



**HAL**  
open science

# Seconds cancers après traitement curatif d'un cancer broncho-pulmonaire

Guillaume Nicolas Eberst

► **To cite this version:**

Guillaume Nicolas Eberst. Seconds cancers après traitement curatif d'un cancer broncho-pulmonaire. Cancer. Université Bourgogne Franche-Comté, 2023. Français. NNT: 2023UBFCE029 . tel-04555605

**HAL Id: tel-04555605**

**<https://theses.hal.science/tel-04555605>**

Submitted on 23 Apr 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

UNIVERSITÉ BOURGOGNE- FRANCHE COMTÉ

École Doctorale Environnements – Santé

THÈSE

Pour obtenir le grade de

Docteur de l'Université de Bourgogne Franche-Comté

Sciences de la Vie et de la Santé

Présentée et soutenue publiquement le 22 Décembre 2023 par

Guillaume EBERST

---

Seconds cancers après traitement curatif d'un cancer broncho-pulmonaire

---

Membres du jury :

Gérard ZALCMAN

Professeur des Universités, Paris, Président

Virginie WESTEEL

Professeur des Universités, Besançon, Directrice de la thèse

Anne-Claire TOFFART

Professeur des Universités, Grenoble, Rapporteur

Pascale TOMASINI

Professeur des Universités, Marseille, Rapporteur

Marie WISLEZ

Professeur des Universités, Paris, Examineur

## REMERCIEMENTS

---

A ma directrice de thèse, le Professeur Virginie WESTEEL. On décrit souvent vos qualités de rigueur dans le travail scientifique, d'ingéniosité, de persévérance, de profonde gentillesse et l'art du consensus. J'y associerais un grand enthousiasme, et une énergie que vous savez transmettre même dans les situations difficiles. J'ai l'honneur de travailler à vos côtés et au sein de l'équipe que vous avez formée et je vous en suis très reconnaissant. Je vous remercie également pour votre accompagnement à l'écriture de ce travail ainsi que votre bienveillance. Je vous prie d'accepter mon profond respect.

A Madame le Professeur Anne-Claire TOFFART. Merci d'avoir accepté d'être rapporteur de ce travail de thèse. Veuillez trouver ici l'expression de ma profonde reconnaissance.

A Madame le Professeur Pascale TOMASINI. Merci d'avoir accepté de juger ce travail. Trouvez ici le témoignage de ma profonde reconnaissance.

A Madame le Professeur Marie WISLEZ. Merci d'avoir eu l'amabilité de faire partie de ce jury. Merci pour votre compagnonnage bienveillant dans mon cursus universitaire. Veuillez trouver ici le témoignage de ma profonde gratitude.

A Monsieur le Professeur Gérard ZALCMAN. Merci pour votre implication dans cette thèse et pour m'avoir permis d'échanger votre expérience tout au long du cursus. Veuillez trouver ici le témoignage de ma profonde gratitude.

A ma chère Famille, mon épouse Cécile, mes deux enfants adorés Adèle et Gaspard, un grand merci pour leur patience et leurs encouragements tout au long de la réalisation du projet de cette thèse de Sciences.

A mes parents, belle-maman, frère et beau-frère, merci pour vos encouragements et l'aide logistique à ce travail de thèse.

A Corynne MARCHAL, François CALAIS et l'équipe du groupe *Cochrane Lung Cancer*.

A Madame le Professeur Isabelle BOUTRON. Je vous suis reconnaissant pour votre accueil au sein de votre équipe du groupe Cochrane France à l'Hôtel-Dieu. Cet échange au sein d'une équipe experte et accueillante restera d'un grand bénéfice dans mon cursus scientifique. Veuillez trouver ici le témoignage de ma profonde gratitude.

A Anna CHAIMANI, Andrea MORENO, Sally YAACOUB et toute l'équipe du groupe *Cochrane France* et du CRESS-UMR1153.

A Monsieur Franck MORIN, et toute l'équipe de recherche de l'Intergroupe Francophone de Cancérologie Thoracique (IFCT).

A toute l'équipe de l'UMQV, particulièrement Dewi Vernerey et Julie Henriques.

A toute l'équipe du service de pneumologie du CHU de Besançon, l'équipe d'oncologie thoracique, l'équipe de radiologie pour leur soutien.

Au Professeur Olivier ADOTEVI, ses conseils et sa bienveillance ainsi qu'à toute l'équipe de l'unité RIGHT – UMR1098.

A Alicia Guillien pour ses conseils en statistiques et mathématiques.

A l'équipe de pneumologie, de radiologie interventionnelle de l'Hôpital Bichat Claude-Bernard.

## SOMMAIRE

---

|   |    |
|---|----|
| Liste des publications et communications issus des travaux de thèse .....   | 6  |
| Préambule .....   | 9  |
| I. Introduction .....   | 11 |
| A. Généralités  |    |
| B. Traitement des patients CBNPC de stade I-IIIB résécables (TNM8)  |    |
| C. Actualité des traitements péri-opératoires   |    |
| D. Surveillance après chirurgie d'un CBNPC  |    |
| E. Les Seconds Cancers Broncho-Pulmonaire Primitifs   |    |
| 1. Définitions  |    |
| 2. Survie des patients avec récurrence ou second cancer pulmonaire  |    |
| F. La collaboration Cochrane  |    |
| G. L'Examen de Ponction-Biopsie sous Scanner  |    |
| II. Objectifs.....  | 21 |
| III. Articles.....  | 22 |
| A. Overall prognosis of recurrence of index lung cancer or of second primary lung cancer in people with non-small cell lung cancer operated with complete resection   |    |
| 1. Contexte et objectif   |    |
| 2. Manuscrit  |    |
| B. Perioperative immunotherapy for resectable non-small cell lung cancer, a living mapping of research and a living systematic review   |    |
| 1. Contexte et objectif   |    |
| 2. Manuscrit  |    |
| C. IFCT 0302  |    |
| 1. Impact of CT scan-based vs. minimal follow-up on patient-reported health-related quality-of-life and penibility outcomes for completely resected non-small cell lung cancer (NSCLC) in the phase III IFCT-0302 trial |    |
| - Contexte et objectif  |    |
| - Manuscrit   |    |
| D. Score prédictif de survenue d'un pneumothorax  |    |
| 1. Score to Predict the Occurrence of Pneumothorax After Computed Tomography-guided Percutaneous Transthoracic Lung Biopsy.   |    |
| - Contexte et objectif  |    |
| - Manuscrit   |    |
| 2. Score to predict the occurrence of pneumothorax after ct-guided percutaneous transthoracic lung biopsy, external validation cohort   |    |
| - Contexte et objectif  |    |
| - Manuscrit   |    |

|     |                    |     |
|-----|--------------------|-----|
| IV. | Conclusion.....    | 167 |
| V.  | Bibliographie..... | 169 |
| VI. | Annexe.....        | 178 |

## LISTE DES PUBLICATIONS ET COMMUNICATIONS ISSUS DES TRAVAUX DE THESE

---

### Articles originaux en rapport avec la thèse :

Laforge L, **Eberst G**, Calais F, Malouf R, Marchal C, Westeel V, Roqué-Figuls M. Overall prognosis of recurrence of index lung cancer or of second primary lung cancer in people with non-small cell lung cancer operated with complete resection (Protocol). Cochrane Database of Systematic Reviews TBD, 2023. Issue TBD. Art. No.: CD015319. DOI: 10.1002/14651858.CD015319.

**Eberst G**, Henriques J, Monchatre M, Giroux-Leprieur E, Kelkel E, Bizieux Thamin A, Ravier P, Bayle S, Audigier Valette C, Berard H, Desliers F, Lagrange A, Bonnefoy P, Langlais A, Vernerey D, Anota A, Morin F, & Westeel V, on behalf of the French Cooperative Thoracic Intergroup (IFCT). Impact of CT scan-based vs. minimal follow-up on patient-reported health-related quality-of-life and penibility outcomes for completely resected non-small cell lung cancer (NSCLC) in the phase III IFCT-0302 trial. In submission.

