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Complication and lung function impairment prediction using perfusion and computed tomography air trapping (CLIPPCAIR): protocol for the development and validation of a novel multivariable model for the prediction of post-resection lung function

Carey Meredith Suehs¹^, Laurence Solovei²^, Kheira Hireche², Isabelle Vachier¹, Denis Mariano Goulart^{3,4}, Lucie Gamon⁵^, Jérémy Charriot¹, Isabelle Serre⁶, Nicolas Molinari⁷, Arnaud Bourdin^{1,4}, Sébastien Bommart^{4,8}

¹Department of Respiratory Diseases, The University of Montpellier, CHU Montpellier, Montpellier, France; ²Department of Thoracic Surgery, The University of Montpellier, CHU Montpellier, Montpellier, France; ³Department of Nuclear Medicine, The University of Montpellier, CHU Montpellier, Montpellier, France; ⁴PhyMedExp, CNRS, INSERM, The University of Montpellier, CHU Montpellier, Montpellier, France; ⁵Department of Medical Information, The University of Montpellier, CHU Montpellier, Montpellier, France; ⁶Department of Pathology, The University of Montpellier, CHU Montpellier, Montpellier, France; ⁷IMAG, CNRS, The University of Montpellier, CHU Montpellier, Montpellier, France; ⁸Department of Radiology, The University of Montpellier, CHU Montpellier, Montpellier, France

Correspondence to: Sébastien Bommart. Department of Radiology, Hôpital Arnaud de Villeneuve, 371 Avenue du Doyen Gaston Giraud, F-34295 Montpellier Cedex 5, France. Email: s-bommart@chu-montpellier.fr.

Background: Recent advancements in computed tomography (CT) scanning and post processing have provided new means of assessing factors affecting respiratory function. For lung cancer patients requiring resection, and especially those with respiratory comorbidities such as chronic obstructive pulmonary disease (COPD), the ability to predict post-operative lung function is a crucial step in the lung cancer operability assessment. The primary objective of the CLIPPCAIR study is to use novel CT data to develop and validate an algorithm for the prediction of lung function remaining after pneumectomy/lobectomy.

Methods: Two sequential cohorts of non-small cell lung cancer patients requiring a pre-resection CT scan will be recruited at the Montpellier University Hospital, France: a test population (N=60) on which predictive models will be developed, and a further model validation population (N=100). Enrolment will occur during routine pre-surgical consults and follow-up visits will occur 1 and 6 months after pneumectomy/lobectomy. The primary outcome to be predicted is forced expiratory volume in 1 second (FEV1) six months after lung resection. The baseline CT variables that will be used to develop the primary multivariable regression model are: expiratory to inspiratory ratios of mean lung density (MLD_{e/i} for the total lung and resected volume), the percentage of voxels attenuating at less than -950 HU (PVOX₋₉₅₀ for the total lung and resected volume) and the ratio of iodine concentrations for the resected volume over that of the total lung. The correlation between predicted and real values will be compared to (and is expected to improve upon) that of previously published methods. Secondary analyses will include the prediction of transfer factor for carbon monoxide (TLCO) and complications in a similar fashion. The option to explore further variables as predictors of post-resection lung function or complications is kept open.

Discussion: Current methods for estimating post-resection lung function are imperfect and can add assessments (such as scintigraphy) to the pre-surgical workup. By using CT imaging data in a novel fashion, the results of the CLIPPCAIR study may not only improve such estimates, it may also simplify patient pathways.

^ ORCID: Carey Meredith Suehs, 0000-0002-2175-3496; Laurence Solovei, 0000-0002-5491-5260; Lucie Gamon, 0000-0003-0322-3384.

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Introduction

Lung cancer is the leading cause of cancer death in men (1) and incidence is increasing in women (2). The standard treatment currently offering the best survival is surgical resection. However, the vast majority of lung cancer patients have lung disability that can limit surgical indications. Predicting the effect of a hypothetical resection on lung function plays an essential role in determining surgical candidates by assessing the risk of postoperative complications and long-term respiratory failure. Current prediction algorithms can involve performing additional specific examinations (such as ventilation perfusion scintigraphy or stress testing) for patients in the “gray zone” and deemed high risk. Perfusion scintigraphy enters the decision algorithm to predict postoperative forced expiratory volume at 1 second (FEV1ppo). Though currently necessary for many patients, such FEV1ppo estimates are not only obviously imperfect (3), they can also delay treatment, thus increasing patient anxiety and loss of opportunity (4,5).

Though certain studies have suggested that computed tomography (CT), in particular dual energy CT, can provide more-precise or at least complementary data during pre-surgical evaluations (6-8), the gains when predicting FEV1ppo (9-12) remained modest compared to scintigraphy. However, recent advancements in CT scanning and post-image processing have provided new means of assessing factors affecting postoperative lung function that until now have remained under-studied: (I) disease severity and especially chronic obstructive pulmonary disease (COPD) heterogeneity (7,13,14); (II) the capacity of residual parenchyma for postoperative compensation or functional expansion, which varies according to the underlying parenchyma and the resected lobe (6); (III) postoperative changes in thoracic perfusion (12).

