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PROTOCOL
LUNG SEGMENTECTOMIES: FROM CORRECT INDICATION TO APPROPRIATE SURGICAL THERAPY, VIA ACCURATE PREOPERATIVE STAGING.
Effect of novel technologies on surgical and oncological outcomes in patients with stage I NSCLC undergoing segmentectomy

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COORDINATING INVESTIGATOR

I have approved this Protocol entitled **LUNG SEGMENTECTOMIES: FROM CORRECT INDICATION TO APPROPRIATE SURGICAL THERAPY, VIA ACCURATE PREOPERATIVE STAGING** and I agree to conduct the study as detailed herein and according to the current version of the World Medical Association Declaration of Helsinki, Good Clinical Practice guideline and applicable regulatory requirements. I will provide all study personnel under my supervision with all information needed to perform the study and I will inform them about their responsibilities and obligations

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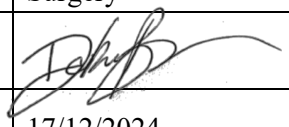
Signature	
Date	17/12/2024

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Date	

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History of substantial amendments

Protocol Sections	Starting Protocol Version *(dd.mm.yyyy)*	Amended Protocol Version *(dd.mm.yyyy)* Changes are in bold	Reason for changes

Abbreviations

CA	Competent Authority
IEC	Indipendent Ethics Committee
eCRF	electronic Case report form
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product

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SUMMARY

Study Title	**LUNG SEGMENTECTOMIES: FROM CORRECT INDICATION TO APPROPRIATE SURGICAL THERAPY, VIA ACCURATE PREOPERATIVE STAGING.** **Effect of novel technologies on surgical and oncological outcomes in patients with stage I NSCLC undergoing segmentectomy**		
Study code	**701** / OSS - **2024**	**Acronym:**	
Version and Date	Version n. 1 – 17/12/ 2024		
Sponsor (Institution)	ICH		
Coordinating Investigator	DEBORA BRASCIA Debora.brascia@hunimed.eu 3921959791		
Supporter	*(If any)*		
Product Name	*(If any)*		
Study indication	Early-stage Lung cancer		
Study population			
Background and rationale	Non-small cell lung cancer (NSCLC) is diagnosed at an early stage in approximately 40% of patients. With the advancement of radiological technologies and the implementation of screening programs, this percentage is expected to increase [1]. Surgical treatment is considered the gold standard in early-stage NSCLC. However, therapeutic failure rates have been reported to be high (30-55%) due to locoregional recurrence and the appearance of distant metastases [2,3]. Historically, lobar resections have always been considered the standard of care in patients with stage I NSCLC. Sublobar resections were widely indicated mostly in patients with limited respiratory function [4]. Several studies in the literature have hypothesized the non-inferiority of segmentectomy vs lobectomy for small solid tumors [5-7]. The current guidelines of the National Comprehensive Cancer Network (NCCN) recommend segmentectomy for patients with nodules ≤2 cm in diameter and satisfying one of the following: positive histology for Adenocarcinoma in situ, ground-glass opacity (GGO) >50%, or doubling time ≥ 400 days [8]. Highly anticipated results from the Japan Clinical Oncology Group JCOG0802/ WJOG4607L) and Cancer and Leukemia Group B randomized phase III trials have shown the efficacy and safety of sublobar resections in clinical stage IA patients, with tumors ≤2 in size [9]. In particular, the JCOG0802/WJOG4607L study [9] showed that segmentectomy is superior to lobectomy in terms of overall survival (OS) and recurrence-free survival for N0 NSCLC, with T<2 cm, suggesting segmentectomy as a standard surgical procedure (rather than lobectomy) for patients with small (<2cm, C/T ratio >0.5) and		

