
Lobectomy	20	0.0957	0.0478	0.144
Lobectomy	40	0.1514	0.0912	0.212
Lobectomy	60	0.2491	0.1609	0.337

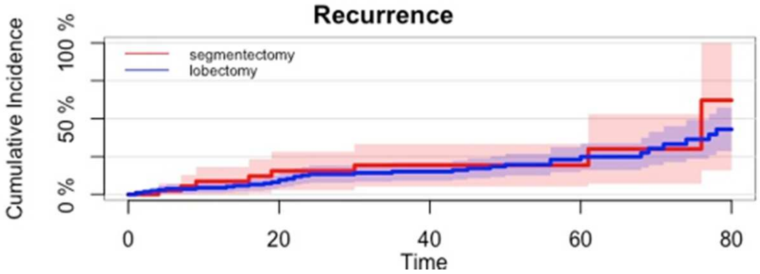

Figure 4 Graphical representation of cumulative recurrence of disease.

also been calculated the results of the HR of overall survival and recurrences rates, visible in Tables XVI and XVII, when comparing the most significant variables modifying these two outcomes.

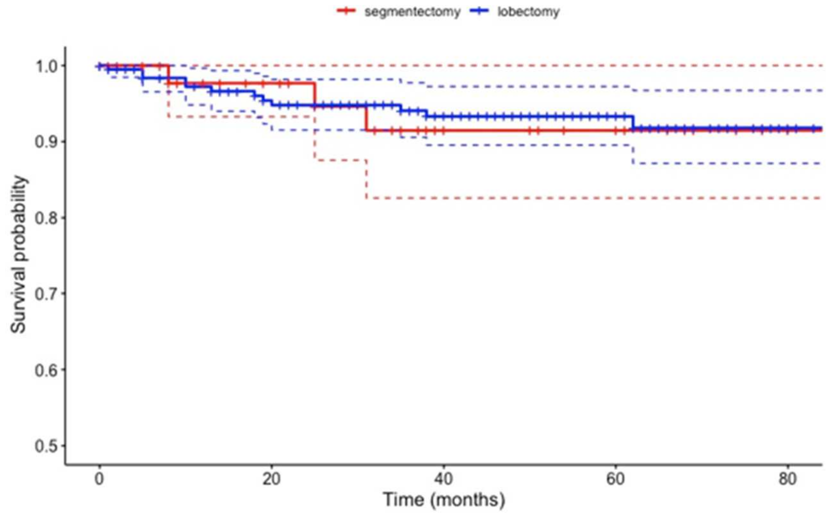

Table XIII Overall survival after 20, 40, and 60 months from the two surgical treatments. Hazard Ratio of lobectomy= 0.89, CI: 0.25, 3.15, p-value=0.854

Group	Time (months)	Surv	Lower IC	Upper IC
Segmentectomy	20	0.977	0.933	1
Segmentectomy	40	0.915	0.826	1
Segmentectomy	60	0.915	0.826	1
Lobectomy	20	0.948	0.915	0.982
Lobectomy	40	0.933	0.895	0.972
Lobectomy	60	0.933	0.895	0.972

Figure 5 OS after the two surgical treatments

Table XIV Explorative statistics on outcome data

Adjuvant therapies	Received	23	23 (8.61%)
	Not received	244	244 (91.39%)
	Biological drug	1	1 (4.17%)
	Chemotherapy	8	8 (33.33%)
	CT-immunotherapy	1	1 (4.17%)
	TKI	2	2 (8.33%)
	immunotherapy	1	1 (4.17%)
	Radiotherapy	4	4 (16.67%)
	Radio+Chemotherapy	1	1 (4.17%)
	tki	6	6 (25.00%)
	Unknown	243	243
Recurrence	No	204	204 (81.93%)
	Yes	45	45 (18.07%)
	Yes, local	30	30 (12.20%)

	Yes, mediastinal nodes	4	4 (1.63%)
	Yes, systemic	7	7 (2.85%)
	Yes, thorax (local or mediastinal)+systemic	1	1 (0.41%)
	Unknown	18	18
Time of recurrence from surgery (months)		262	25 (2, 51)
	Unknown	5	
Treated for recurrence		41	41 (15.65%)
	Unknown	5	
Death	Yes	15	15 (6.02%)
	No	234	234 (93.98%)
	Unknown	18	
Cause of death	Alive	207	207 (91.19%)
	Cancer	16	16 (7.05%)
	Other (specify)	4	4 (1.76%)
	Unknown	40	
Time of death from surgery		265	41 (17, 64)
	Unknown	2	
Followup		266	41 (16, 64)
	Unknown	1	
1 year survival	Yes	210	210 (97.22%)
	No	6	6 (2.78%)
	Unknown	51	
3 year survival	Yes	155	155 (90.12%)
	No	17	17 (9.88%)
	Unknown	95	
5 year survival	Yes	77	77 (80.21%)
	No	19	19 (19.79%)
	Unknown	171	
Second pulmonary resection if any	Yes	12	12 (4.49%)
	No	255	255 (95.51%)

Table XV Inferential statistics on outcome data

Characteristics	Values	N	Segmentectomy (N=55)	Lobectomy (N=212)	p-value
Adjuvant therapies	No	244	52 (94.55%)	192 (90.57%)	0.4
	Yes	23	3 (5.45%)	20 (9.43%)	
Type adjuvant therapies	biological drug	1	0 (0.00%)	1 (4.76%)	0.6
	ct	8	3 (100.00%)	5 (23.81%)	
	ct immuno	1	0 (0.00%)	1 (4.76%)	
	ct tki	2	0 (0.00%)	2 (9.52%)	
	immuno	1	0 (0.00%)	1 (4.76%)	
	rt	4	0 (0.00%)	4 (19.05%)	
	rt ct	1	0 (0.00%)	1 (4.76%)	
	tki	6	0 (0.00%)	6 (28.57%)	
	Unknown	243	52	191	
Recurrence	No	204	44 (83.02%)	160 (81.63%)	0.8
	Yes	45	9 (16.98%)	36 (18.37%)	
	Unknown	18	2	16	
Site of recurrence	No recurrence	204	44 (83.02%)	160 (82.90%)	0.6
	Local	30	8 (15.09%)	22 (11.40%)	
	Nodal mediastinal	4	1 (1.89%)	3 (1.55%)	
	Systemic	7	0 (0.00%)	7 (3.63%)	
	Thorax (local or mediastinal)+systemic	1	0 (0.00%)	1 (0.52%)	
	Unknown	21	2	19	
Time of recurrence from surgery		262	16 (4, 40)	28 (2, 53)	0.3
	Unknown	5	2	3	
Treatment for recurrence	0	221	46 (86.79%)	175 (83.73%)	0.6
	1	41	7 (13.21%)	34 (16.27%)	
	Unknown	5	2	3	