Micro-scanning studies (15-19) have demonstrated that distal airway rarefaction precedes emphysema and functional limitation due to COPD and starts in the early phase of the disease before symptoms appear. Approximately 80% of the distal airways are destroyed in the final stage of the disease (GOLD 4). The degree of distal obstruction may thus play

a role in the genesis of postoperative respiratory disability. Obstruction of the distal airways (<2 mm) is not directly visible via CT, but can be indirectly quantified by measuring expiratory air-trapping (20-22).

A vascular origin for COPD was also mentioned as early as the 1950s and illustrated by vascular rarefaction on pulmonary angiographies. The latter was recently updated by advanced processing of CT images (23). Additionally, CT perfusion measurements were more accurate than lung scintigraphy in predicting postoperative lung function (24). However, the latter study did not include an appropriate validation population and their true predictive value or generalizability therefore remains unknown. Given the diverse ways in which CT data may now improve FEV1ppo estimates (via new methods for describing air-trapping and perfusion variables), our study aims to fill this gap. If the CT scan currently often required for assessing the extent of pulmonary cancer can simultaneously provide precise values for FEV1ppo, recourse to pre-surgical pulmonary scintigraphy would no longer be necessary and the preoperative planning pathway thus simplified.

Objectives

The primary objective of the CLIPPCAIR study is to construct and validate a new algorithm for predicting postoperative FEV1 values (FEV1ppo) for lung resection candidates using dual energy chest CT scan data. Secondly, the predictions made using traditional scintigraphic data will be compared with those from the new algorithm, and cumulative contrast media and irradiation doses associated with imaging will be presented. How other measures of pulmonary function [e.g., transfer factor of the lung for carbon monoxide (TLCO)] and the presence/absence of operative complications might be predicted will also be investigated. Additionally, we will also take the opportunity to explore the potential links between (I) pre-surgical imaging data, (II) post-surgical changes in respiratory function, and (III) changes in health related quality of life. Finally, the creation of a tissue sample collection will provide the means for an ancillary micro CT study.

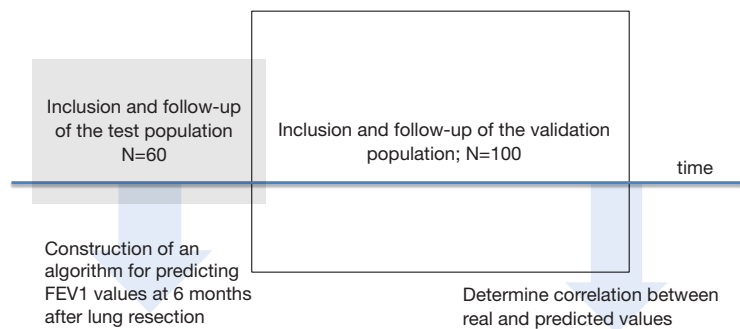


Figure 1 Separate “test” and “validation” groups will be recruited.

Methods

Study design

The CLIPPCAIR study is an open, prospective study designed for the development and validation of an algorithm based on novel CT data for the prediction of residual lung function 6 months after lung resection surgery. This study will be conducted according to the principles of the Declaration of Helsinki (as revised in 2013) and was approved by a randomly assigned, independent, ethics committee (Comité de Protection des Personnes Sud-Est III, reference number: 2018- 050 B) as per French law on 28 December 2018. The study was registered on clinicaltrials.gov (NCT03885765) and reporting will be performed according to TRIPOD guidelines (available at <https://dx.doi.org/10.21037/atm-21-214>) (25,26). Two study groups will be recruited, consisting of the first 60 patients (the “test” group) for algorithm development and the subsequent 100 patients for external validation (the “validation” group) (Figure 1). Predicted values for post-surgical FEV1 (% predicted, determined according to novel CT data (primary objective) or classic methods (a segment-counting algorithm (27), the British Thoracic Society algorithm (28), and lung perfusion scintigraphy)) will be confronted with real values using correlation statistics, the goal being to improve said correlation.

Setting and participant eligibility

This study will take place at the Arnaud de Villeneuve Hospital, Montpellier University Hospitals, Montpellier, France. The targeted study population corresponds to non-small cell lung cancer patients requiring pulmonary resection or lobectomy or pneumonectomy and who need to update their CT scan prior to surgery. Detailed

eligibility criteria are given in Table 1. With the exception of those that directly affect lung function, subjects may participate in other cancer treatment studies as well, given that this represents a real-life situation for most cancer patients, and we do not wish to deprive patients of novel treatment opportunities. Written, informed consent for study participation is required of all study candidates prior to enrolment. The single payer national health insurance program in France provides health care to all residents/citizens; the recruited patients should therefore represent a large range of socioeconomic and urban-versus-rural backgrounds.

Predicted and explanatory variables

Outcomes to be predicted

The primary outcome to be predicted is the FEV1 (% predicted and then in litres) from routine spirometry at 6 months following lung resection surgery (Table 2). The correlation between predicted and real values for post-surgical FEV1% predicted will also be considered as a main outcome. Secondly, we will also develop predictive models for TLCO and the presence/absence of complications and their severity grade according to the Seely classification (29).