	peripheral NSCLC. A multicenter, international non-inferiority study confirmed these results, the CALGB140503 [10], which demonstrated that sublobar resections (wedge and segmentectomies) are not inferior to lobectomies for patients with peripheral NSCLC, stage cT1aN0, with dimensions ≤2 cm without hilar and mediastinal lymph node metastases, achieving 5-year disease-free-survival (DFS) rates of 63.6% vs 64.1%, respectively (HR: 1.01; P = .0176) and OS at 5 years of 80.3% vs 78.9%, respectively (HR: 0.95; P = .014). However, despite the evidence supporting the curative intent of segmentectomy in stage IA NSCLC, clear surgical guidelines on the correct execution of the same still persist. In particular, the most discussed surgical critical issues that are closely related to the success of the segmentectomy are the obtaining of adequate surgical margins and an adequate lymph node dissection that allows an oncologic correct resection and, above all, an adequate oncological staging.
Study Objectives	This research aims to investigate segmentectomies as a potential surgery of the future by examining their clinical indications, surgical and oncological outcomes, and the latest scientific evidence. Specifically, the study will focus on three main objectives. Firstly, to explore new parameters such as positivity and extent of SUVmax on PET/CT and serum CEA levels which may indicate higher malignancy of the disease, even in pulmonary nodules < 2 cm or in areas GGO/subsolid, and therefore require systematic lymph node dissection. Secondly, to compare the surgical adequacy of segmentectomies performed using different techniques such as open, VATS, and RATS, by evaluating surgical margins, the number of lymph nodes removed, upstaging to the definitive pathology, and local/distant recurrence during follow-up of patients. Thirdly, to assess whether the use of 3D preoperative planning has helped to achieve adequate surgical margins by reducing the recurrence rate in patients. The final aim is to eliminate the size of the nodule as the only indication parameter for segmentectomy and consider both morphological and biomolecular data expressing the malignancy of the disease.
Study Endpoints/Outcomes	Primary study endpoints/outcomes: Recurrence rate, mortality rate Secondary study endpoints/outcomes: Risk factors for recurrence and mortality
Study design	The concept is to conduct a research study on patients who have undergone lung resection for NSCLC in stage IA (<2cm, N0) using open, VATS, or RATS techniques from 2014 to 2023, with the aim of creating a database of clinical, surgical, and oncological data for subsequent analysis, as explained in the study objectives. The study will focus on various endpoints including overall survival (OS), recurrence-free-survival (RFS), and time-to-recurrence (TTR). All patients will undergo follow-up with control CT scans at 3, 6, 12 months, and then annually.
Eligibility Criteria	Inclusion criteria: adult (>18y) pts with NSCLC in stage IA (<2cm, N0) using open, VATS, or RATS Exclusion criteria: pediatric patients, advanced stages, bilobectomy, pneumonectomy, neoadjuvant treatments.

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Study Procedures	This is an observational retrospective study, so we will be collecting retrospectively data from pts with NSCLC in stage IA (<2cm, N0) who had undergone lung resection using either open, VATS, or RATS
Number of patients (planned)	Number of patients projected for the entire study: -400 segmentectomies -1000 lobectomies
Sample size and statistical consideration	Sample size calculation not needed
Study timetable	Time necessary for data extraction: 4-6 months Time necessary for data analysis: 2 weeks
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki and applicable guidelines as well as all national legal and regulatory requirements.

BACKGROUND

Non-small cell lung cancer (NSCLC) is diagnosed at an early stage in approximately 40% of patients. With the advancement of radiological technologies and the implementation of screening programs, this percentage is expected to increase [1]. Surgical treatment is considered the gold standard in early-stage NSCLC. However, therapeutic failure rates have been reported to be high (30-55%) due to locoregional recurrence and the appearance of distant metastases [2,3]. Historically, lobar resections have always been considered the standard of care in patients with stage I NSCLC. Sublobar resections were widely indicated mostly in patients with limited respiratory function [4].

Several studies in the literature have hypothesized the non-inferiority of segmentectomy vs lobectomy for small solid tumors [5-7]. The current guidelines of the National Comprehensive Cancer Network (NCCN) recommend segmentectomy for patients with nodules ≤2 cm in diameter and satisfying one of the following: positive histology for Adenocarcinoma in situ, ground-glass opacity (GGO) >50%, or doubling time ≥ 400 days [8]. Highly anticipated results from the Japan Clinical Oncology Group (JCOG0802/WJOG4607L) and Cancer and Leukemia Group B randomized phase III trials have shownthe efficacy and safety of sublobar resections in clinical stage IA patients, with tumors ≤2 in size [9]. In particular, the JCOG0802/WJOG4607L study [9] showed that segmentectomy is superior to lobectomy in terms of overall survival (OS) and recurrence-free survival for N0 NSCLC, with T<2 cm, suggesting segmentectomy as a standard surgical procedure (rather than lobectomy) for patients with small (<2cm, C/T ratio >0.5) and peripheral NSCLC. A multicenter, international non-inferiority study confirmed these results, the CALGB140503 [10], which demonstrated that sublobar resections (wedge and segmentectomies) are not inferior to lobectomies for patients with peripheral NSCLC, stage cT1aN0, with dimensions ≤2 cm without hilar and mediastinal lymph node metastases, achieving 5-year disease-free-survival (DFS) rates of 63.6% vs 64.1%, respectively (HR: 1.01; P = .0176) and OS at 5 years of 80.3% vs 78.9%, respectively (HR: 0.95; P = .014). However, despite the evidence supporting the curative intent of segmentectomy in stage IA NSCLC, clear surgical guidelines on the correct execution of the same still persist. In particular, the most discussed surgical critical issues that are closely related to the success of the segmentectomy are the obtaining of adequate surgical margins and an adequate lymph node dissection that allows an oncologically correct resection and, above all, an adequate oncological staging.