Death	No	234	49 (94.23%)	185 (93.91%)	>0.9
	Yes	15	3 (5.77%)	12 (6.09%)	
	Unknown	18	3	15	
Cause of death	alive	207	47 (94.00%)	160 (90.40%)	0.6
	cancer	16	2 (4.00%)	14 (7.91%)	
	other (specify)	4	1 (2.00%)	3 (1.69%)	
	Unknown	40	5	35	
Time of death from surgery		81	34 (9, 54)	47 (21, 67)	0.011
	Unknown	2	0	2	
1 year survival	No	6	1 (2.44%)	5 (2.86%)	>0.9
	Yes	210	40 (97.56%)	170 (97.14%)	
	Unknown	51	14	37	
3 year survival	No	17	3 (11.54%)	14 (9.59%)	0.7
	Yes	155	23 (88.46%)	132 (90.41%)	
	Unknown	95	29	66	
5 year survival	No	19	3 (20.00%)	16 (19.75%)	>0.9
	Yes	77	12 (80.00%)	65 (80.25%)	
	Unknown	171	40	131	
Second pulmonary resection if any	No	255	54 (98.18%)	201 (94.81%)	0.5
	Yes	12	1 (1.82%)	11 (5.19%)	

Table XVI Analysis of the Hazard ratio for overall survivall

HR for OS for the most significant variables (considering the risk in segmentectomy as a reference for this univariate analysis)				
Variable	**Possible values of the variable**	**Hazard Ratio**	**Confidence Interval 95%**	**p-value**
Surgical technique (segmentectomy as reference from here on)		0.89	[0.25;3.15]	0.854
SUV max of the main lesion at PET scan		1.01	[0.92, 1.11]	0.844
Maximum clinical tumor diameter		1.03	[0.97, 1.09]	0.399
Predominant histological subtype in case of ad	Lepidic	Reference		
	Papillary	0.00	[0.00, Inf]	0.998
	Acinar	1.85	[0.24, 14.49]	0.556
	Solid	4.39	[0.40, 48.50]	0.227
	Others	0.00	[0.00, Inf]	1.000
	Lepidic	Reference		

Other histological subtypes in case of ad	Papillary	0.86	[0.09, 8.40]	0.9
	Acinar	1.67	[0.34, 8.30]	0.529
	Micropapillary	0.00	[0.00, Inf]	0.998
	Solid	1.43	[0.24, 8.56]	0.695
	Complex glands/cribriform	0.00	[0.00, Inf]	0.999
STAS Spread Through Air Space (No STAS as reference)	1	1.23	[0.45, 3.41]	0.687
Lymphovascular invasion (LVI present as reference)	1	1.48	[0.47, 4.66]	0.499
Stations of dissected N2 lymph nodes		1.22	[0.89, 1.68]	0.221
Dissected N2 lymph nodes		0.96	[0.88, 1.05]	0.385
Stations of dissected N1 lymph nodes		0.92	[0.68, 1.25]	0.593
Parenchymal margin distance minimum		0.99	[0.95, 1.02]	0.47
Ilar margin distance		1.00	[0.96, 1.04]	0.924
Pleural invasion (no invasion as reference)	1	0.78	[0.25, 2.42]	0.665
Ratio between the margin of resection and neoplasia diameter		0.65	[0.27, 1.53]	0.322
Presence of GGO components (absence of GGO components as reference)	1	0.80	[0.25, 2.52]	0.704
Maximum diameter of the total size of the main lesion		1.00	[0.93, 1.08]	0.928
HR for OS for multivariate Cox regression analysis considering all the patients of the database not stratified				
Variable	**Possible values of the variable**	**Hazard Ratio**	**Confidence Interval 95%**	**p-value**
Ratio between the margin of resection and neoplasia diameter	NA	0.82	[0.32, 2.07]	0.673
Pleural invasion	1	1.49	[0.27, 8.16]	0.644

Table XVII Hazard ratios for recurrence

HR for recurrence for univariate Fine-Gray analysis (considering the recurrence= 0 whether the patient is alive and without recurrence, =1 whether there is recurrence, independently from the death, and =2 whether the death event competitively happened before any eventual recurrence)			
Variable	**Hazard Ratio (coefficient to the exponent)**	**Confidence Interval 95%**	**p-value**
Surgical technique (segmentectomy as reference from here on)	0.835	[0.40;1.78]	0.64
SUV max of the main lesion at PET scan	1.04	[1.01, 1.07]	**0.027**
Maximum tumor diameter	1.06	[1.03, 1.08]	**<0.001**
STAS Spread Through Air Space (Present vs absent)	2	[1.09, 3.69]	**0.026**

Lymphovascular invasion (Present vs absent)	2.01	[1.03, 3.89]	**0.04**
Stations of dissected N2 lymph nodes	1.19	[0.94, 1.52]	0.15
Number of dissected N2 lymph nodes	0.98	[0.93, 1.03]	0.4
Stations of dissected N1 lymph nodes	1.01	[0.84, 1.21]	0.91
Parenchymal margin distance minimum	0.99	[0.98, 1.01]	0.53
Ilar margin distance	0.99	[0.97, 1.01]	0.5
Pleural invasion (Present vs Absent)	1.82	[0.96, 3.46]	**0.07**
Ratio between the resection margin and the neoplasia diameter	0.64	[0.42, 0.98]	**0.04**
Presence of GGO components (Present vs absent)	0.60	[0.28, 1.26]	0.17
HR for recurrence for multivariate Fine-Gray analysis considering all the patients of the database not stratified			
Ratio between the margin of resection and neoplasia diameter	0.64	[0.40, 1.01]	**0.06**
Pleural invasion (no invasion as reference)	1.99	[0.88, 4.47]	**0.10**