Marchal C, **Eberst G**, Calais F, Westeel V, Malouf R. Peri-operative immunotherapy for resectable non-small cell lung cancer, a living mapping of research and a living systematic review (Protocol). Cochrane Database of Systematic Reviews TBD, 2023; Issue TBD. Art. No.: CD015819. DOI: 10.1002/14651858.CD015819.

Lamfichekh Y, Lafay V, Hamam J, Guillien A, Puyraveau M, Behr J, **Eberst G**, Grillet F, & Westeel V. Score to Predict the Occurrence of Pneumothorax After Computed Tomography-guided Percutaneous Transthoracic Lung Biopsy. Journal of Thoracic Imaging, 2023; 38 (5): 315-324.

**Eberst G**, Waqaas M, Guillien A, Khalil A, Hamam J, Behr J, Manzoni P, Calame P, Grillet F, Zalcman Gérard, Gounant V, & Westeel V. Score to predict the occurrence of pneumothorax after ct-guided percutaneous transthoracic lung biopsy, external validation cohort. European Radiology, in review

### Autres articles :

**Eberst G**, Claudé F, Laurent L, Meurisse A, Roux-Claudé P, Barnig C, ... & Westeel, V. Result of one-year, prospective follow-up of intensive care unit survivors after SARS-CoV-2 pneumonia. Annals of Intensive Care, 2022 ; 12 (1): 23.

Kroemer M, Spehner L, Vettoretti L, Bouard A, **Eberst G**, Floury SP, ... & Bouiller K. COVID-19 patients display distinct SARS-CoV-2 specific T-cell responses according to disease severity. Journal of Infection, 2021 ; 82 (2): 282-327.

Traore I, **Eberst G**, Claudé F, Laurent L, Meurisse A, Paget-Bailly S, ... & Westeel V. Prevalence and Characteristics of Sleep Apnea in Intensive Care Unit Survivors After SARS-CoV-2 Pneumonia. Nature and Science of Sleep, 2022; 2213-2225.

Noureddine S, Roux-Claudé P, Laurent L, Ritter O, Dolla P, Karaer S, **Eberst G**, Westeel V, & Barnig C. Evaluation of long-term sequelae by cardiopulmonary exercise testing 12 months after hospitalization for severe COVID-19. BMC pulmonary medicine, 2023; 23 (1): 1-13.

Laheurte C, Dosset M, Vernerey D, Boullerot L, Gaugler B, Gravelin E, Kaulek V, Jacquin M, Cuche L, **Eberst G**, ... & Adotévi O. Distinct prognostic value of circulating anti-telomerase CD4+ Th1 immunity and exhausted PD-1+/TIM-3+ T cells in lung cancer. *British journal of cancer*, 2019; 121 (5): 405-416.

Adotévi O, Vernerey D, Jacoulet P, Meurisse A, Laheurte C, Almotlak H, Jacquin M, Kaulek V, Boullerot L, Malfroy M, Orillard E, **Eberst G**, ... & Westeel V. Safety, immunogenicity, and 1-year efficacy of universal cancer peptide-based vaccine in patients with refractory advanced non-small-cell lung cancer: a phase Ib/phase IIa de-escalation study. *Journal of Clinical Oncology*, 2023; 41 (2): 373-384.

**Eberst G**, Vernerey D, Laheurte C, Meurisse A, Kaulek V, Cuche L, & Westeel V. Prognostic value of CD4+ T lymphopenia in non-small cell lung Cancer. *BMC cancer*, 2022; 22 (1) : 529.

Picard E, Godet Y, Laheurte C, Dosset M, Galaine J, Beziaud L, Romain Loyon, Boullerot L, Lauret E, Spehner L, Jacquin M, **Eberst G**, ... & Adotévi, O. Circulating Nkp46+ Natural Killer cells have a potential regulatory property and predict distinct survival in Non-Small Cell Lung Cancer. *Oncoimmunology*, 2019; 8 (2): e1527498.

**Eberst G**, Anota A, Scherpereel A, Mazieres J, Margery J, Greillier L, ... & Westeel, V. Health-related quality of life impact from adding bevacizumab to cisplatin-pemetrexed in malignant pleural mesothelioma in the MAPS IFCT-GFPC-0701 phase III trial. *Clinical Cancer Research*, 2019; 25 (19): 5759-5765.

Mouillet G, Falcoz A, Fritsch J, Almotlak H, Jacoulet P, Pivot X, Villanueva C, Mansi L, Kim S, Curtit E, Meneveau N, Adotévi O, Jary M, **Eberst G**, ... & Paget-Bailly S. Feasibility of health-related quality of life (HRQoL) assessment for cancer patients using electronic patient-reported outcome (ePRO) in daily clinical practice. *Quality of Life Research*, 2021; 1-12.

Anota A, Pozet A, Lemasson H, Cotté FE, Falcoz A, **Eberst G**, ... & Westeel, V. Impact of open-label versus blinded study design on patient-reported outcomes data in randomized clinical trials of immunotherapy in advanced or metastatic cancer patients: a systematic review. *Quality of Life Research*, 2022; 1-13.

Sultana H, De Vos T, Malouf R, Calais F, Marchal C, **Eberst G**, Westeel V, Barnig C. Prognosis value of blood eosinophils for predicting survival and treatment outcomes in patients with non-small cell lung cancer (Protocol). *Cochrane Database of Systematic Reviews* TBD, 2023. Issue TBD. Art. No.: CD015383. DOI: 10.1002/14651858.CD015783

## **Articles sollicités:**

Westeel V, & **Eberst G**. Immunothérapie en situation péri-opératoire: les essais en cours et leurs objectifs. *La lettre du cancérologue*, Janvier 2019.

## **Editorial:**

Seitlinger J, **Eberst G**, Mangiameli G. Special Issue "Molecular and Cellular Research on Lung Cancer: A Development toward Precision Medicine". *Biomedicines*, 2023.



## **Communications Orales :**

### **Congrès de Pneumologie de Langue Française:**

**Eberst G**, Vernerey D, Laheurte C, Kaulek V, Meurisse A, Cuche L, ... & Westeel, V. Valeur pronostique de la lymphopénie T CD4+ dans le cancer du poumon non à petites cellules. Revue des Maladies Respiratoires Actualités, 2021 ; 13 (1) : 124.

### **European Society for Medical Oncology (ESMO) Congress 2023:**

**Eberst G** , Henriques J, Monchatre M, Giroux-Leprieur E, Kelkel E, Bizieux Thaminy A, Ravier P, Bayle S, Audigier Valette C, Berard H, Desliers F, Lagrange A, Bonnefoy P, Langlais A, Vernerey D, Anota A, Morin F, & Westeel V, on behalf of the French Cooperative Thoracic Intergroup (IFCT). 1262MO, Impact of a minimal versus CT-scan-based follow-up on patient-reported outcomes for completely resected non-small cell lung cancer (NSCLC) in phase III IFCT-0302 trial. Annals of Oncology, 2023; 34: S732.

## PREAMBULE

---

Le premier des objectifs du plan cancer 2014-2019 était de guérir plus de malades en favorisant les diagnostics plus précoces. Cet objectif laisse espérer davantage de diagnostic à des stades précoces accessibles à une résection chirurgicale. A l'heure actuelle, la chirurgie exérèse d'un cancer broncho-pulmonaire non à petites cellules (CBNPC) est le traitement offrant le plus d'espoir de guérison. Ce travail de thèse s'intéresse tout particulièrement au devenir des patients opérés.

Malgré une intention curatrice, les patients opérés d'un CBNPC sont à risque de récurrence du cancer opéré mais ont également un risque de second cancer, et en particulier de second cancer broncho-pulmonaire primitif (SCBP), supérieur à celui de la population générale, de l'ordre de 20% d'incidence cumulée à 10 ans. Ce travail de thèse est structuré autour de trois axes :

- un axe pronostique, pour une meilleure connaissance des facteurs de risque de survenue des récurrences et SCBP, ainsi que leur devenir ;
- un axe thérapeutique, avec l'objectif de réduire le risque de récurrence et SCBP par les stratégies péri-opératoires ;
- un axe diagnostique, allant de la surveillance des patients opérés d'un CBNPC à l'obtention d'une preuve histologique de récurrence ou SCBP.