Explanatory variables

The novel predictive data in this study includes 5 predefined variables derived from baseline thoracic CT scans as indicated in Table 2. The latter cover expiratory to inspiratory ratios of mean lung density ($MLD_{e/i}$), the percentage of voxels attenuating at less than -950 HU ($PVOX_{-950}$) and iodine concentrations for both the total lung and for resected sections. $MLD_{e/i}$ estimates the extent of air-trapping experienced by the patient, while $PVOX_{-950}$

Table 1 Inclusion and exclusion criteria for participants

| Inclusion criteria | Exclusion criteria |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • Adult patient over 18 years of age • Patient diagnosed with non-small cell lung cancer • Indication for pulmonary excision surgery • Patient requiring a more recent pre-surgical computed tomography scan (CT scan) • The patient has been correctly informed about the study and has signed the consent form • The patient is affiliated with or a beneficiary of the French single-payer social security programme (national health insurance) | <ul style="list-style-type: none"> • Patient in an exclusion period determined by another protocol • Participation in another study that may affect the results of the present study[†] • Patient under legal or judicial protection[‡] • Contraindication for surgery or iodine injection[§] • Pregnant or lactating women |

[†], patients participating in the present study can also participate in cancer treatment studies and this reflects the real-life situation of many patients. However, if the investigator feels that participation in such a study may directly affect lung function, the patient will not be included. [‡], for example, patients under legal guardianship of any kind, or prisoners. [§], for example, unfit for surgery (e.g., any of the following: FEV1 <50% of predicted values, predicted post-operative FEV1 of <1 litre (according to xenon perfusion scintigraphy scanning), peak VO₂ values from exercise testing (pre-operative or predicted post-operative) <15 mL/kg/min, 6 minute walking distance <350 m, left ventricle ejection fraction <40%, a tricuspid regurgitation velocity >3 m/s, PaCO₂ <50 mmHg or PaO₂ <60 mmHg at baseline without any treatable cause other than chronic obstructive pulmonary disease (COPD) or lung cancer), renal insufficiency or allergy to iodinated contrast media.

represents the extent of emphysema as explained in *Figure 2*. The performance of any new predictive models developed for the primary outcome will be compared with analogous previously published algorithms as presented in *Table 2*. We will also be exploring CT data for further potential variables with predictive capabilities that are currently unknown.

Blinding

Given that this study is based on routine practices with assessments performed by separate teams, and furthermore that modelling occurs after completed data collection for a given subsequent population, the blinding of predicted and explanatory variables when performing assessments was deemed unnecessary.

Describing the study population: baseline and treatments

Basic demographics (age, sex, weight, height and body mass index), comorbidities (specifically, the starting dates for renal insufficiency, diabetes, diffuse interstitial pneumonia, or ischemic heart disease, if present), whether or not the patient is participating in another interventional study, as well as commonly used scores (Charlson score, WHO score, ASA score and Thoracoscore) will be used to describe the population at baseline. Baseline pulmonary function will also be recorded. A listing of any concomitant treatments

will be maintained for each patient throughout the study, including adjuvant radio- or chemotherapy. Surgical resection will be characterised by type (pneumonectomy, bi-lobectomy, lobectomy, or lobectomy with anastomosis resection), whether or not lymph node dissection was performed, and whether or not the resection was atypical. Cancer staging using the TNM system will be described once at baseline based on imaging data (cTNM), and again following surgery and incorporating pathology results from excised tissue (pTNM).

Assessments

Spirometry and plethysmography

Spirometry/plethysmography will be carried out as recommended by the European Respiratory Society (30) using Body Box equipment (Medisoft Bodybox 5500, Sorinnes, Belgium). With the exception of the FEV1/FVC ratio, which is calculated as litres/litres, all outcomes listed in *Table 2* will be calculated as both % predicted values and as litres.

Single-breath carbon monoxide uptake in the lung

The uptake of carbon monoxide by the lung will be described by the TLCO (mL/min/mmHg) according to current recommendations (31).

Table 2 Patient-specific measure and time frames

Respiratory function at baseline and at 6 months after surgery

Spirometry

Forced expiratory volume in 1 second (FEV1)[†]

Forced vital capacity (FVC)

FEV1/FVC

Plethysmography

Total lung capacity (TLC)

Residual volume (RV)

Functional residual capacity (FRC)

Carbon monoxide transfer study

Transfer factor of the lung for carbon monoxide (TLCO) (mL/min/mmHg)[‡]

Incremental exercise testing

Maximum volume of oxygen utilized per unit time (VO₂Max), in mL/kg/mn and % predicted

6-minute walking test

Distance walked (meters)

Lung computed tomography (CT) Scan (baseline)

Expiratory to inspiratory ratio of mean lung density (MLDe/i), total[§]MLDe/i of the section to be excised/MLDe/i total[§]Percentage of emphysema according to voxel thresholding at -950 HU (PVOX-950), total[§]PVOX-950 for the section to be excised[§]Iodine concentration [I] of the section to be excised/[I] total[§]

Other exploratory measures

Estimates of post-surgical lung function based on segment counting on baseline CT scan

 $FEV1_{\text{post-seg-1}} = FEV1_{\text{pre-op}} \times (1 - 0.0526 \times N)$, where N is the number of segments to be excised (27)[¶] $FEV1_{\text{post-seg-2}} = FEV1_{\text{pre-op}} \times [(19 - a - b)/(19 - a)]$, where a is the number of non-obstructed segments to be excised and b is the number of obstructed segments to be excised (28)[¶]