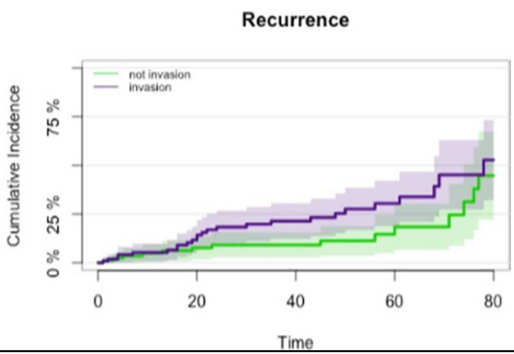

Figure 6 and Table XVIII Recurrence on the basis of presence or not of visceral pleura invasion.

Group	Time (months)	Cuminc	Lower IC	Upper IC
Not invasion	20	0.0767	0.0174	0.136
Not invasion	40	0.0913	0.0264	0.156
Not invasion	60	0.1843	0.0662	0.302
Invasion	20	0.1426	0.0671	0.218
Invasion	40	0.2141	0.1225	0.306
Invasion	60	0.3045	0.1872	0.422

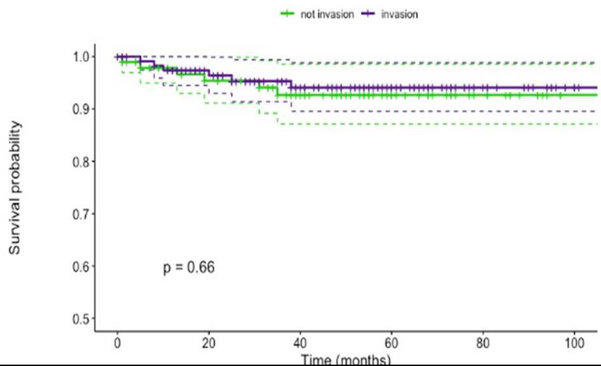

Figure 7 and Table XIX Survival rates on the basis of presence or not of VPI.

Group	Time (months)	Surv	Lower IC	Upper IC
Not invasion	20	0.954	0.911	0.999
Not invasion	40	0.927	0.872	0.985
Not invasion	60	0.927	0.872	0.985
Invasion	20	0.964	0.930	0.999
Invasion	40	0.941	0.896	0.989
Invasion	60	0.941	0.896	0.989

5. DISCUSSION

According to the latest studies, visceral pleural invasion is an important prognostic factor, affecting lung cancer specific survival and recurrence outcomes. A 2018 meta-analysis (43) found that, probably depending on the dissemination throughout the visceral pleura, pathological PL2, which is the maximum extent of pleural invasion, in pT1b-staged tumors is associated with a worse overall survival than PL1, which has it, in turn, worse than PL0, and these associations are independent from the staining methods. When comparing segmentectomy with lobectomy in VPI-positive NSCLC, according to H. Y. Deng and Q. Zhou (44) and a previous study, the number of deaths were inferior in the lobectomy group compared to segmentectomy, and a 2024 systematic meta-analysis (45) evidenced that deaths were inferior in segmentectomy than subsegmentectomy too (46). However, the results in this meta-analysis were pretty inconclusive, since the HR of mortality was 1.10 with a low certainty of evidence in the not-RCT studies, and two other RCT studies had an HR of 0.80, with a moderate certainty of confidence instead, further complicated by the low level of heterogeneity of the RCT studies, requiring a cautious interpretation.

Regarding the 5-years survival rates, the post-hoc analysis of the CALGB140503 (27,47) found that it was 70% in VPI+, whereas it was superior (80%) in VPI-negative. Moreover, a 2022 analysis of the SEER database found that this indicator was positively influenced by female sex and marriage status, and negatively by elevated age, G2/G3 status, bigger tumor size and having received radio and chemotherapy, independently from the N-status. Moreover, the number of harvested lymph nodes is usually bigger in the lobectomy group, but without implying significant differences in post-surgical complications (such as post-surgical air-leaks) between segmentectomy and lobectomy, or differences in the mean hospital stay lenght (45).

Another influent characteristic modified by the VPI status is RFS, Relapse-Free Survival, or Disease-Free Survival, which is defined as the time between randomization and disease recurrence of the index cancer or death of all causes, whichever came first. Patients who did not experience a recurrence event are usually censored at the time of last follow-up (27). In a 2018 meta-analysis (43) PL0 RFS was bigger than that of PL1, which was it, in turn, than that of PL2, but a correlation was not found. However, these findings and the presence of heterogeneity imposed the stratification and searching for confounding factors, since, in case this correlation effectively existed, it would require the upstaging of the T1 tumors to T2 with subsequent staging Ia becoming Ib. Moreover, T2 could be both T2a and T2b, since they have the same Lung Cancer Specific Survival (LCSS), but they were staged as IB or IIA, entailing different prognosis in the 7th edition of the TNM classification system. Apart for this meta-analysis, also a 2024 study on Deep Learning techniques as an investigation method for the assessing of VPI, conducted by Xiaofeng et All. (24), and, one year before, Altorki et All. (47), had found a correlation between visceral pleural invasion and DFS, recurrence rates and risk of recurrence for peripheral (in the outer third of lung parenchyma) T1 and T2 tumors, independently from the type of surgical treatment (lobectomy versus segmentectomy). These findings raised the question whether an adjuvant therapy is effectively necessary and whether there is a preferential surgical treatment, given the comparability of post-surgical recurrence rates (around 30% of recurrences, metastasis or death after the surgery, with a mean RFS of around 90 months) between the two stagings. The correlation between DFS and visceral pleural status had also been found in a 2018 study of Yoshida et All. (43), who had thus proposed to upgrade each T to the following T status, and also in 2022 from data of the SEER database, which suggested, after differentiating the tumors for the N and for the T status, to maintein the N0 T1a and b PL0 or PL1, and the N0 T1c PL0 in T1, and upstage the N0T1a or b PL2, as well as N0T1cPL1 and all the PL2 to T2. Finally, local recurrences were specifically higher in segmentectomy group (despite the inconclusive data in RCT studies) in the 2024 systematic meta-analysis (45).