Lorsque survient une lésion pulmonaire de même diagnostic histologique que le cancer opéré, le diagnostic différentiel entre récurrence du cancer opéré ou SCBP est difficile. Plusieurs définitions existent. En se basant sur l'hypothèse que les récurrences sont le témoin d'une agressivité de la maladie cancéreuse, et donc le plus souvent de plus mauvais pronostic que les deuxièmes cancers, nous avons conduit dans un premier temps une revue systématique Cochrane de l'ensemble des définitions utilisées dans la littérature afin d'identifier celle qui offre la meilleure distinction pronostique, sur laquelle se baser pour le diagnostic différentiel entre récurrence du cancer opéré et SCBP.

Il y a quelques années, l'immunothérapie s'est imposée dans l'arsenal thérapeutique du cancer broncho-pulmonaire. D'abord utilisée en situation métastatique, l'immunothérapie est maintenant testée en situation péri-opératoire dans de nombreux essais. Cependant, en raison de la diversité des combinaisons et des stratégies thérapeutiques, qui n'ont pas toutes été comparées entre elles, une incertitude demeure quant à la meilleure thérapie péri-opératoire pour les patients opérés d'un CBNPC de stade précoce. Nous avons initié une revue systématique d'essais interventionnels avec méta-analyse en réseau selon la méthode Cochrane portant sur l'efficacité de ces traitements péri-opératoires chez les patients atteints de cancer du poumon non à petites cellules.

L'étude IFCT-0302 est la seule large étude randomisée de surveillance des opérés d'un CBNPC. Elle a inclus 1775 patients. Son objectif était de comparer la survie globale de deux stratégies de surveillance : par clinique

et radiographies thoraciques dans le groupe contrôle, et par clinique, radiographies thoraciques et scanners thoraco-abdominaux dans le groupe expérimental. La qualité de vie décrite par le patient (QdV) est une mesure de trois domaines de la santé perçue : physique, social et émotionnel. La QdV est impactée par une condition médicale ou son traitement. L'évidence suggère que la chirurgie du cancer du poumon a un impact significatif sur la QdV. L'objectif de notre travail a été d'évaluer l'influence du type de surveillance sur la QdV dans la population de l'étude IFCT-0302.

Lorsqu'une image pulmonaire anormale est détectée, son diagnostic histologique s'obtient fréquemment par ponction transthoracique guidée par le scanner. La principale complication du geste est le pneumothorax. Les contraintes hospitalières ne permettent pas d'hospitaliser tous les patients après une ponction transthoracique. Nous avons dans ce troisième axe, travaillé à la validation d'un score prédictif de survenue d'un pneumothorax retardé après une ponction-biopsie transpariétale pulmonaire scannoguidée, afin de sélectionner les patients qui doivent être surveillés en hospitalisation conventionnelle. Ce travail a été réalisé sur une cohorte de patients du CHU de Besançon, une partie de la cohorte ayant permis d'élaborer le score, l'autre de le valider. Enfin un travail de validation externe sur une cohorte de patients de l'Hôpital Bichat – Claude Bernard a été réalisé.

## I. INTRODUCTION

---

### A. Généralités

Selon les données de GLOBOCAN, 2 206 771 cancers du poumon ont été diagnostiqués dans le monde en 2020. Il représentait 14.3% des cancers chez l'homme (14% en France) et 8.4% chez la femme (10% en France) (1, 2). Le cancer du poumon non à petites cellules (CBNPC) est le type de cancer du poumon le plus courant, représentant 85 % des cancers bronchiques (1). Parmi les CBNPC, plusieurs sous-types histologiques existent (3) : l'adénocarcinome, le carcinome épidermoïde, le carcinome à grandes cellules et les tumeurs neuroendocrines. L'extension de la maladie est décrite selon la classification TNM, dont la dernière et 8ème révision date de 2016 (4). Les stades IA-1, IA-2, IA-3, IB, IIA, et IIB correspondent à des tumeurs dites localisées. Les stades IIIA, IIIB et IIIC correspondent à des tumeurs dites localement avancées. Les stades IV-A et IV-B correspondent à des tumeurs métastatiques. Le pronostic diffère selon le stade clinique au moment du diagnostic, avec dans les CBNPC, un taux de survie à 24 mois de 87 à 97 % pour le stade I et de 10 à 23 % pour le stade IV en 2017 (2). L'évaluation précise du statut ganglionnaire (N) est cruciale pour la prise en charge et le pronostic du cancer du poumon non à petites cellules non métastatique. Dans la publication récente des propositions de la 9<sup>ème</sup> classification TNM, l'ajout de nouveaux sous-descripteurs du statut N2 est faite avec la description d'une seule station (N2a) et l'infiltration de plusieurs stations (N2b) (5).

La chirurgie avec ou sans traitement systémique péri-opératoire reste la pierre angulaire du traitement du CBNPC de stade précoce résécable chez un patient opérable (6). L'indication de chimiothérapie péri-opératoire est systématique chez tous les patients en état physique et physiologique de la recevoir pour les tumeurs de plus de 4 cm soit les stades pII et pIII de la 8<sup>ème</sup> classification TNM (4). En cas de chimiothérapie adjuvante, la chimiothérapie est préférentiellement débutée dans les 4 à 8 semaines suivant l'acte chirurgical. L'utilisation d'un protocole contenant du cisplatine (plus de 300mg/m<sup>2</sup> de dose totale) et de la vinorelbine est privilégiée suivant un schéma de 21 jours, 4 cycles. En cas d'âge > 75 ans, PS>1, ou comorbidités contre-indiquant la chimiothérapie, l'efficacité de cette chimiothérapie adjuvante n'a pas été démontrée (7). L'association d'une chimiothérapie et d'une immunothérapie préopératoire est depuis peu le nouveau standard dans le traitement d'un cancer bronchique non à petites cellules résécable à haut risque de récurrence, dont les tumeurs expriment PD-L1 au seuil  $\geq 1$  % et dont les tumeurs ne présentent pas de mutation sensibilisante de l'EGFR connue, ni de translocation ALK connue (8, 9).

### B. Traitement chirurgical des CBNPC de stade I-IIIB résécables (TNM8)

La décision thérapeutique repose sur la résécabilité de la tumeur, évaluée en réunion de concertation pluridisciplinaire mais dont la définition est complexe, particulièrement dans les stades III (10) où l'atteinte

ganglionnaire médiastinale comprend différentes sous-catégories allant de l'atteinte non visible au staging clinique du N2, à l'atteinte dite « bulky » avec enveloppement des structures proximales (5). L'EORTC-Lung Cancer Group a mené un projet de consensus Delphi pour établir une définition consensuelle de la résecabilité dans le CPNPC de stade III. Sur 37 combinaisons TNM possibles, un consensus était atteint pour 24 combinaisons seulement (65 %) (11). Dans une revue systématique sur les critères de résecabilité décrits dans la littérature, on retrouvait comme facteurs acceptables pour la résection (12): une station N2 unisite (11 %), une maladie N2 de petite taille (4 %), un *downstaging* (8 %) et une assurance de marge saine R0 (8 %). Les recommandations de l'ESMO en 2017, actualisées en 2021, considéraient la maladie N2 uni-site comme résecable (13, 14). Pour un autre panel d'experts français, la chirurgie doit être aussi réservée pour les N2 uni-site et lorsque plusieurs sites ganglionnaires N2 sont atteints, le patient doit être orienté vers une chimiothérapie et radiothérapie concomitante puis une immunothérapie de consolidation (15). Les recommandations chirurgicales actuelles préfèrent la lobectomie pour le traitement des CBNPC de stade I et II. Une segmentectomie peut se proposer pour le traitement des stades I périphériques (16, 17). La résection atypique n'est pas anatomique et ne constitue, pour l'heure, pas une technique de choix. Enfin, un curage ganglionnaire est systématiquement réalisé et doit comporter la résection de 3 groupes ganglionnaires minimum. Les critères de qualité de la chirurgie carcinologique sont essentiels pour la survie des patients et l'analyse des facteurs pronostiques pour les études cliniques. Le but principal d'une résection chirurgicale pour un CBNPC est d'obtenir une résection complète (R0), à la fois de la tumeur et du curage des ganglions lymphatiques homolatéraux à la lésion, ce qui est l'élément pronostique essentiel impactant la survie à long terme des patients. Cette résection R0 repose sur les constatations peropératoires décrites par le chirurgien et celles décrites par l'anatomopathologiste analysant l'ensemble des prélèvements. L'IASLC a proposé la terminologie suivante (18) :