Lung scintigraphy (baseline)

FEV1_{pre-scinti} = the pre-operative estimate of FEV1 provided by scintigraphy (litres/sec)

Regional FEV1 distribution: the fraction of total FEV1 represented by each of the following regions of interest (ROI): (I-II) left and right upper lobes, (III-IV) left and right lower lobes, (V) the middle lobe, and (VI) the two lingular segments

FEV1_{post-scinti}: estimated post-operative FEV1 deduced from the regional FEV1 distribution[§]

Quality of life questionnaires

EQ-5D-5L, a general health outcome instrument

QLQ-C30 Version 3.0 and associated lung module (QLQ-LC13)

Complications[‡] (per-operative and up to 6 months of follow-up)

The presence/absence of each of the following: reintubation; >48 h mechanical ventilation; cardiac arrhythmia, infarctus, stroke, pneumonia, atelectasis, respiratory arrest, pulmonary embolism, acute respiratory distress syndrome, tracheostomy, bronchopleural fistula, haemothorax, haemoptysis, bleeding requiring reoperation, death

For a given patient, the highest grade of complications according to the classification by Seely *et al.* (29)

[†], the primary outcome to be predicted at 6-months post-surgery; [‡], secondary outcomes that will also be predicted at 6-months post-surgery; [§], novel data that will be used to predict the primary outcome in the primary analysis; [¶], classic methods for predicting the primary outcome.

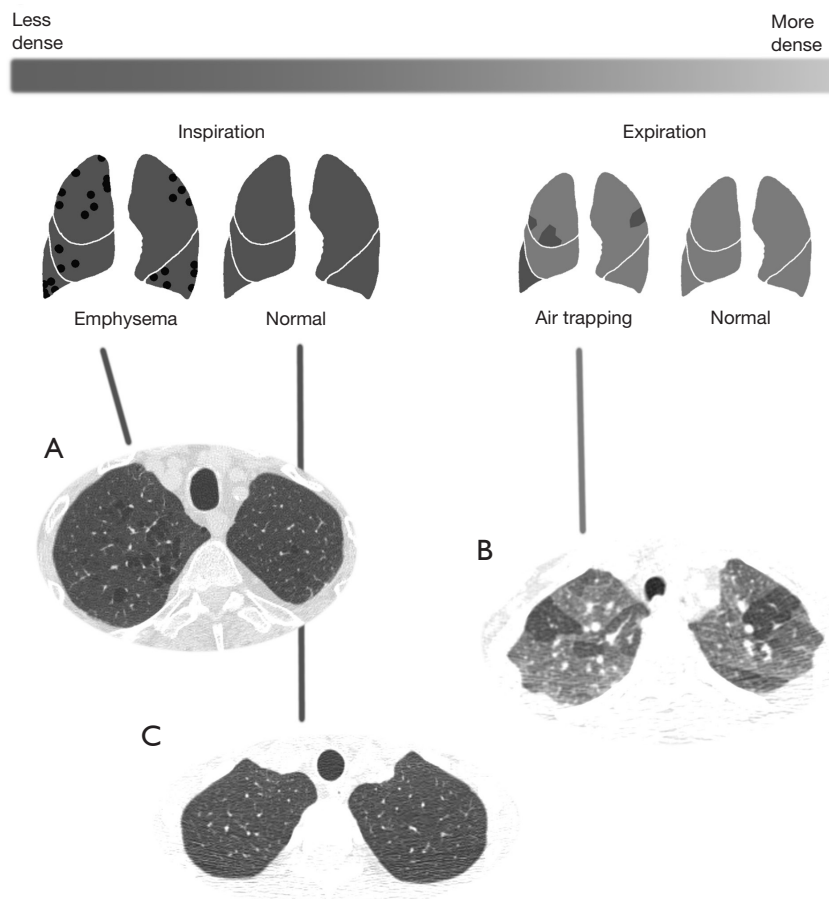


Figure 2 Computed tomography (CT) scan attenuation forms a gradient from less dense (darker grey) to more dense (lighter grey). Emphysema is visualized on inspiratory CT as relatively darker spots or areas, as seen on Panel A. The proportion of voxels attenuating below a given threshold (PVOX-950: <950 Hounsfield Units (HU)) represents the extent of emphysema. Panel B gives an example expiratory lung cross-section with air trapping. The latter is visualized on expiratory CT scans as darker zones corresponding to sections of lung where obstruction prevents the escape of air. These zones are less dense and therefore darker. The air-filled parenchyma from an example inspiratory CT scan (Panel C) are similarly dark. The extent of air trapping can vary in darkness and in coverage. To estimate the extent of air trapping, we calculate the ratio of expiratory to inspiratory mean lung density (MLDe/i) by dividing the mean lung density on expiration (Panel B) by the mean lung density on inspiration (Panel C). A normal inspiratory CT scan as seen in Panel C is homogeneously dark. The darker the air trapping zones detected on an expiratory CT scan (Panel B), the closer the ratio MLDe/i will be to '1'.