The comparison between the outcomes of segmentectomy versus lobectomy in early stage NSCLC was actual also when VPI is negative. The 2023 CALGB140503 (47), regarding peripheral cT1, pathologically confirmed to be N0, NSCLC, pointed out a similar 5-years overall survival between segmentectomy and lobectomy (of about 80%), with similar 30-days mortality and a 90-day mortality higher in the lobectomy group, even if with a not clinically significant difference of 2%. However, another study (48) found similar 30-days mortality but higher 90-days mortality in segmentectomy. Similar results of 5-years OS were reached also by the JCOG0802 (47) and the post-hoc analysis of the CALGB140503 (27,47), both for T1 and T2 stages. On the contrary, OS of segmentectomy had be found to be bigger than that one of lobectomy by the JCOG0802/WJOG4607L (49), in which segmentectomy was defined as the removal of maximum two pulmonar segments with systematic or at least selective lymph nodal dissection, in single, totally resectable, N0M0, peripheral, pure-solid on thin-CT, pT1a or pT1b tumors. The same benefit of segmentectomy in OS was evidenced also by LCSG821 (50). Moreover, in subgroup analysis for the OS outcome in the JCOG0802/WJOG4607L (49), the advantage in OS for segmentectomy was evidenced only for male and 70 years-old patients, whereas in case of presence of GGO components, lobectomy became similar to segmentectomy in terms of OS. As well as the JCOG0802/WJOG4607L and the LCSG821, the confirmatory study JCOG1211 (50), investigating the survival outcomes (and the 5-years OS specifically) in bigger (T1c of 2-3 cm), GGO-dominant (CTR= 0.25-0.5), central (in the two central thirds) tumors, found that those malignancies decreased the 5-years OS of segmentectomy. This was in any case of 98.2% for the aforementioned surgical technique, and in any case it was not inferior to the outcomes of lobectomy, thus meeting the primary endpoint (even if with a slight decrease on the percentage of patients reaching the endpoint for more pathologically invasive lung cancers). However, when surgical margins could be guaranteed, pulmonary residual function was better in segmentectomy, thus resulting in an overall better suitability of segmentectomy for early stage, with low or moderate malignant behaviour or for old and comorbid patients, according to the CALGB140503, JCOG0802/WJOG4607L and JCOG1211. The CALGB140503 also discovered that OS is decreased by a CEA level > 0.5 ng/mL, a tumor size > 1.5 cm and not adenocarcinoma histologies. Finally, regarding the survival, JCOG0802/WJOG4607L (49) found that Lung Cancer Specific Survival at 7 years was similar between the two sex and the two surgical techniques, because even if segmentectomy gives more frequently recurrences, they are also more treated, whereas deaths due to other causes, including second primary lung cancer, are more common among lobectomies.

Concerning the 5-year RFS, in the CALGB140503 (47) it was similar between segmentectomy and lobectomy and around 70% in VPI negative tumors, with a 30% of recurrences being for one third locoregional and for more than a half systemic, thus making the authors assuming the presence of micrometastasis from the diagnosis, thus arising the question whether an adjuvant therapy is effectively necessary (which would necessitate of high numbers of included patients to be verified). According to this study, RFS is higher for T1 stages (72.5%) than T2 (58.4%) for VPI-negative tumors. Instead, concerning VPI-positive LC, 5-years RFS was around 73% and 58% for pT1 and pT2, respectively, with 70% of the recurrences of pT2 and 60% of those of pT1 occurring within 3 years from the surgery, and with comparable RFS among subgroups of pT1 independently from the used surgical technique. With this result, segmentectomy is not inferior to lobectomy for VPI-positive, <2cm, peripheral, N0 NSCLC. Similar outcomes between the two surgical procedures, with a low level of heterogeneity, were obtained also in the JCOG0802/WJOG4607L (49) and another study (51). Moreover, in subgroup analysis, RFS after lobectomy was bigger than that of segmentectomy in less than 70 years old and female patients, with the recurrence in segmentectomy occurring more frequently, but also being more treated. In multivariate analysis of the same study, possibly depending on the different smoking habits (and this would explain the higher frequency of other diseases (52)), RFS was inferior in males, >70 years-old patients, not adenocarcinoma histologies, with pure-solid appearance, >1.5 cm, localized in the left lingular segment (53), and sized more than the distance to the pleura, tumors. Regarding peri-operative major morbidity, a study (48) observed it is inferior in the segmentectomy group, as well as the number of harvested lymph nodes, which however does not compromise the OS, probably because, independently from the localisation, segmentectomy leaves a reservoir of parenchyma for resection. For this reason, also this research indicated segmentectomy in T1a and T1b, less than 2 cm tumors with feasable complete extensive lymphadenectomy.

When comparing segmentectomy to lobectomy depending on the affected lobe, in (48) it was found that larger lobes were the strongest predictors of receiving segmentectomy, even if 5-year OS of lobectomy was bigger than that of segmentectomy, although not remaining significant in Cox proportional hazard analysis.

Regarding lymph nodal dissection, ths procedure affects OS, distant disease and local recurrence, thus influencing the necessity for adjuvant therapy. The IASCL, for its importance, recommends a systematic dissection in order to reduce lymph nodal metastasis and increase the oncological outcomes (54). The ESTS too (55) advocates it, even if it notes that this technique is not applied in practice by many surgeons, preferring LN sampling, systematic mediastial LN sampling or lobe-specific systematic lobe dissection. Regarding the number of harvested LN, the NCCN recommends at least 3 N2 lymph nodes, whereas the ESMO at least 6 lymph nodes from at least three stations, including the subcarinal ones.