- Résection complète (R0) : marges de résections histologiquement saines (marges vasculaires, bronchiques, périphérie des structures résecuées en-bloc), réalisation d'un curage ganglionnaire systématique ou au moins d'un curage sélectif « lobe-spécifique » comportant au minimum 6 unités ganglionnaires (3 scissuraux et hilaires N1 – 3 médiastinaux N2 provenant de 3 sites différents dont le site sous-carénaire), absence de rupture capsulaire au niveau des éléments du curage ou sur la pièce d'exérèse à la marge de celle-ci, et ganglions les plus distaux histologiquement sains (sites 2 et 9). L'importance du curage ganglionnaire et donc du staging ganglionnaire peropératoire est aussi un critère majeur de qualité de la chirurgie pourtant encore non complètement respecté. Cette évidence est cependant peu partagée, non seulement dans la pratique clinique quotidienne, mais aussi en recherche clinique (19). Dans cette analyse rétrospective de qualité de la chirurgie sur 9626 vétérans américains publiés Heiden BT *et coll*, les paramètres de qualité ont été évalués comme tel (20): intervention chirurgicale effectuée en temps opportun (6 633 [68,9 %]), approche mini-invasive (3 986 [41,4 %]), lobectomie (6 843 [71,1 %]) ou segmentectomie (532 [5,5 %]), curage ganglionnaire adéquat (3 278 [34,0 %]) et marge chirurgicale négative (9 312 [96,7 %]). Dans l'essai randomisé ACOSOG Z4032 comparant la résection infra-lobaire seule à l'association d'une résection infra-lobaire et d'une curiethérapie chez des patients atteints d'un CBNPC de stade clinique I, plus d'un tiers des patients opérés n'avaient eu

aucune évaluation ganglionnaire peropératoire (21). Dans les stades cliniques N0, plus l'exérèse ganglionnaire du curage est large, meilleur est le pronostic (22). Enfin il est démontré dans les stades N1-2 que le ratio ganglionnaire (rapport nombre de ganglions N+/nombre total de ganglions examinés) plus élevé est associé de façon indépendante à une moins bonne survie globale et survie sans progression (23). Dans les essais récemment publiés sur les immunothérapies péri-opératoires, il n'y a pas de données publiées sur la qualité de la chirurgie (24).

### C. Actualité des traitements péri-opératoires

La résection chirurgicale seule n'est pas curative chez de nombreux patients atteints d'un CBNPC à un stade précoce, le taux de récurrence augmentant avec un stade plus élevé. La chimiothérapie péri-opératoire à base de platine a longtemps été le standard pour les patients atteints d'une maladie résecable de stade II-III A, bien que les avantages en termes de survie soient modestes, avec une augmentation de la survie globale (SG) d'environ 5 % (25). Récemment, l'immunothérapie a été intégrée aux schémas thérapeutiques néo-adjuvants et adjuvants sur la base de données démontrant une amélioration de la survie sans événement (EFS) et de la survie sans maladie (DFS), respectivement, pour les CBNPC de stades localisés ou localement avancés, résecables, sans mutation activatrice.

#### Sans mutation activatrice

Le rationnel biologique de la chimiothérapie péri-opératoire est la destruction des micro-métastases, réduisant ainsi les récurrences et ainsi le risque de décès (26). Dans cette optique, l'immunothérapie adjuvante a été développée pour améliorer ces résultats contre la maladie micro-métastatique, qui est théoriquement associée à une charge néoplasique plus faible et à une plus faible différenciation clonale des cellules cancéreuses. La chirurgie affecte la réponse immunitaire. En effet, les effets du stress chirurgical et postopératoire immédiat sur l'immunité ont été correctement caractérisés et incluent l'immunosuppression médiée par l'augmentation des niveaux de cytokines et de facteurs de croissance liés au stress, tels que les catécholamines, les prostaglandines et les cytokines inflammatoires (IL-6, IL-8, IL-10 et TNF) (27). L'inflammation conduit à une immunosuppression persistante à la fois dans le microenvironnement du lit tumoral et au niveau systémique. Ces réponses inflammatoires postopératoires au stress pourraient potentiellement être combinées – de préférence dans la période postopératoire immédiate – avec une stimulation immunitaire par l'immunothérapie pour surmonter les effets pro-métastatiques et pro-angiogéniques directs de la chirurgie, inverser l'immunosuppression et améliorer les réponses immunitaires antitumorales. IMpower-010 était le premier essai de phase III ayant démontré un bénéfice en DFS de l'immunothérapie, après une résection chirurgicale complète, une chimiothérapie adjuvante, puis une année d'*Atézolizumab* adjuvant chez les patients atteints d'un CBNPC, PD-L1 positif de stade II-III A (28). Ce traitement, a été approuvé par l'agence européenne et américaine du médicament. Il convient de noter que même si l'étude a démontré un bénéfice en matière de

DFS chez les patients avec PD-L1 positif de stade II-IIIa (*Hazard Ratio* [HR], 0,66 ; IC à 95 %, 0,50 à 0,88), une analyse post-hoc a indiqué que le bénéfice était majoritairement dû aux patients présentant une expression tumorale de PD-L1  $\geq 50$  %. Le *hazard ratio* était de 0,87 et 0,43 pour les patients avec PD-L1 1% < 50% et  $\geq 50$ %, respectivement. Compte tenu du manque de bénéfice pour les tumeurs PD-L1 de 1 % à 49 %, la Commission européenne a approuvé l'*Atezolizumab* uniquement pour les patients atteints de PD-L1  $\geq 50$  %. Cette stratégie n'est pas prise en charge par l'assurance maladie en France.

L'essai KEYNOTE-091 (29) a également démontré une amélioration de la DFS chez les patients CBNPC de stade IB ( $\geq 4$  cm) à IIIa avec l'association au traitement standard d'un an de *Pembrolizumab* en adjuvant. Il est intéressant de noter qu'il n'y avait aucune association entre une plus grande ou une moindre efficacité dans l'Essai KEYNOTE-091 par expression PD-L1.

L'expérience de l'immunothérapie prescrite dans d'autres situations du CBNPC, dans d'autres pathologies comme le mélanome, a laissé émerger l'hypothèse que l'efficacité de l'immunothérapie serait maximisée lorsque la tumeur primitive est toujours en place et présenterait alors une charge élevée de néoantigènes avec une hétérogénéité limitée parce que les cellules cancéreuses n'ont pas encore été exposées à l'immunothérapie (29). Vraisemblablement, la présence de la tumeur en place pendant un traitement néoadjuvant d'immunothérapie permettrait une plus large réponse anti-tumorale des lymphocytes T en raison de l'exposition à un large répertoire d'antigènes tumoraux (30). L'administration néoadjuvante d'immunothérapies permet le conditionnement de la tumeur et l'expansion des lymphocytes T mémoire spécifiques de la tumeur au début de l'évolution de la maladie (31). Dans les modèles précliniques publiés, une charge tumorale élevée et une hétérogénéité limitée des antigènes tumoraux étaient associées à de meilleurs résultats de l'immunothérapie ce qui suggèrerait qu'une prescription néoadjuvante d'immunothérapie serait à prioriser dans la stratégie péri-opératoire. Dans cette situation néo-adjuvante, un essai de phase III, CheckMate-816 a démontré une amélioration de l'EFS avec le *Nivolumab* plus chimiothérapie pendant trois cycles par rapport à la chimiothérapie seule pour les patients présentant un stade IB à IIIa résecable, EGFR et ALK sauvage (8). Les traitements néo-adjuvants peuvent s'évaluer par l'analyse de la pièce opératoire qu'on appelle la réponse pathologique. L'amélioration de l'EFS avec la chimiothérapie/*Nivolumab* était fortement associée à l'obtention d'une réponse pathologique complète (pCR) dans l'étude checkmate 816 (HR à 0,13 vs pas de pCR). Cette étude a permis l'autorisation en accès précoce du *Nivolumab*, en association à une chimiothérapie à base de sels de platine dans le traitement néoadjuvant des patients adultes, atteints d'un cancer bronchique non à petites cellules résecable à haut risque de récurrence, dont les tumeurs expriment PD-L1 au seuil  $\geq 1$  % et dont les tumeurs ne présentent pas de mutation sensibilisante de l'EGFR connue, ni de translocation ALK connue.