Incremental exercise testing

The maximal oxygen consumption (VO_{2max}) during incremental exercise testing will be determined. The latter will be performed according to the American Thoracic Society/American College of Chest Physicians statement (32) using a stationary bicycle (Ergoselect, Sorinnes, Belgium). Briefly, theoretical maximum power is first calculated according to age, sex and body mass index (BMI). The test then starts with a 3-minute warm-up period at 20% of maximum power. Subsequently, power is incremented every

minute with increments chosen according to the physician's discretion. The test ends with volitional fatigue.

6-minute walking test

The distance walked during a 6-minute walking test performed according to current recommendations (33) will be recorded.

Thoracic CT scans and image post-processing

CT is performed using "Revolution CT" (General Electric)

equipment and with respiratory gating (WinspiroPRO, Medical International Research, version 7.9.0). Dual energy acquisitions employing rapidly changing kilovoltage will be used (the x-ray generator will rapidly commute between 80 and 140 kV during a single acquisition). Inspiratory acquisitions (DLP <30 mGy-cm) are performed at total lung capacity and expiratory acquisitions (DLP <30 mGy-cm) at residual volume according to recommendations set by the French Radiology Society (<http://www.sfrnet.org>). The injected contrast media used will be Iomeperol at 350 mg iodine per mL (Iomeron, Bracco Imaging, France).

Image post-processing will be performed by a single radiologist (SB) at a General Electric AW Volumeshare 7 station and will generate (I) a pulmonary perfusion map for visualizing zones of hypoperfusion, (II) measures of mean lung density, and (III) the percentages of voxels attenuating at <-950 HU. For pulmonary perfusion mapping, Gemstone Spectral Imaging software will be used and the concentration of iodine [I] in the chosen zone measured. Myrian software (Intrasense, Montpellier, France) will be used to determine mean lung density of a given zone. The latter software will also be used to segment emphysematous tissues according to an attenuation threshold at -950 HU, as in Gevenois *et al.* (34). Measures (as listed in *Table 2*) will be made for the total lung acquisition, as well as for future resected zones.

Perfusion lung scintigraphy

Perfusion lung scintigraphy is performed for those patients who are considered at increased risk for post-operative lung insufficiency (i.e., those with COPD and impaired pre-operative FEV1, who are likely to undergo postoperative respiratory insufficiency). The patients are installed in a seated, upright position and 185 MBq of ^{99m}Tc-macroaggregated albumin are injected intravenously. Subsequently, scintigraphic data are acquired using a large-field-of-view dual-head gamma-camera as in (35) and according to current recommendations (36). Scintigraphic images are recorded in planar mode using the two detectors of the gamma-camera facing the back of the patient in left and right posterior oblique incidences. The contribution of each lung lobe to the global FEV1 is estimated and a simple subtraction of FEV1 fractions corresponding to regions-to-be-resected provides an estimate of post-surgical FEV1 (see *Table 2*).

Quality of life questionnaires

Two validated quality of life questionnaires available in

French will be administrated. The first is a generic measure of health status (EQ-5D-5L) applicable to any patient population (37,38), while the second (QLQ-C30 Version 3.0) was designed for cancer patients (39-42), with a submodule (QLQ-LC13) specific to lung cancer (43,44). The EQ-5D-5L results in a single index score describing a general health profile ranging from 0 to 1, as well as a visual analogue scale score for overall health evaluation. The QLQ-C30 Version 3.0 results in three scale scores [(I) level of function, (II) global health status, and (III) symptomatology/problems] with higher scores (ranging from 0 to 100) representing a higher response level (45). The QLQ-LC13 provides an additional lung-cancer-specific symptom scale ranging from 0 to 100 with higher scores indicating worse symptomatology (45).

Patient pathways

Throughout the study, patient pathways, i.e., episodes of hospitalization, intensive care, and mechanical ventilation, will be separately characterised by their beginning and end dates. The duration of the initial hospitalization will be determined, as well as the cumulative number of days of each episode type at the end of the study. In addition, the cumulative days alive and non-hospitalized at the end of the study will be determined for each patient. These episodic data are important descriptors of disease severity.

Harms

The potential burdens associated with imaging will be characterized via the quantities of iodine products administered and x-ray exposition data (in Dose length product (DLP) and mSv).

The risk-adjusted morbidity and mortality for lung resection for lung cancer as endorsed by the Society of Thoracic Surgeons (<https://www.sts.org/quality-safety/performance-measures>) will be calculated for the study population. Complications (i.e., any deviation from a normal post-operative cursus) will also be recorded on a per-patient basis and will specifically note the presence/absence of elements listed in *Table 2*. In addition, each complication encountered will be graded according to Seely *et al.* (29):

- ❖ Grade 1: any complication without need for pharmacologic treatment or other intervention;
- ❖ Grade 2: any complication that requires pharmacologic treatment or minor intervention only;
- ❖ Grade 3: any complication that requires surgical, radiologic, endoscopic intervention or multitherapy;