Concerning the possible employing of wedge resection instead of anatomical resection, it must be said that in the CALGB140503 60% of the segmentectomies were wedge, not guaranteeing adequate surgical margins and assessment and dissection of lymph nodes, with subsequent inferior local control and prognosis (56). On the contrary, in JCOG0802/WJOG4607L, only anatomical segmentectomies were performed, and GGO components were all evaluated.

The main results coming out from the statistical descriptive analysis of the present work, comparing segmentectomy to lobectomy, are as follows (Table XIV and Table XV), considering higher p-values compatible with the null hypothesis H_0 of equality of the statistical variable between the segmentectomy and the lobectomy group. Instead, in case of small p-value, being inferior to the fixed $\alpha = 0.05$, the observed value of the variable is not compatible with the H_0 hypotesis, thus being more compatible with the H_1 of $\mu_A \neq \mu_B$. Significant differences among the two treatments group can be observed, with a $p < 0.001$, in the smoking history, since in the segmentectomy group there are higher proportions of currently smoker, to the detriment of previous smoker (having stopped for more than one year), whereas never-smoking patients were present in similar percentages among the two treatment groups (25.45% in segmentectomy vs 28.77% in lobectomy). Significant differences (p-value <0.001) were observed also in the CCI, Charlson Comorbidity Index, predicting the 10-year mortality based on patient's comorbidities (such as cancers, leukemia and lymphoma, diabetes, cardiovascular disease etc.): patients of segmentectomy were more comorbid (CCI=5.00, QI= 4.00, 6.00) than those of lobectomy (CCI= 4.00, QI= 3.00, 5.00). Segmentectomy patients had also more lesions (variable of presence or not of multiple lesions), with a p-value =0.011, with 18.52% of segmentectomies (10 patients) having multiple lesions against 7.18% (15 patients) receiving lobectomy. The lesions were significantly more located in the left lobes (for instance in the LUL the 41.82% of segmentectomy vs 30.66% of lobectomies, and in the LLL the 23.64% of segmentectomies vs 8.96% of lobectomies), in different segments. Moreover, no significant differences (p-value= 0.7) were observed in the presence of GGO-components, whereas significant differences (p-value <0.001) were observed in the maximum diameter of the total size of the main lesion, which was 16 cm (QI: 12, 21) for segmentectomy and 20 (QI: 16, 25), so bigger, for lobectomy. The maximum SUV too is different, with more hypercaptivating lesions in lobectomy (4.2, QI: 2.7, 7.0, vs 2.9, QI: 1.3, 4.2, p-value <0.001). Moreover, the cT were different, with cT1a more in the segmentectomy group (20% of the segmentectomy vs 6.13% of lobectomies) and cT1c in higher amount among lobectomies (48.58% vs 36.36%), with a p-value =0.008, whereas no statistical differences could be found in the pathological T. Statistical significant differences (p-value= 0.002) can be noticed also in the total volume of chest drainage, which is 800 mL (QI: 420, 1345) in lobectomies, and 540 mL (QI: 293, 798) in segmentectomies. Statistical differences can not be observed in the visceral pleura involvement, whereas they can in lymphovascular invasion, which, with a p-value=0.042, is present in 12.73% of segmentectomies and 25.71% of lobectomies. Significant variation, with a p-value <0.001, was noted also in the number of N2 dissected stations (3.00, QI: 2.00, 4.00 in segmnetectomy vs 4.00, QI: 3.00, 5.00 in lobectomy) and N2 lymph nodes (5.00, QI: 3.00, 8.00 in segmentectomy and 9.00, QI: 6.00, 14.00), in the number of N1 lymph nodes (6.00, QI: 4.00, 7.00 in segmentectomy vs 8.00, QI: 5.00, 12.00 in lobectomy), as well as in the ilar margin distance, which is higher in lobectomy, with a p-value= 0.026. Instead, among the outcomes data, statistical significant differences could be evidenced only in the time of death from surgery.

With a focus on the survival and recurrence results, the hazard ratios were calculated for the most significant variables, selected in accordance to what had shown significance in the literature. Regarding the HRs for OS, no significant p-values were found for the different variables among segmentectomy and lobectomy, thus not suggesting, in this study, a significant variation of OS due to these characteristics. This can not support the results of previous studies, such as the JCOG0802/WJOG4607L (49) or the LCSG821 when comparing the survival outcomes of the two surgical techniques, since they evidenced a bigger OS of segmentectomy than lobectomy. However, the CALGB140503 (47) and its post-hoc analysis (27), as well as the JCOG0802, had found that the 5-years OS of the two surgical techniques in NSCLC were around 80% for both the surgical methods in NSCLC, which is slightly inferior to the OS survival percentages in the present study (91.5% of survival probability of segmentectomy, IC: 0.826, 1, and 93.3% for lobectomy, IC: 0.895, 0.972, which are both superior). Regarding the recurrence outcomes between the two treatment groups, no differences could be found at 5-years DFS, with overlapping CI of 0.0524, 0.334 for segmentectomy and a CI of 0.1609, 0.337 for lobectomy, aligning to the comparable 70% of RFS of both segmentectomy and lobectomy found in the CALGB140503 (47), and to a comparability of the two surgical techniques found by JCOG0802/WJOG4607L (49) and another study (51).

The presence of VPI-status positive too in this study does not show a clear trend in terms of survival, overlapping the 1 value of HR (HR= 0.78, CI: 0.25, 2.42) and with a low statistical significance (p-value= 0.665). Regarding OS analysed on the basis of the VPI status, studies such as the post-hoc analysis of the CALGB140503 (27) or others (44) showed a decrease in 5-years survival rates (around 70% for VPI+), with the present study not being as significant as these ones (p-value= 0.665, HR= 0.78, CI: 0.25, 2.42). Also the negative influence on 5-years OS of higher tumoral grades and tumor size, as well as the employing of radio and chemotherapy, evidenced by the CALGB140503, could not be verified in the present study with statistical significance.