D'autres études ont associé immunothérapie adjuvante et néo-adjuvante comme AGEAN qui a évalué dans une étude de phase III l'activité du *Durvalumab* et de la chimiothérapie administrée avant chirurgie par rapport au placebo et à la chimiothérapie administrée dans un contexte néoadjuvant et adjuvant pour les patients atteints d'un CBNPC résecable à un stade précoce (IIa-IIIb). Après un suivi médian de 11,7 mois, l'EFS médiane était non atteinte dans le bras immunothérapie versus 25,9 mois dans le bras chimiothérapie seule (32).

Dans ce même design d'étude, où le *Pembrolizumab* était proposé avec la chimiothérapie (4 cycles avant la chirurgie puis pendant 1 an seul après la résection). La survie sans événement à 24 mois était de 62,4 % dans le groupe pembrolizumab et de 40,6 % dans le groupe placebo (risque relatif de progression, de récurrence ou de décès : 0,58 ; intervalle de confiance [IC] à 95 % : 0,46 à 0,72 ;  $P < 0,001$ ) (33).

L'immunothérapie en situation péri-opératoire a transformé le traitement des patients atteints d'un CBNPC résécable (stade I–IIIA/B). Il existe plusieurs schémas thérapeutiques péri-opératoires en termes de produit d'immunothérapie, de combinaison à d'autres immunothérapies, à la chimiothérapie et en termes de chronologie d'administration (néoadjuvant, adjuvant, les deux), ou encore de durée. De même, les stratégies testées sont également différentes. Par conséquent, en l'absence d'un grand nombre d'essais contrôlés randomisés comparant tous les schémas thérapeutiques péri-opératoires, l'incertitude demeure quant à la meilleure option pour les patients opérables atteints d'un CBNPC résécable (34).

Le ciblage des patients reste une autre question ouverte car tout le monde ne semble pas en bénéficier, voir pour certains patients en tirer préjudice comme les patients présentant des altérations moléculaires (mutations activatrices de l'EGFR, réarrangement de ALK).

#### Avec addiction

Des thérapies ciblées sont plus appropriées pour ces patients, comme l'Osimertinib, thérapie ciblée de l'EGFR, qui est recommandé en traitement adjuvant après résection tumorale complète et après chimiothérapie adjuvante (si indiquée) des patients adultes atteints d'un CBNPC de stade IB – IIIA avec mutations activatrices du récepteur du facteur de croissance épidermique (EGFR) par délétion de l'exon 19 ou substitution de l'exon 21 (L858R) (35).

Enfin très récemment, selon une analyse intermédiaire de l'essai ALINA, l'alectinib (thérapie ciblée de ALK) était associé à des bénéfices significatifs en termes de survie sans maladie (DFS) par rapport à la chimiothérapie à base de platine seule, observés en situation adjuvante dans la population CBNPC de stade II et IIIA ( $n = 231$  ; risque relatif [HR] 0,24 ; intervalle de confiance [IC] à 95 % 0,13–0,45 ;  $p < 0,0001$ ) (36).

La stratégie thérapeutique des CBNPC de stades III est donc la plus complexe, pouvant également faire appel à une chimio-radiothérapie concomitante suivie d'une immunothérapie par durvalumab. Lung ART a évalué la radiothérapie post-op chez les patients N2 après résection complète et chimiothérapie néoadjuvante ou adjuvante. Dans cet essai, la radiothérapie adjuvante n'était pas associée à une meilleure survie et ne peut donc plus être recommandée chez les patients atteints d'un CPNPC de stade IIIA-N2 (37).

Albain KS et coll, dans l'essai *intergroupe 0139*, ont présenté une étude de phase III dans laquelle les patients atteints d'un cancer N2 étaient randomisés entre une chimio-radiothérapie néo-adjuvante plus une intervention chirurgicale ou une chimio-radiothérapie seule. Au total, 164 patients ont été opérés. Bien que cela ne soit pas statistiquement significatif, les patients du bras chirurgical auraient une meilleure survie sans progression (SSP). La survie globale (SG) n'était pas différente entre les deux bras, principalement en raison du manque



de puissance dû au manque et au nombre réduit de cycles de chimiothérapie pouvant être administrés dans le bras chirurgical, mais également en raison du taux de mortalité élevé des patients ayant été opérés d'une pneumonectomie. Par conséquent, une analyse exploratoire a été menée montrant une amélioration de la SG chez les patients soumis à une lobectomie par rapport à un groupe apparié traité par chimio-radiothérapie seule. L'étude a conclu que les deux thérapies peuvent être suggérées dans ce sous-groupe de patients (38).

Ainsi, différents traitements multimodaux sont décrits, où la place de la chirurgie est souvent remise en question. Dans une revue systématique sur la prise en charge des stades IIIA-N2, aucun facteur prédictif ni pronostic n'a pu être identifié, ce qui ne facilite pas l'avancée décisionnelle concernant le rôle de la chirurgie dans ce sous-groupe (39). Girard N et coll, ont démontré dans une analyse de pratique, une reproductibilité des décisions en réunion de concertation pluridisciplinaire de 70% lorsqu'ils rediscutaient le même dossier après un intervalle de temps (40).

#### D. Surveillance après chirurgie d'un CBNPC

Une fois que le patient est opéré, et que les éventuels traitements péri-opératoires sont terminés, un schéma de surveillance clinique et radiologique est indiqué. L'objectif de cette surveillance est de rechercher l'apparition d'effets secondaires au traitement, de détecter la survenue de récurrences locales ou systémiques, de seconds cancers ou des comorbidités. La programmation d'une imagerie thoracique régulière a pour but de détecter la récurrence pulmonaire ou le second cancer pulmonaire (SCBP) à des stades précoces, et ainsi proposer de nouveau un traitement avec une intention curatrice. Les recommandations sur la surveillance des patients opérés d'un cancer broncho-pulmonaire reposent sur des avis d'experts (41, 42, 43). Un examen clinique et un scanner thoracique sont recommandés tous les 6 mois les deux premières années de surveillance, puis une fois par an. Le TEP-scanner n'est pas recommandé, ni l'imagerie cérébrale, ni le dosage de biomarqueurs sanguins. L'étude IFCT-0302 est le seul large essai randomisé multicentrique qui a comparé deux schémas de surveillance chez les patients opérés d'un CBNPC de stade I, II, IIIA ou T4 (selon la 6ème édition de la classification TNM) quel que soit le traitement péri-opératoire reçu. Le groupe contrôle avait une surveillance semestrielle par examen clinique et radiographie thoracique pendant deux ans puis la surveillance était annuelle jusqu'à la 5ème année. Le groupe expérimental avait la même surveillance au même rythme avec en plus un scanner thoraco-abdominal avec injection de produit de contraste et une fibroscopie bronchique (44). Le suivi médian était de 8,7 années et aucune différence sur la survie globale n'a été démontrée selon le schéma de surveillance, avec une survie à 8 ans de 51% chez les patients avec la surveillance « simple » et d'environ 55% chez les patients avec la surveillance par scanner thoraco-abdominal. La surveillance post-thérapeutique des CBNPC par scanner systématique n'a donc pas montré de bénéfice sur la survie globale. Toutefois, celle-ci a montré que les diagnostics de récurrences, en particulier de récurrences pulmonaires, et de SCBP étaient plus fréquents et plus souvent alors qu'asymptomatiques. Ces diagnostics de SCBP, de récurrences précoces se faisaient à un stade plus précoce et donc accessible à un traitement chirurgical ou de radiothérapie dans le

groupe de suivi basé sur la tomодensitométrie que dans le groupe de suivi minimal. Groupe. Il est vraisemblable que l'étude a manqué de puissance pour mettre en évidence un bénéfice en termes de survie globale. Outre l'habitude de surveiller les patients opérés d'un CBNPC par scanner thoracique, les résultats de l'étude peuvent donc justifier de poursuivre une surveillance clinique et scannographique.