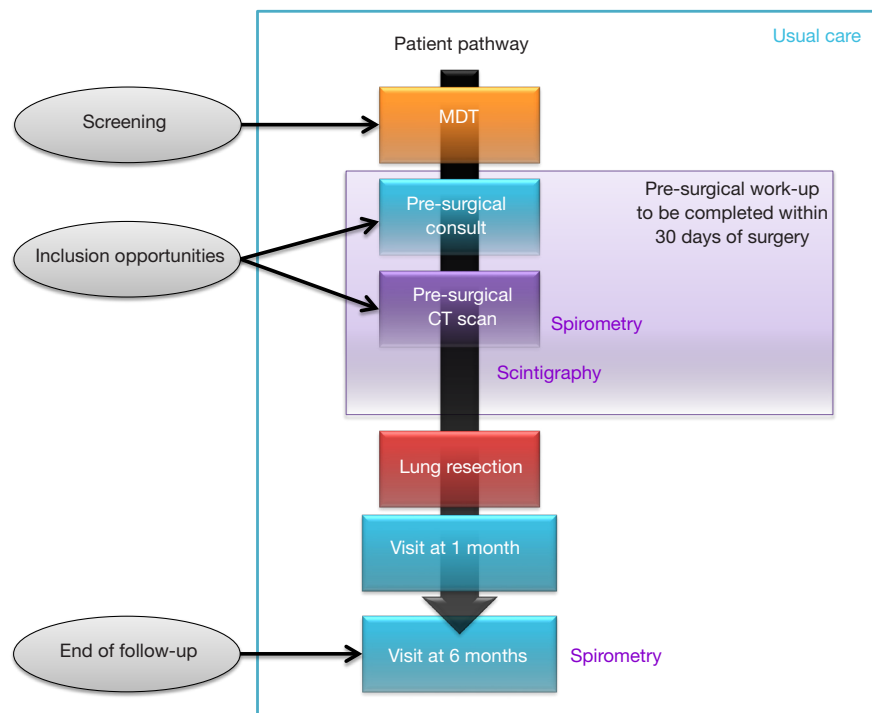


Figure 3 The visits required during the study correspond to usual care for the study population. Preliminary patient screening is discussed during weekly multidisciplinary team (MDT) meetings, and enrolment takes place during routine visits required during the pre-surgical workup to lung resection. The latter work-up requires that spirometry, a thoracic computed tomography (CT) scan and lung scintigraphy (only for high-risk patients) be performed within 30 days of surgery. Additional data will be acquired during routine follow-up visits at 1- and 6-months following surgery.

- ❖ Grade 3a: intervention does not require general anaesthesia;
- ❖ Grade 3b: intervention requires general anaesthesia;
- ❖ Grade 4: any complication requiring intensive care unit management and life support;
- ❖ Grade 4a: single organ dysfunction;
- ❖ Grade 4b: multiorgan dysfunction;
- ❖ Grade 5: any complication leading to the death of the patient.

Finally, any other adverse events will also be recorded and reported in line with French regulations in force.

Logistics

Screening, enrolment and baseline assessments

The visits required during this study correspond to usual, routine care, and are listed in *Figure 3* with corresponding interventions and assessments detailed in *Table 3*.

Preliminary patient screening will take place during

weekly multidisciplinary team (MDT) meetings during which lung cancer cases requiring resection will be discussed; confirmation of eligibility and enrolment will be carried out by investigators during visits required for the pre-surgical workup (*Figure 3*). Care will be taken during the screening and enrolment process to retain sufficient data for the production of a flow chart demonstrating how the study population was constituted.

The study will be presented to eligible patients by investigators during a pre-surgical consult, and the signature of the study consent form collected by the investigator during the visit required for thoracic CT scanning (the timing of the latter two visits may be inverted as long as the patient is correctly informed about the study and has sufficient time to consider study participation). Following enrolment and prior to surgery, the required baseline data will be recorded and the patient will be asked to fill out quality of life questionnaires; outcomes (*Table 2*) pertaining to baseline spirometry, scintigraphy and CT scan data will

Table 3 The schedule for enrolment, interventions, assessments, and visits for participants

| | Multidisciplinary team meeting | V1 D-20 to D-2 | Pre-surgical workup | Surgery D0 | Hospitalization D0 to discharge | V2 M1 (W4 to W6) | V3 M6 (±14 D) |
|------------------------------------------------------------------|-----------------------------------|-------------------|------------------------|----------------------|------------------------------------|---------------------|------------------|
| Inclusion | | | | | | | |
| Verification of eligibility criteria | ✓ | ✓ | ✓ | | | | |
| Presentation of the study | | ✓ | ✓ | | | | |
| Signature of the consent form | | | ✓ | | | | |
| New source of predictive data | | | | | | | |
| Thoracic computed tomography (CT) scan | | | ✓ | | | | |
| Surgical intervention (according to routine practice) | | | | | | | |
| Pulmonary resection | | | | ✓ | | | |
| Safety/Harms | | | | | | | |
| Quantity of contrast media injected; mSv irradiation per patient | | | ✓ | | | | |
| Recording and classification of complications | | | | ✓ | ✓ | ✓ | ✓ |
| Adverse event reporting | | | | Throughout the study | | | |
| Assessments | | | | | | | |
| Baseline demographics and scores | | | ✓ | | | | |
| Scintigraphy [†] | | | ✓ | | | | |
| Exercise testing | | | ✓ | | | | |
| 6 minute walking test | | | ✓ | | | | |
| Single breath carbon monoxide (CO) uptake | | | ✓ | | | | ✓ |
| Spirometry/plethysmography | | | ✓ | | | | ✓ |
| Quality of life questionnaires | | | ✓ | | | | ✓ |
| Surgery data | | | | ✓ | | | |
| Cancer staging | | | ✓ | | ✓ | | |
| Treatments and patient pathway data | | | ✓ | ✓ | ✓ | ✓ | ✓ |

[†], for high-risk patients only.

be gathered and recorded in the study CRF.