Instead, some significant results were found, in terms of HR of recurrence outcomes, with Fine-Gray analysis. In particular, with a p-value= 0.027 and an HR=1.04 (CI-95%: 1.01, 1.07) with segmentectomy taken as reference, the SUV max of lobectomy is significantly higher than that of segmentectomy. Neoplasias with this characteristic of higher metabolism, which are more frequently operated with lobectomy, also shows significantly higher recurrence rates than those of segmentectomy. This is compatible with the finding of a correlation between hypermetabolism at preoperative PET and increase in lymph nodal recurrences (45) and poorer prognosis (35–38). The maximum tumor diameter, with an HR= 1.06, CI-95%: 1.03, 1.08 and a p-value <0.001, was positevely correlated too to recurrence, thus being more frequent in lobectomy. This makes sense since, as shown by the correlation between preoperative cT stage and type of surgery assigned, with high statistical significance (p-value=0.008), the more the tumors increased the T, the more they were assigned to lobectomy instead of segmentectomy. The results that dimensions of the tumor correlate with recurrence outcomes is in accordance with what was found by CALGB140503 (47), which had also evidenced a positive correlation between dimensions of the tumor (pT stage) and precocity of the recurrence, with a major-of-10% amount of recurrences occurring within 3 years from the surgery. Another variable highly positively correlated, with its presence, to an increased risk of recurrence, was STAS, Spread Through Air Space, with a p-value= 0.026, and an HR=2 [CI-95%: 1.09, 3.69]. This is not consistent with the results of Nicotra et All. Group (42), who had found that STAS positive status is not correlated to DFS, on the contrary of vascular invasion, which, as well as in that study, in the present work is found to be positively correlated (with the lymphatic vessel invasion too) to an increase in recurrence (HR= 2.01, CI-95%: 1.03, 3.89, p-value= 0.04).

Regarding visceral pleura invasion, instead, even if a clear statistical significance (p-value= 0.07) was not present, in this study there is a tendence of VPI to be significant (HR=1.82, CI: 0.96, 3.46). This acquire more relevance especially when considering the margin of resection, which, if minor, and with contemporary presence of VPI, it causes an increased risk of recurrence (p-value of the ratio resection margins-neoplasia diameter = 0.04, HR= 0.64, CI: 0.42, 0.98). Another type of statistical method, which is the Fine-Gray analysis, was used to calculate the HR or recurrence for the variables “ratio resection margin and diameter of the neoplasia” and “pleural invasion”. Unlike the Cox cause-specific model analysis, which estimates the HR of the istantaneous risk, conditioned by the absence of events, the Fine-Gray regression returns HRs relatively to cumulative risk, considering the competition of recurrence with the events of death before the recurrence.

For this reason, the results obtained with the two methods are slightly different, even if not changing the signification of what is found. In particular, the HR of the ratio resection margin- diameter of the neoplasia with multivariate Fine-Gray regression model is always 0.64, but with CI-95%: 0.40, 1.01 and a slightly inferior statistical significance (p-value= 0.06). The pleural invasion too loses in statistical significance when analysed with the Fine-Gray (p-value=0.10, HR=1.99, CI: 0.88, 4.47). These results, even if with little statistical significance, align with previous studies analysing the relationship between an higher (or, at least, the presence of) visceral pleura invasion with the RFS, which had brought to an upstaging of tumors from T1 to T2 when VPI is positive in the 8th TNM edition. This correlation was underlined, apart for the 2018 meta-analysis, also by a 2024 study on Deep Learning techniques (24), by Altorki et All. In the JCOG0802 (47), in the post-hoc analysis of the CALGB140503 (27), by a 2022 study on the SEER database and by Yoshida et All. (43), as already discussed.

However, this study has some limits that is important to underline: the analysis was done retrospectively and only on 267 patients (so the number of the cohort is limited), of which only 55 within the segmentectomy group, which is a sample size of a small entity.

Moreover, since the patients were recruited within the courts from 2016 to 2021, it was not possible to properly follow-up them for a total of 5 years, with the patients of 2021 and the majority of the patients operated in 2020 who could not receive a proper follow-up of 5 years. Thus, it was not possible to have a meaningful DFS and OS of all the patients enrolled for the duration of the entire post-operative oncological surveillance process, falling into a possible selection bias, and making necessary to pursue the follow-up and the enlistment of further patients subjected to this type of interventions.

Others weak features of the present study are the low-level of evidence from retrospective studies (due to the possible presence of selection bias due to the existence of important confounders, such as tumor size, use of adjuvant therapy, smoking status and pathological type, which were used for stratifying the patients in the present study but after they had been assigned to one of the two treatment groups of segmentectomy or lobectomy, or incomplete resections, which information was not collected in this research). For this reason, a randomised prospective study comparing lobectomies with segmentectomies in case of VPI with early stage NSCLC would be necessary (57).

Moreover, eventual missing data calculated from HR were extrapolated from reported data from survival curves (thus making assumptions according to the methods described by Tierney et al. (43)), the majority of the patients were Caucasian (and, in any case, there was not a stratification for ethnicity), and it was not performed an analysis stratifying by the VPI status, which could explain part of the results.

6. CONCLUSION

As a conclusion, lobectomy and segmentectomy remained equally suitable for early-stage NSCLC in terms of survival. Recurrence revealed to be associated to pathological variables and radiological variables, such as the maximum SUV at PET scan, tumor size, STAS, LVI, VPI, and the ratio between the resection margin and the diameter of the neoplasia, supporting what early phenomena are hidden inside the NSCLC even in an early phase of disease. In this study, VPI does not show a difference in survival rates in accordance to its status of positivity or negativity, whereas it demonstrated a trend toward significance to recurrence. This provides additional evidence to the current literature that its association to relapse may justify the pathological upstaging deserved to early-stage VPI+ NSCLCs.