#### E. Les Seconds Cancers Broncho-Pulmonaire Primitifs

Si une lésion suspecte apparaît sur une imagerie thoracique réalisée au cours de la surveillance d'un patient opéré d'un cancer broncho-pulmonaire, la différence entre une récurrence du premier cancer et l'apparition d'un second cancer pulmonaire n'est pas aisée. Lorsque l'anatomopathologie est différente du cancer opéré, il n'y a aucun doute sur un diagnostic de second cancer pulmonaire. Différentes définitions permettant de distinguer les récurrences des SCBP ont été proposées (45, 47, 50). La plupart des études traitant sur le second cancer pulmonaire utilise les critères de Martini et Melamed qui datent de 1975 (45). Selon ces critères, une deuxième tumeur de type histologique différent peut être classée comme métachrone, même si la plupart des études portant sur des patients traités chirurgicalement atteints de plusieurs cancers primitifs du poumon (soit synchrone ou métachrone) ont rapporté un type histologique identique entre les 2 tumeurs dans > 50 % des cas (46, 47, 48, 49). Lorsque l'histologie est identique entre les deux tumeurs, un intervalle libre de deux ans entre les tumeurs, ou une origine d'un carcinome *in situ*, ou une seconde tumeur dans un lobe ou un poumon différent sans adénopathie commune et sans métastase extra-pulmonaire, permet le diagnostic de SCBP.

Un ensemble révisé de critères a ensuite été proposé par Antakli *et al* (50), puis par Colice *et al* (51), qui ont prolongé l'intervalle sans maladie requis jusqu'à 4 ans. Des approches alternatives utilisant des critères de tests histomorphologiques ou moléculaires ont été proposées dans des rapports plus récents (52). Ces critères ont été repris par l'American College of Chest Physicians (ACCP) (53): le diagnostic de SCBP est resté basé sur l'histologie lorsqu'elle est différente du premier cancer ou lorsque les caractéristiques génétiques moléculaires sont différentes ou résultent d'un foyer distinct de carcinome *in situ* ; lorsque l'histologie est identique au premier cancer, le second cancer pulmonaire est retenu si le délai d'apparition est de plus de 4 ans, en l'absence de métastase à distance ; enfin si l'histologie est identique et que les deux cancers se situent dans 2 poumons différents sans adénopathie N2 ou N3 et sans métastases impliquées, le SCBP est retenu. La différence principale avec les critères de Martini et Melamed réside dans l'intervalle diagnostique entre les deux tumeurs: 2 ans ou 4 ans selon la définition.

Cette distinction n'est pas un hasard. Le risque global de récurrence locorégionale ou à distance varie de 20 à 42 % chez les patients opérés d'un CBNPC de stade IA à IIB (54, 55). Ce risque est maximal durant les 2 premières années post-opératoires. Dans l'étude de Lou *et al.*, le risque de récurrence tombe à 2 % la 4<sup>ème</sup> année de surveillance (54). Le risque de second cancer pulmonaire suit une courbe différente puisqu'il varie de 1 à 2 % par an dès la première année post-opératoire, sans jamais décroître par la suite. Ce risque est cumulatif puisqu'il atteint 20 % après 10 années de surveillance (56, 57).

D'autres définitions existent, l'intervalle diagnostique entre les deux tumeurs reste le critère qui varie le plus. Par exemple, l'étude de Pairolero et al. (58) n'utilise pas le critère de temporalité pour séparer les tumeurs d'histologie identique, et cette définition a été reprise dans plusieurs études (59, 60). Aussi, l'étude de Von Bodegom *et al.* retient un intervalle libre de 3 ans entre deux tumeurs d'histologie différente pour un diagnostic de second cancer pulmonaire (61).

Les patients opérés d'un cancer du poumon sont donc à risque de récurrence du cancer opéré mais ont également ce risque de second cancer, et en particulier de second cancer du poumon, supérieur à celui de la population générale, de l'ordre de 20 % à 10 ans. A compter du diagnostic de récurrence, le taux de survie à 5 ans est estimé entre 16 et 23 % (62, 63), la survie moyenne est d'environ 25 à 30 mois (63, 64, 65). Le taux de survie à 5 ans des patients présentant un second cancer pulmonaire est estimé entre 23 et 77 % (64), la survie moyenne est d'environ 49 mois (65).

## F. La Collaboration Cochrane

La collaboration Cochrane est une organisation à but non lucratif indépendante qui regroupe plus de 28 000 volontaires dans plus de 100 pays. Cette collaboration s'est formée à la suite d'un besoin d'organiser de manière systématique les informations issues de la recherche médicale. Elle a pour but de regrouper des données scientifiquement validées de manière accessible et résumée. Elle conduit à des revues systématiques et des méta-analyses d'essais randomisés contrôlés d'interventions en santé. Ces travaux sont publiés dans la bibliothèque Cochrane (Cochrane library, <http://www.cochranelibrary.com/>).

La collaboration est reconnue comme organisation non gouvernementale par l'Organisation mondiale de la santé (OMS) depuis janvier 2011.

Le Cochrane Lung Cancer Group est l'un des groupes de la collaboration. Il est situé à Besançon depuis Octobre 2013 et est dirigé par le Professeur V. WESTEEL (Université de Franche-Comté / Centre Hospitalier Régional et Universitaire de Besançon).

Créé en 2010 à l'hôpital Hôtel-Dieu à Paris et dirigé par le Professeur Isabelle Boutron, le Centre Cochrane Français fait partie des 14 centres de la Collaboration Cochrane dans le monde.

Une revue systématique est une manière approfondie, globale et explicite d'interroger la littérature médicale. Dans le cadre de la Collaboration Cochrane, il s'agit d'une démarche scientifique rigoureuse constituée de plusieurs étapes :

- 1) Vérification de l'absence de revue Cochrane, de titre soumis ou de protocole en cours sur le sujet
- 2) Élaboration et soumission du titre
- 3) Élaboration et soumission du protocole
- 4) Recherche de toutes les études existantes, essais cliniques ou autres études appropriées, publiées ou non, qui ont répondu à une même question clinique précise ; par exemple, tous les essais cliniques effectués afin d'évaluer l'efficacité d'un traitement.

5) Évaluation de la qualité de chaque étude et sélection de celles qui correspondent à un standard de qualité élevé

6) Synthèse des résultats obtenus dans les études sélectionnées.

7) Finalement, si les données le permettent, effectuer une analyse statistique, appelée méta-analyse. Elle permet de regrouper les résultats quantifiés provenant de plusieurs études en un résultat résumé.

Initialement, le groupe *Lung Cancer* proposait essentiellement des revues systématiques d'intervention. La collaboration est de plus en plus intéressée à fournir des synthèses des données provenant d'essais de puissance et de niveau de preuve différents, soit en comparant les données des études d'observation avec celles des essais randomisés, soit en complétant les informations par une analyse rigoureuse de la littérature et en répondant à une question complémentaire de celle des essais contrôlés randomisés. Cette méthodologie s'applique aux revues pronostiques dont le groupe *lung cancer* souhaite développer son expertise.

De plus, la collaboration Cochrane développe une méthodologie en comparaison indirecte à l'aide des méta-analyses en réseau.

La synthèse des données, par revue systématique ou méta-analyse, peut être régulièrement mise à jour et former le concept de revue systématique vivante (*living systématique review*). Les revues systématiques vivantes sont également développées dans une méthodologie rigoureuse.

Les résultats d'une revue systématique peuvent être présentés de manière qualitative ou quantitative (méta-analyse). Dans les deux cas, la synthèse doit résumer la direction de l'effet traitement, la taille de l'effet, la cohérence des résultats entre les études et le niveau de rigueur des preuves.