Surgery, hospitalization, and follow-up

Surgery (which defines 'day 0' for the study) will be carried

out as per usual care with no particular constraints imposed by the present study. Throughout the initial hospitalization, data recording will include treatments, the occurrence and characterization of surgical complications and adverse

Table 4 Inclusion and exclusion criteria for resected tissue entry into ancillary study

| Inclusion criteria | Exclusion criteria |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • The investigator deems that sample recovery is feasible • The distance between the cancerous lesion and an air-trapping zone that can be micro-scanned is judged to be sufficiently large/distinct by the investigator • The patient gave consent for the use of his/her remaining excised tissue specifically for this ancillary study | <ul style="list-style-type: none"> • Unavailability of tissue sample due to routine analysis requirements • Patient with atelectasis • Patient with pulmonary infection • Patient with a pulmonary lesion linked to the surgical intervention (surgical wound) |

events, the results from the routine pathological analysis of excised tissues (pTNM characterisation), as well as patient pathway data (episodes of intensive care and/or mechanical ventilation, plus length of initial hospital stay).

The recording of treatments, complications, adverse events, and patient pathway data will continue throughout the 6 months of follow-up required for this study. Medical records and routine visits at 1 month and 6 months will be used to recover these data. In addition, during the 6-month visit, patients will be requested to re-fill out the study questionnaires, and their lung function will be characterized via spirometry, plethysmography and TLCO testing. If required, the latter assessment is postponed in case of intercurrent infection or residual thoracic pain.

Resection samples and tissue library

Resected lung tissues will be primarily dedicated to routine pathological analysis. However, if the eligibility criteria in *Table 4* are met, a block of paraffin-embedded lung tissue may be retained for an ancillary micro-scanning study. The specific micro-scanning procedures used will be detailed in the separate ancillary study protocol foreseen for N=40 patients.

Sample size

We assume that a model with a maximum of 5 predictive parameters will be developed and have allowed for 10 subjects per parameter. An additional 10 subjects are considered in order to allow for potentially unusable data, resulting in a test-group samples size of 60. This number of subjects is quite similar to that of the study by Chae *et al.* (24), who developed a similar model with a population of N=51, but performed no validation study. A validation sample of 100 further subjects was chosen based on our recruitment capacity. Though based on a rule that is more

empirical than statistical (there is no data in the literature on which we can base a specific hypothesis), the total size (N=160) of the sample is compatible with our inclusion potential and the size of the validation cohort allows a good estimate of the prediction error for the sample.

Potentially missing data

This study is based on routinely available data sources with no experimental changes to patient pathways, and we therefore expect few missing data. Only complete cases (i.e., those with a CT scan at baseline and spirometry at baseline and at 6 months) will be analysed.

Statistical analysis

Statistical analyses will be performed by the Clinical Research and Epidemiology Unit (CREU) at the University Hospitals of Montpellier (Montpellier, France). The programming environments used may include SAS (SAS Institute, Cary, NC, USA), R (46), or Julia (47). The statistical methods presented here will serve as a general guide, and a detailed statistical analysis plan (SAP) will be developed prior to N=50 inclusions (i.e., before the end of the test-population inclusions). Any deviations from the SAP must be justified, approved by the study methodologist (NM) and included in the final study report.

The main parameters studied (demographic and clinical data, predictors and outcomes) will be compiled at each time point for each group. Care will be taken to juxtapose results for the test versus validation groups so that differences in centrality and/or variation can be identified. Before considering the use of statistical tests, the underlying assumptions will be verified with appropriate methods (e.g., Shapiro's normality test), guiding relevant

data transformations. Where appropriate, the Box-Cox transformation is preferred to arbitrary transformations.

Descriptive statistics will be presented as numbers and percentages for qualitative variables, means \pm standard deviations for quantitative variables whose distribution is Gaussian, and medians with interquartiles for other variables. Sample sizes demonstrating missing data will be presented for each variable.

The general strategy of the primary analysis is to use data from the test population to create a predictive model for post-operative outcomes at six months after resection surgery. Primary (FEV1) and secondary (TLCO, complications) outcomes will be predicted using (A) five a priori-specified variables (expiratory to inspiratory ratios of mean lung density ($MLD_{e/i}$ for the total lung and resected volume), the percentage of voxels attenuating at less than -950 HU ($PVOX_{-950}$ for the total lung and resected volume) and the ratio of iodine concentrations for the resected volume over that of the total lung), (B) previously published variable combinations, and (C) exploratory combinations of variables.

The preferred method for predicting post-resection FEV1 or TLCO is multivariable linear regression, while logistic regression will be used for predicting post-resection complications. In case of non-linearity between continuous variables, the following may be used: variable transformation, restricted cubic splines or fractional polynomial functions (the model with the best fit statistics will be retained). The categorization of continuous variables is not foreseen and discouraged, and if used must be thoroughly justified and approved by the study methodologist. For each model, an automated backward-stepwise process minimizing the Akaike Information Criterion (AIC) will be used to select the most appropriate combination of explanatory variables.