BIBLIOGRAPHY

1. Cancer Tomorrow [Internet]. [citato 23 maggio 2025]. Disponibile su: https://gco.iarc.who.int/today/

2. EpiCentro. La mortalità per tumore del polmone [Internet]. [citato 23 maggio 2025]. Disponibile su: https://www.epicentro.iss.it/fumo/WTD2013Mortalita

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. gennaio 2020;70(1):7–30.

4. Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest. gennaio 2003;123(1 Suppl):21S-49S.

5. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med. gennaio 2000;161(1):5–8.

6. Lorigan P, Radford J, Howell A, Thatcher N. Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. Lancet Oncol. ottobre 2005;6(10):773–9.

7. Huang YJ, Huang TW, Lin FH, Chung CH, Tsao CH, Chien WC. Radiation Therapy for Invasive Breast Cancer Increases the Risk of Second Primary Lung Cancer: A Nationwide Population-Based Cohort Analysis. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. maggio 2017;12(5):782–90.

8. Kirk GD, Merlo C, Driscoll PO, Mehta SH, Galai N, Vlahov D, et al. HIV Infection Is Associated with an Increased Risk for Lung Cancer, Independent of Smoking. Clin Infect Dis Off Publ Infect Dis Soc Am. 1 luglio 2007;45(1):103–10.

9. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet Lond Engl. 7 luglio 2007;370(9581):59–67.

10. Jeon J, Holford TR, Levy DT, Feuer EJ, Cao P, Tam J, et al. Smoking and Lung Cancer Mortality in the US from 2015-2065: a comparative modeling approach. Ann Intern Med. 20 novembre 2018;169(10):684–93.

11. Wolf AMD, Oeffinger KC, Shih TY, Walter LC, Church TR, Fontham ETH, et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. CA Cancer J Clin. gennaio 2024;74(1):50–81.

12. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med. 1 marzo 2018;142(3):321–46.

13. Mujoomdar A, Austin JHM, Malhotra R, Powell CA, Pearson GDN, Shiau MC, et al. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. Radiology. marzo 2007;242(3):882–8.

14. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. Chest. gennaio 2003;123(1 Suppl):137S-146S.

15. Funai K, Yokose T, Ishii G ichiro, Araki K, Yoshida J, Nishimura M, et al. Clinicopathologic characteristics of peripheral squamous cell carcinoma of the lung. Am J Surg Pathol. luglio 2003;27(7):978–84.

16. Ho C, Tong KM, Ramsden K, Ionescu DN, Laskin J. Histologic classification of non-small-cell lung cancer over time: reducing the rates of not-otherwise-specified. Curr Oncol. giugno 2015;22(3):e164–70.

17. Kish JK, Ro JY, Ayala AG, McMurtrey MJ. Primary mucinous adenocarcinoma of the lung with signet-ring cells: a histochemical comparison with signet-ring cell carcinomas of other sites. Hum Pathol. novembre 1989;20(11):1097–102.

18. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. settembre 2015;10(9):1243–60.

19. Quint LE. Staging non-small cell lung cancer. Cancer Imaging. 22 ottobre 2007;7(1):148–59.

20. Mahabadi N, Goizueta AA, Bordoni B. Anatomy, Thorax, Lung Pleura And Mediastinum. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [citato 23 maggio 2025]. Disponibile su: http://www.ncbi.nlm.nih.gov/books/NBK519048/

21. Detterbeck FC, Woodard GA, Bader AS, Dacic S, Grant MJ, Park HS, et al. The Proposed Ninth Edition TNM Classification of Lung Cancer. Chest. ottobre 2024;166(4):882–95.

22. How We Diagnose Non-Small Cell Lung Cancer | Dana-Farber Cancer Institute [Internet]. [citato 23 maggio 2025]. Disponibile su: https://www.dana-farber.org/cancer-care/types/non-small-cell-lung-cancer/diagnosis

23. Alaparthi SS, Ho A, Rshaidat H, Whitehorn G, Madeka I, Ishwar A, et al. Outcomes of Segmentectomy With or Without Preoperative Biopsy in Non-Small Cell Lung Cancer (NSCLC). Clin Lung Cancer. 1 giugno 2025;26(4):299–306.

24. Lin X, Liu K, Li K, Chen X, Chen B, Li S, et al. A CT-based deep learning model: visceral pleural invasion and survival prediction in clinical stage IA lung adenocarcinoma. iScience. 19 gennaio 2024;27(1):108712.

25. Chapet O, Kong FM, Quint LE, Chang AC, Haken RKT, Eisbruch A, et al. CT-based definition of thoracic lymph node stations: An atlas from the University of Michigan. Int J Radiat Oncol Biol Phys. 1 settembre 2005;63(1):170–8.

26. Kim JH, van Beek EJ, Murchison JT, Marin A, Mirsadraee S. The International Association for the Study of Lung Cancer Lymph Node Map: A Radiologic Atlas and Review. Tuberc Respir Dis. luglio 2015;78(3):180–9.

27. Altorki N, Wang X, Damman B, Jones DR, Wigle D, Port J, et al. Recurrence of Non-Small Cell Lung Cancer With Visceral Pleural Invasion: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 1 settembre 2024;10(9):1179–86.

28. Kasapoglu US, Arınç S, Gungor S, Irmak I, Guney P, Aksoy F, et al. Prognostic factors affecting survival in non-small cell lung carcinoma patients with malignant pleural effusions. Clin Respir J. 2016;10(6):791–9.

29. Sharma S, Boster J. Malignant Pleural Effusion. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [citato 23 maggio 2025]. Disponibile su: http://www.ncbi.nlm.nih.gov/books/NBK574541/

30. Lee MC, Stefanov DC, Angert MB, Cohn EC, Kohn N, Esposito MJ, et al. Impact of clinical and pathological variables on stage I non-small cell lung cancer outcomes. J Clin Oncol. 20 maggio 2020;38(15_suppl):e21071–e21071.

31. Gregg JP, Li T, Yoneda KY. Molecular testing strategies in non-small cell lung cancer: optimizing the diagnostic journey. Transl Lung Cancer Res. giugno 2019;8(3):286–301.