La méta-analyse conventionnelle est la combinaison statistique des résultats d'au moins deux études distinctes comparant deux traitements donnés (traitement actif versus placebo ou traitement actif versus un autre traitement actif). Cette méthode permet :

- d'augmenter la puissance c'est-à-dire la possibilité de détecter une différence statistiquement significative si elle existe ;
- d'améliorer la précision de l'estimation de l'effet traitement,
- de réaliser des analyses en sous-groupes,
- d'explorer les raisons de résultats divergents entre études.

Les revues systématiques Cochrane et les méta-analyses qui en découlent sont contrôlées par des instances très rigoureuses. Ainsi, cela en fait des outils de références pour les décisionnaires de santé.

#### G. L'examen de ponction-biopsie sous scanner

Dans l'idéal, toute nouvelle image pulmonaire suspecte de récurrence ou SCBP, devrait faire l'objet d'une preuve anatomopathologique, qui permettrait une comparaison morphologique, immunohistologique et moléculaire du cancer index et de la nouvelle lésion. Au cours de la surveillance, la découverte de nodules pulmonaires au

cours de la surveillance postopératoire d'un CBNPC peut justifier la réalisation d'une ponction-biopsie pulmonaire (PBP) percutanée guidée par scanner puisque l'endoscopie bronchique est souvent non contributive, notamment dans les lésions périphériques et de petite taille (66).

Dans une méta-analyse récente, Di Bardino et al. ont évalué la précision diagnostique de la biopsie thoracique guidée par tomodensitométrie à 92,1 % (9 567/10 383), avec une sensibilité de 92,1 % (7 343/7975) et une spécificité d'environ 100 % pour le diagnostic de malignité (67). Les principales complications des PTP sont en premier lieu le pneumothorax, suivi des hémorragies (intra-alvéolaires en chef de file, hémoptysies, hémothorax), loin devant l'embolie gazeuse et la dissémination tumorale le long du trajet de l'aiguille (68). La létalité de l'examen est très faible : dans les rares études la rapportant, souvent nulle, elle atteint au maximum mentionné 0,12 %, imputée essentiellement à des hémothorax, des hémoptysies ou des embolies gazeuses fatales (69, 70).

Le taux d'incidence du pneumothorax en particulier, dont la définition exacte diffère selon les articles (pneumothorax sur les coupes scannographiques immédiates post-PTP, ou pneumothorax retardé sur les radiographies thoraciques de contrôle post-PTP), oscille entre 4 et 54 %. Dans la méta-analyse récente de Heerink et al, il est en moyenne de 25,3 % avec 5,6 % de pneumothorax requérant une intervention thérapeutique (71). Aucun consensus n'existe pour la prise en charge spécifique de ces pneumothorax iatrogènes. Généralement, ceux-ci surviennent sur table au décours immédiat, sinon dans la première heure suivant le geste. Cependant, par crainte du pneumothorax retardé, qui apparaît chez 3,3 % des patients dans l'article de Choi et al, la plupart des équipes surveillent leurs patients plusieurs heures après la procédure et parfois la nuit entière (72). En outre, plusieurs facteurs de risque de survenue de pneumothorax post-PTP sont rapportés. Huo et al, dans une méta-analyse de 2020, en ont identifié les facteurs suivants : une lésion de petite taille, une profondeur intra-parenchymateuse de la lésion importante (suggérant une grande quantité de parenchyme aéré traversé par l'aiguille), un poumon emphysémateux, et le passage de l'aiguille à travers une bulle d'emphysème ou une scissure (73).

Dans les recommandations proposées par la *British Thoracic Society*, une radiographie thoracique doit être réalisée une heure après l'intervention (74), sans qu'aucune surveillance spécifique ne soit requise après une PTP sans complication. À notre connaissance, aucune recommandation ou consensus d'experts n'utilise de scores prédictifs pour personnaliser la surveillance post-PTP.

## OBJECTIFS

---

Notre travail avait pour objectif une meilleure connaissance des facteurs de risque de survenue des récurrences et deuxièmes cancers pulmonaires primitifs (axe pronostique), la synthèse des données sur les stratégies thérapeutiques péri-opératoires (axe thérapeutique) et la meilleure compréhension de leurs difficultés diagnostiques (axe surveillance et diagnostique).

### Axe pronostic :

- une revue systématique pronostique selon la méthode Cochrane pour définir le pronostic des récurrences et des seconds cancers broncho-pulmonaires primitifs chez les patients opérés d'un cancer broncho-pulmonaire index afin de différencier ces 2 entités.

### Axe thérapeutique :

- une revue systématique en réseau selon la méthode Cochrane d'essais interventionnels pour évaluer l'efficacité et la tolérance des stratégies de traitements péri-opératoires d'immunothérapie chez les patients atteints de cancer du poumon non à petites cellules résecables.

### Axe diagnostique :

- Évaluer l'influence du type de surveillance sur la qualité de vie dans la population de l'étude IFCT-0302
- Valider un score prédictif de survenue d'un pneumothorax retardé après une ponction-biopsie transpariétale pulmonaire scannoguidée, afin de sélectionner les patients qui doivent être surveillés en hospitalisation conventionnelle.

*Axe pronostique*

*SURVIE GLOBALE DES RECIDIVES OU DES SECONDS CANCERS PULMONAIRES  
CHEZ LES PATIENTS OPERES D'UN CARCINOME BRONCHOPULMONAIRE NON  
A PETITES CELLULES :  
REVUE SYSTEMATIQUE PRONOSTIQUE*

## **Résumé**

Après une chirurgie du cancer du poumon à visée curative, la récurrence de ce cancer ou un second cancer pulmonaire primitif (SCBP) sont les principales causes de décès chez les personnes atteintes d'un cancer du poumon non à petites cellules opéré. De nombreuses études ne font pas de distinction entre la récurrence du cancer index et le SCBP, alors que notre point de vue est qu'il s'agit de 2 entités différentes. L'amélioration du diagnostic respectif de la récurrence du cancer du poumon index et du SCBP pourrait identifier 2 histoires naturelles différentes, aux possibilités de diagnostic et de traitement différentes, et donc affecter le pronostic de ces deux entités distinctes.

### Objectifs

Comparer la survie globale chez les personnes présentant une récurrence et un SCBP après une chirurgie du cancer du poumon. Si la survie diffère entre la récurrence du cancer du poumon index et le SCBP, il pourrait être possible d'explorer et d'identifier ultérieurement la définition la plus discriminante parmi toutes celles publiées.

### Méthodes de recherche

Nous avons effectué des recherches dans les bases de données suivantes sans aucune restriction, basées sur la langue, la date de publication ou le statut de publication : MEDLINE via PubMed (de 1951 à la date de la recherche) et Embase (de 1947 à la date de la recherche).

### Les critères de sélection

Nous avons inclus des études longitudinales prospectives et rétrospectives, quelle que soit la durée de suivi, qui examinaient le pronostic de la récurrence du cancer du poumon index, du SCBP ou des deux après résection d'un cancer pulmonaire. Nous avons exclu les études transversales, car il n'était pas possible de déterminer le pronostic à partir de ce modèle.

### Collecte et analyse de données

Deux auteurs de la revue (GE et RZ) ont sélectionné les études pour inclusion et ont entrepris l'extraction des données, l'évaluation du risque de biais et l'évaluation selon les recommandations GRADE. Nous avons évalué



la survie globale (SG) pour la récurrence et le SCBP sous forme de moyennes ou de médianes, avec leurs estimateurs de variabilité correspondants. Si les études incluses mesuraient la valeur pronostique (degré d'association) de la récurrence par rapport au SCBP, nous avons utilisé les HR avec leurs intervalles de confiance plutôt que les médianes et les moyennes pour estimer le pronostic par la SG.

### Principaux résultats

A l'heure de la rédaction de ce travail de thèse, la sélection des articles est terminée, le recueil des données a été réalisé permettant de présenter le rapport d'analyse des biais ainsi qu'une revue narrative des données synthétisées. Ces résultats préliminaires sont présentés à la fin du manuscrit du protocole.