Predictive scores generated using the test population will be externally validated using data from the subsequently recruited validation population (see *Figure 1*). Least-square errors for predicted versus real values will be calculated, and the prediction error calculated with a 95% confidence interval. Given the small samples size of this first study, risk-stratified sub-groups will not be addressed. Following validation of the primary models, model updating using the combined test and validation sets will be performed on an exploratory basis, with internal validation via bootstrapping.

Data entry and quality verifications

Individual patient data will be entered in a password-

protected, web-accessible eCRF (Ennov Clinical; <https://en.ennov.com>) by participating investigators or their approved delegates. A paper-version of the eCRF will be made available at <https://osf.io/2m7z4/>, and can be used to facilitate field requirements for speed or provide a back-up data collection tool in case of temporary electronic system unavailability. In as much as possible, eCRF data entry will occur in real-time, thus taking advantage of specifically designed data format, range and coherence rules. The Clinical Research and Epidemiology Unit (CREU) at the University Hospitals of Montpellier (Montpellier, France) will oversee coherence rules, database maintenance and data management procedures. eCRF content will be audited against source documents by sponsor-designated data-monitoring personnel throughout the study, and corrections made via a well-documented (traceable) system of queries and responses.

De-identifying data

In the eCRF and subsequent study database, participants will be de-identified and represented by a study number. Publicly available deliverables listing individual data will be completely de-identified, with any data suspected of facilitating patient re-identification removed. Public availability will be subject to specific foreseen usage criteria, as specified in the study data sharing plan (available at <https://osf.io/2m7z4/>).

Monitoring study conduct

The project will be monitored by sponsor CRAs via regular on-site inspections, the frequency of which will be adapted to the rhythm of inclusions. The following visits are planned at the time of this publication: study initiation, end of inclusions for the test cohort, end of follow-up for the test cohort, end of inclusions for the validation cohort, study closure. All monitoring visits will be the subject of a written report and will cover consent procedures, primary endpoint data quality, and protocol adherence.

Study steering committee and communication activities

(I) The CLIPPCAIR steering committee (SB, AB, IV, NM, CMS) will supervise study implementation and execution, (II) the creation and management of the associated tissue resection collection, and (III) oversee communication activities in accordance with the data-sharing plan. Access to key study documents (participant information materials,

statistical analysis plan, analytic code, data sharing plan) will be centralized via the study's Open Science Framework website: <https://osf.io/2m7z4/>.

Aggregated study results will be made available on clinicaltrials.gov and via publication in a peer reviewed journal. Authorship will be attributed according to the criteria stipulated by the ICMJE. In accordance with French regulations, study participants will be provided with results upon request. Finally, the study data-sharing plan stipulates that in accordance with French regulations, data will be made available to persons having received approval from the National Commission for Informatics and Liberties (CNIL, France) for a re-analysis protocol.

Study time frames and status

The initial planning for the CLIPPCAIR study calls for eighteen months of inclusions, followed by 6 months of follow-up. At the time of publication of this work, the study is in the early phases of inclusion. The first inclusion occurred on 21 September 2020.

Discussion

This study will produce a novel prediction algorithm for estimating post-resection lung function using novel CT scan data. This algorithm will be presented with all required coefficients and explanations for implementation by the wider scientific community for individual prediction. Should the resulting predictions be comparable or superior to those provided by lung perfusion scintigraphy, patient pathways may be simplified by eliminating the need for the scintigraphy (thus economising time and opportunity for cancer patients, and health care resources for the state).

There are certain limitations to this protocol. First, sample size was determined in quite a practical fashion. There is also a risk that the test and validation samples may differ in some unforeseen way, perhaps due to seasonality. Nevertheless, the planned size of this study is comparable to a previous, similar, influential study that lacked external validation (24). Our perspectives therefore include the construction of a novel prediction algorithm based on more recent imaging post-treatment techniques, accompanied by an improved evidence base via external validation.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://dx.doi.org/10.21037/atm-21-214>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-214>). Dr. Suehs reports grants from Astra Zeneca, outside the submitted work. Dr. Molinari reports personal fees from Astra Zeneca, grants from GSK, outside the submitted work. Dr. Bourdin reports grants, personal fees, non-financial support and other (Ad Board; participation in congress; investigator) from Astra Zeneca, grants, personal fees and other (Ad Board; participation in congress; investigator) from GSK, grants, personal fees, non-financial support and other (Ad Board; participation in congress; investigator) from Boeringher Ingelheim, personal fees, non-financial support and other (Ad Board; participation in congress; investigator) from Novartis, personal fees and other (Ad Board; investigator) from Teva, personal fees and other (Ad Board; investigator) from Regeneron, personal fees, non-financial support and other (Ad Board; participation in congress; investigator) from Chiesi Pharmaceuticals, personal fees, non-financial support and other (Ad Board; participation in congress; investigator) from Actelion, other (Investigator) from Gilead, personal fees, non-financial support and other (Ad Board; investigator) from Roche, outside the submitted work.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study will be conducted according to the principles of the Declaration of Helsinki (as revised in 2013) and was approved by a randomly-assigned, independent, ethics committee (Comité de Protection des Personnes Sud-Est III, reference number: 2018- 050 B) as per French law on 28 December 2018. Informed, written consent for study participation is required of all study candidates prior to enrolment.

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