2.2. RADICALITY AND SURGICAL MARGINS

Currently, there is no agreement on how wide surgical margins should be to prevent local recurrence. Various studies suggest safety margins of at least 15mm in the deflated lung or 20mm in the inflated lung [11]. On the other hand, the NCCN guidelines recommend safety margins of at least 2 cm or the size of the resected nodule. Nodule size is a significant prognostic factor in stage I non-small cell lung cancer. A nodule size of 2 cm or smaller, or a margin-to-tumor ratio greater than 1, has been shown to significantly reduce the risk of local and distant recurrence [12,13].

2.2.1. SAFE SURGICAL MARGINS AND 3D RECONSTRUCTIONS

The advent of high-resolution CT scans has led to the development of new three-dimensional reconstruction systems, which have become widely used in the medical field. These systems can overcome some of the limitations of traditional CT scans, particularly in pre-operative planning for certain cases. 3D reconstructions can be especially helpful for segmentectomy procedures, as they allow the surgeon to determine the correct surgical approach and evaluate the width of the surgical margins beforehand. This can help to adjust the surgical intervention, extending it to lobectomy if necessary. In most cases, it is difficult to establish the safety of the surgical margin during the preoperative phase due to the absence of clear fissures visible on CT scans between the lung segments. The resection margins, which coincide with the intersegmental planes, are typically identified intraoperatively.

2.3. RADICALITY AND LYMPHADENECTOMY

According to Matsamura et al. [14], lymph nodes that are located in a different segmental bronchus or isolated from the segmental bronchus affected by anatomical resection are known as isolated lobarsegmental lymph nodes (iLSN). These lymph nodes are the most challenging to remove during surgery. Lobectomy has an advantage over segmentectomy in that it allows for easier removal of these lymph nodes.

2.3.1 LYMPHADENECTOMY AND SURVIVAL

All clinical studies have demonstrated that lymph node staging is essential in predicting the prognosis for NSCLC. Recently, Thomas [15] emphasized that a complete lymph node dissection is crucial for performing a "radical segmentectomy", despite the current NCCN guidelines not mandating invasive mediastinal nodal staging in patients with stage IA peripheral lung cancer [7].Yendamuri et al. [16] haverecently published the results of a large series of patients treated with sublobar resections for stage I NSCLC. They demonstrated how the only prognostic factor for 5-year survival was the number of lymph nodes examined, highlighting the importance of lymph node dissection in sublobar resections.

2.3.2. RISK FACTORS FOR LYMPH NODE INVOLVEMENT

Sun et al. [17] analyzed 200 patients with cT1N0M0 NSCLC and found that patients with an SUVmax<2.5 or maximum tumor diameter ≤1 cm have a low chance of lymph node metastasis. In contrast, Lutfi et al. [18] showed that in patients with stage IA NSCLC who underwent segmentectomy, the size of the nodule and the number of lymph nodes removed were the risk factors for N1/2 lymph node metastasis. Another study by Lee et al. [19] found that the rate of N2 lymph node positivity in patients with stage I NSCLC was directly correlated to the size of the nodule (6.5% in patients with T1 NSCLC vs 8.7% in patients with T2 nodule) and to the SUVmax of the primary nodule (1.9% if ≤4 and 10.5% if >4). Tsutani et al. [20] discovered that the negative predictive criteria for lymphatic invasion in patients with clinical stage IA adenocarcinoma were a size less than 0.8 cm or a max SUV less than 1.5. Further studies showed that SUVmax was a prognostic factor for patients with adenocarcinoma but not with squamous carcinoma. Also, an SUVmax > 5 was a strong predictive factor of lymphatic metastases. Currently, there is no evidence of a correlation between the SUVmax value and the status of isolated lobar-segmental lymph nodes (iLSN). In addition to the factors mentioned above, the genomic characterization of early-stage lung tumors can also serve as a potential predictive factor of more aggressive pathology and potential loco-regional lymphatic invasion [21-23]. However, this area of research remains largely unexplored. It is important to note that pure ground-glass opacity (GGO) lesions or subsolid lesions (SSL) require long-term radiological follow-up to differentiate between benign and potentially malignant lesions. This subgroup of lesions is critical for research due to multiple reasons. First, they are becoming more and more common due to the increase in screening programs and improvement in radiological technologies.