32. Lee GM, Stowell JT, Pope K, Carter BW, Walker CM. Lymphatic Pathways of the Thorax: Predictable Patterns of Spread. AJR Am J Roentgenol. marzo 2021;216(3):649–58.

33. The Pleurae - Visceral - Parietal - TeachMeAnatomy [Internet]. [citato 23 maggio 2025]. Disponibile su: https://teachmeanatomy.info/thorax/organs/pleurae/

34. Fang P, Cheng J, Lu Y, Fu L. Rethinking the Selection of Pathological T-Classification for Non-Small-Cell Lung Cancer in Varying Degrees of Visceral Pleural Invasion: A SEER-Based Study. Front Surg. 2022;9:902710.

35. Clark SB, Alsubait S. Non–Small Cell Lung Cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [citato 23 maggio 2025]. Disponibile su: http://www.ncbi.nlm.nih.gov/books/NBK562307/

36. Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, et al. Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. maggio 2010;5(5):620–30.

37. Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst. luglio 1980;65(1):25–32.

38. Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte JJ, et al. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. maggio 2010;5(5):612–9.

39. D'Angelo SP, Janjigian YY, Ahye N, Riely GJ, Chaft JE, Sima CS, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. dicembre 2012;7(12):1815–22.

40. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg. febbraio 2007;83(2):409–17; discussioin 417-418.

41. Delluc A, Miranda S, den Exter P, Louzada M, Alatri A, Ahn S, et al. Accuracy of the Ottawa score in risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism: a systematic review and meta-analysis. Haematologica. maggio 2020;105(5):1436–42.

42. Nicotra S, Melan L, Pezzuto F, Bonis A, Silvestrin S, Verzeletti V, et al. Significance of Spread Through Air Spaces and Vascular Invasion in Early-stage Adenocarcinoma Survival: A Comprehensive Clinicopathologic Study of 427 Patients for Precision Management. Am J Surg Pathol. 1 maggio 2024;48(5):605–14.

43. Wang T, Zhou C, Zhou Q. Extent of Visceral Pleural Invasion Affects Prognosis of Resected Non-small Cell Lung Cancer: A meta-analysis. Sci Rep. 8 maggio 2017;7(1):1527.

44. Deng HY, Zhou Q. Pleural Invasion in Non-small Cell Lung Cancer: An Important Characteristic during Clinical Decision-Making. Ann Surg Oncol. 1 agosto 2024;31(8):4851–2.

45. Bertolaccini L, Tralongo AC, Del Re M, Facchinetti F, Ferrara R, Franchina T, et al. Segmentectomy vs. Lobectomy in stage IA non-small cell lung cancer: A systematic review and meta-analysis of perioperative and survival outcomes. Lung Cancer Amst Neth. novembre 2024;197:107990.

46. Song X, Xie Y, Zhu Y, Lou Y. Is lobectomy superior to sub-lobectomy in non-small cell lung cancer with pleural invasion? A population-based competing risk analysis. BMC Cancer. 13 maggio 2022;22(1):541.

47. Altorki N, Wang X, Kozono D, Watt C, Landrenau R, Wigle D, et al. Lobar or Sublobar Resection for Peripheral Stage IA Non–Small-Cell Lung Cancer. N Engl J Med. 8 febbraio 2023;388(6):489–98.

48. Wong LY, Kapula N, Elliott IA, Liou DZ, Backhus LM, Lui NS, et al. Segmentectomy vs Lobectomy for Non-Small Cell Lung Cancer: The Impact of Tumor Location. Ann Thorac Surg Short Rep. 1 settembre 2024;2(3):458–63.

49. Hattori A, Suzuki K, Takamochi K, Wakabayashi M, Sekino Y, Tsutani Y, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer with radiologically pure-solid appearance in Japan (JCOG0802/WJOG4607L): a post-hoc supplemental analysis of a multicentre, open-label, phase 3 trial. Lancet Respir Med. febbraio 2024;12(2):105–16.

50. Aokage K, Suzuki K, Saji H, Wakabayashi M, Kataoka T, Sekino Y, et al. Segmentectomy for ground-glass-dominant lung cancer with a tumour diameter of 3 cm or less including ground-glass opacity (JCOG1211): a multicentre, single-arm, confirmatory, phase 3 trial. Lancet Respir Med. giugno 2023;11(6):540–9.

51. Fletcher J. What is heterogeneity and is it important? BMJ. 13 gennaio 2007;334(7584):94–6.

52. Suzuki K, Watanabe SI, Wakabayashi M, Saji H, Aokage K, Moriya Y, et al. A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer. J Thorac Cardiovasc Surg. gennaio 2022;163(1):289-301.e2.

53. Nakagawa K, Watanabe S ichi, Wakabayashi M, Yotsukura M, Mimae T, Hattori A, et al. Risk Factors for Locoregional Relapse After Segmentectomy: Supplementary Analysis of the JCOG0802/WJOG4607L Trial. J Thorac Oncol. 1 febbraio 2025;20(2):157–66.

54. Handa Y, Tsutani Y, Mimae T, Miyata Y, Ito H, Shimada Y, et al. Systematic Versus Lobe-Specific Mediastinal Lymphadenectomy for Hypermetabolic Lung Cancer. Ann Surg Oncol. novembre 2021;28(12):7162–71.

55. Manfredini B, Zirafa CC, Filosso PL, Stefani A, Romano G, Davini F, et al. The Role of Lymphadenectomy in Early-Stage NSCLC. Cancers. 23 luglio 2023;15(14):3735.

56. Okada M, Mimae T, Miyata Y. Segmentectomy and Wedge Resection Should Be Distinguished as Sublobar Resections for Lung Cancer. Ann Thorac Surg. ottobre 2023;116(4):859.

57. SILVESTRI M. Segmentectomia tipica del segmento S6 in toracoscopia videoassistita: outcome post-operatorio e oncologico. 25 febbraio 2025 [citato 4 giugno 2025]; Disponibile su: https://thesis.unipd.it/handle/20.500.12608/10582