Second, the molecular pathways and genomic characterization responsible for the development of thesepremalignant lesions into early-stage lung tumors are not well-defined. A better genomic definition of lesions with the highest risk of evolution could be useful in defining the most appropriate surgical treatment. In Asian populations, mutational analysis of GGO or SSL lesions showed a prevalence of the EGFR gene mutation in 42% of cases, followed by the KRAS gene in 21% [24-27]. Furthermore, the solid and semisolid portions of early-stage lung tumors also showed overexpression of some genes, including Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), which encodes CEA, currently being evaluated as a predictive biomarker in the context of such lesions, as shown in some recent studies. In particular, Nakao et al. [28], in a large study of GGOs and resected SSLs, showed much higher serum CEA values in solid lesions than in GGOs, and Woodard et al. [29] showed higher CEA levels in both the lepidic and solid components. These results, although still preliminary and awaiting validation in larger studies, could pave the way for the identification of biomarkers that, together with radiology and histology, can stratify subsolid

lesions, to initiate less stringent follow-ups for indolent ones and initiate surgical therapy for more aggressive ones.

2.3.3. SURGICAL APPROACH AND LYMPH NODE UPSTAGING

The nodal upstaging rate measures the percentage of patients who display nodal upstaging (cN0 ->pN1/N2) following a definitive pathological analysis. It has been demonstrated multiple times that an adequate lymph node dissection can bridge the survival gap between sublobar and lobar resection. Various studies have revealed that the number of lymph nodes and lymph node stations removed varies depending on the surgical approach utilized. In particular, most studies have shown that the robotic approach and, to a similar degree, the VATS approach (as opposed to open surgery) are linked with a higher number of lymph nodes removed. As a result, they are associated with better staging and a higher upstaging rate [30, 31].

RATIONALE

Despite the evidence supporting the curative intent of segmentectomy in stage IA NSCLC, clear surgical guidelines on the correct execution of the same still persist. In particular, the most discussed surgical critical issues that are closely related to the success of the segmentectomy are the obtaining of adequate surgical margins and an adequate lymph node dissection that allows an oncologically correct resection and, above all, an adequate oncological staging.

STUDY OBJECTIVES

4.1. Objectives

This research aims to investigate segmentectomies as a potential surgery of the future by examining their clinical indications, surgical and oncological outcomes, and the latest scientific evidence. Specifically, the study will focus on three main objectives. Firstly, to explore new parameters such as positivity and extent of SUVmax on PET/CT and serum CEA levels which may indicate higher malignancy of the disease, even in pulmonary nodules < 2 cm or in areas GGO/subsolid, and therefore require systematic lymph node dissection. Secondly, to compare the surgical adequacy of segmentectomies performed using different techniques such as open, VATS, and RATS, by evaluating surgical margins, the number of lymph nodes removed, upstaging to the definitive pathology, and local/distant recurrence during follow-up of patients. Thirdly, to assess whether the use of 3D preoperative planning has helped to achieve adequate surgical margins by reducing the recurrence rate in patients. The final aim is to eliminate the size of the nodule as the only indication parameter for segmentectomy and consider both morphological and biomolecular data expressing the malignancy of the disease.

4.1.1. Primary objective

Analyze the recurrence rate and the mortality rate in the entire population, by comparing the result by type of surgery, type of surgical access and histology.

4.1.2. Secondary objectives

Identify risk factors for recurrence and mortality

4.2. Endpoints

4.2.1. Primary endpoint

Recurrence rate and mortality

4.2.2. Secondary endpoint

Risk factors for recurrence and mortality

STUDY POPULATION

5.1. Inclusion criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the study:
Subjects fulfilling all of the following inclusion criteria are eligible for the study:

- Adult patients (>18y)
- Diagnosed with NSCLC stage IA (<2cm, N0) NSCLC
- No neoadjuvant treatement

5.2. Exclusion criteria

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject:

- Neoadjuvant treatment
- Advanced lung cancers
- Bilobectomy/Pneumonectomy performed

5.3. Recruitment

A retrospective data collection from clinical records will be perfomed, following the above mentioned inclusion criteria.

STATISTICAL CONSIDERATIONS

1.1. Sample size

No sample size calculation needed since it is a retrospective analysis, so all patients respecting the inclusion criteria from ten years back will be collected.

1.2. Analysis

Descriptive statistical analysis will be performed on the basic clinical characteristics of the study population, laboratory test results, biopsies, and surgical procedure data. Continuous variables will be reported as means ± SD, while categorical variables will be reported as numbers and percentages. Comparisons between groups will be performed using the Chi-square test. To estimate the probability of OS, RFS, and TTR in patients undergoing segmentectomy, we can use Kaplan-Meier analysis. This will be done with regard to the following variables: (1) OPEN, VATS orRATS techniques, (2) SUVmax and serum CEA values, and (3) surgical margins. Differences will be compared using the log-rank test. To examine the factors actually associated with OS, RFS, and TTR at follow-up, Cox regression models(univariate and multivariate analysis) can also be used

QUALITY ASSURANCE AND CONTROL Quality Assurance and Quality Control systems based on written SOPs are in place at the Sponsor site.

QUALITY ASSURANCE AND CONTROL

Quality Assurance and Quality Control systems based on written SOPs are in place at the Sponsor site.

1.3. Data handling and record keeping / archiving

The investigator must keep the documents on file for at least 7 years after completion or discontinuation of the study. After that period, the documents may be destroyed, subject to local regulations.

1.4. Case Report Forms

The collected data will be processed by the investigator of the study for the exclusive purposes connected with the fulfilment of the present study, made anonymous and, in this form, aggregates in the project database, solely on the basis of the realization of the study itself and the achievement of objectives.

The data will not be disclosed except in strictly anonymous and aggregated form.

Source documents

Source data must be available at the site to document the existence of the study participants. Source data include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

CONFIDENTIALITY OF PATIENT RECORDS

The investigator assures that patients' anonymity should be maintained and that their identities are protected from unauthorized parties. Particular attention should be paid whenever patient data are supplied to third parties and may be autonomously processed.

The investigator should keep in a confidential way a patient identification log recording both patient code and name. Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

ETHICAL CONSIDERATIONS

The Coordinating Investigator ensures that this study is conducted in agreement with this protocol, the Good Clinical Practice, the current version of Declaration of Helsinki and the applicable regulations.

The protocol and any amendments are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

INFORMED CONSENT AND INFORMATION ON THE TREATMENT OF PERSONAL DATA

Humanitas Mirasole S.p.A. as Data Controller will not require to patients a specific consent for this research project, because it is an "*Istituto di Ricovero e Cura a carattere Scientifico*" (I.R.C.C.S.) and, as established by law, the scientific research is considered instrumental to healthcare activities, so it is allowed to process personal and particular data, originally collected for treatment purposes, for carrying out research activities, pursuant to art. 9, paragraph 2, letter. j) of EU Regulation 2016/679 and art. 110-bis, paragraph 4, of the Privacy Code (Legislative Decree 196/2003).

In any case, all information on the research project will be available to patients on the web page www.humanitas.it/privacy. Everytime they can request to be excluded from the project (so-called opt-out right).

DATA OWNERSHIP

Istituto Clinico Humanitas is the owner of the data resulting from the study.

PUBLICATION POLICY

After completion of the study, the Coordinating Investigator prepares a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript is delivered to the co-authors for comments and then sent to a scientific journal for publication.

FUNDING AND SUPPORT

None

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APPENDICES

EXPECTED RESULTS

The study aims to achieve two main objectives. Firstly, it seeks to establish a relationship between the Maximum standardized uptake value (SUVmax) and serum carcinoembryonic antigen (CEA) levels and the level of aggressiveness of lung cancer. Specifically, the study aims to identify a cut-off value for SUVmax

and CEA levels that can be combined with the morphology of the nodule and its doubling time in a prognostic score. This score will help to stratify patients and determine the most appropriate surgical therapy for each patient, i.e., segmentectomy or lobectomy.

Secondly, the study focuses on analyzing the surgical outcomes of segmentectomies. The study aims to demonstrate the effectiveness of using new three-dimensional reconstruction technologies in preoperative planning, which will help in evaluating surgical margins. This will positively impact the reduction of local and/or remote recurrences. Additionally, the study aims to demonstrate the superiority of minimally invasive segmentectomies over open-technique segmentectomies in terms of the quality of lymph node staging.