Nous avons identifié 86 études (30 252 adultes). Quarante-cinq étaient des études monocentriques, une menée dans deux centres et huit étaient des études multicentriques. Six études ont comparé l'association survie globale des récurrences et des SCBP. Sur ces six études, le pronostic était influencé par le stade au diagnostic, car 2 études ne prenant en compte que les récurrences accessibles à une chirurgie, n'ont pas retrouvé de différence en termes de survie globale entre les récurrences et les SCBP.

### Conclusion :

Nous avons constaté que la survie des patients atteints d'un CPNPC résecté de stade I à IIIA semble être influencée par le stade au diagnostic de la récurrence ou du SCBP. Comme les SCBP sont plus souvent diagnostiqués à un stade localisé, ils semblent avoir un meilleur pronostic.

# Overall prognosis of recurrence of index lung cancer or of second primary lung cancer in people with non-small cell lung cancer operated with complete resection

## Table of contents

Abstract Background

Description of the health condition and context Health outcomes  
Why it is important to do this review

Objectives Methods

Criteria for considering studies for this review Search methods for identification of studies Data collection  
Data synthesis

Acknowledgements Contributions of authors Declarations of interest Sources of support

Internal sources

External sources Appendices

Appendix 1. MEDLINE search strategy Appendix 2. Embase search strategy Appendix 3. Data collection form

References

Additional references

Editors: Cochrane Lung Cancer Group

Contact Person: Louis Laforge (louislaforge@hotmail.fr) Besançon, France

Louis Laforge [1] Guillaume Eberst [1] [2] François Calais [3] Reem Malouf [4] Corynne Marchal [5] Virginie Westeel [6] Marta Roqué-Figuls [7]

[1] Department of Chest Diseases and Thoracic Oncology, University Hospital of Besançon, Besançon, France

[2] Université Bourgogne Franche-Comté, INSERM, EFS BFC, UMR 1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire et Génique, Besançon, France

[3] Bibliothèque Universitaire de Santé, Université de Franche-Comté, Besançon, France

[4] National Perinatal Epidemiology Unit (NPEU), University of Oxford, Oxford, UK

[5] Department of Thoracic Oncology, University Hospital of Besançon, Besançon, France

[6] Thoracic Oncology, University Hospital of Besançon, Besançon, France

[7] Iberoamerican Cochrane Centre, Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

## Citation

Laforge L, Eberst G, Calais F, Malouf R, Marchal C, Westeel V, Roqué-Figuls M. Overall prognosis of recurrence of index lung cancer or of second primary lung cancer in people with non-small cell lung cancer operated with complete resection (Protocol). Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: [CD015319](#). DOI: [10.1002/14651858.CD015319](#).

## Dates

Revision published: Issue TBD, TBD (TBD)  
Version published (citation changed): Issue TBD, TBD (TBD) Review first published: N/A  
Protocol first published: Issue TBD, TBD

## Abstract objectives

This is a protocol for a Cochrane Review (prognosis). The objectives are as follows:

This is a protocol for a Cochrane prognosis review. We aim to compare overall survival in people with recurrence and SPLC after lung cancer surgery. If survival differs between index lung cancer recurrence and SPLC, it might be possible to subsequently explore and identify the most discriminant definition among all those published.

Our review question and eligibility criteria are based on the following PICOTS table ([Debray 2017](#); [Moons 2014](#)).

|              |  |
|--------------|--|
| Population   | People aged over 18 years who underwent complete resection of stage T1–3 N0–2 NSCLC according to the eighth edition of the TNM classification or equivalent ( <a href="#">Goldstraw 2016</a> ), and who have a recurrence of the index lung cancer or an SPLC, regardless of perioperative treatment |
| Intervention | Not applicable   |
| Comparator   | Not applicable   |
| Outcome      | Overall survival (OS)  |
| Timing       | Prospective and retrospective longitudinal studies, reporting on index lung cancer recurrence, or SPLC or both after surgery for an index lung cancer. We will also include randomised controlled trials (RCTs).   |
| Setting      | No restrictions regarding setting  |

## Background

### Description of the health condition and context

Lung cancer remains the leading cause of cancer-related death worldwide, accounting for 18% of total cancer deaths in 2020 ([Sung 2021](#)). More than half of people with lung cancer (57%) are diagnosed with a metastatic disease ([Howlader 2020](#)). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 84% of all diagnoses ([Howlader 2020](#)). In NSCLC, outcomes differ according to stage at diagnosis, with a 60-month survival rate of 68% to 92% for stage I and of 0% to 10 % for stage IV ([Goldstraw 2016](#)).

Surgery with or without perioperative chemotherapy remains the cornerstone treatment of early-stage lung cancer ([Ettinger 2020](#)). Most international recommendations suggest follow-up after lung cancer surgery to detect treatment-related complications, index lung cancer recurrence or a second primary lung cancer (SPLC). Experts recommend radiological and clinical control twice yearly for two years and once yearly between two and five years after surgery ([Colt 2013](#); [Postmus 2017](#); [Schneider 2020](#)).

People treated for lung cancer with curative intent are at high risk of disease recurrence and SPLC development (Lou 2013; Stirling 2021). If a suspicious lung lesion appears during follow-up, it is challenging to distinguish between these two occurrences, although several sorting strategies exist. In 1975, Martini and colleagues proposed the following criteria: differing histology is indicative of a second primary cancer; and where the histological type is the same, indications of second primary cancer include an interval between the two cancers of at least two years, carcinoma in situ, and location in another lobe or lung in absence of lymphatic involvement and extrapulmonary metastases (Martini 1975). In all proposed definitions, the diagnostic interval between the two tumours is the most inconstant criterion. Recommendations published in 2003 from the American College of Chest Physicians (ACCP) proposed a new definition of SPLC for histologically similar tumours, with a four-year disease-free interval (Detterbeck 2003).

## Health outcomes

The five-year survival rate of people with lung cancer treated with curative intent ranges from 36% to 92% according to stage (Goldstraw 2016). The leading cause of death is cancer disease, whether index lung cancer recurrence or an SPLC (Fink-Neuboeck 2020). Risk of recurrence is highest during the first two postoperative years (around 10%) and decreases thereafter (Lou 2013). The risk of developing an SPLC does not follow the same trend: it is around 1% to 2% per year and does not decrease over time, with a cumulative risk of 20% at 10 years (Antakli 1995; Johnson 1998; Ripley 2014; Leroy 2019).

One systematic review published in 2021 reported that scheduled surveillance programmes significantly increased curative retreatment for SPLC or recurrence (Stirling 2021). However, it was not possible to distinguish between index lung cancer recurrence and SPLC, as most studies did not provide separate data for these two outcomes.

## Why it is important to do this review

Many studies do not distinguish between index lung cancer recurrence and SPLC despite the available criteria for separating these diagnoses. Improving the respective diagnosis of index lung cancer recurrence and SPLC might identify different natural histories, diagnosis and retreatment possibilities, and therefore affect the prognosis of these two distinct diseases.

Clinical implication, could even be wider as a better knowledge of these two natural histories could make it possible to personalize the monitoring of operated people or even personalize perioperative treatments.

Finally, in clinical research, standardizing the definition of SPLC could allow a better evaluation of the impact of perioperative treatments currently under development on the occurrence of SPLC.

## Objectives

This is a protocol for a Cochrane prognosis review. We aim to compare overall survival in people with recurrence and SPLC after lung cancer surgery. If survival differs between index lung cancer recurrence and SPLC, it might be possible to subsequently explore and identify the most discriminant definition among all those published.

Our review question and eligibility criteria are based on the following PICOTS table (Debray 2017; Moons 2014).

## Methods

This section is based on the general protocol template provided by the Cochrane Prognosis Method Group.

## Criteria for considering studies for this review

We will include studies reporting index lung cancer recurrence, SPLC or both after surgery for an index lung cancer.

## Types of studies

We will include prospective and retrospective longitudinal studies. We will exclude cross-sectional studies, as it is not possible to determine prognosis from this design.

We will exclude studies that do not distinguish between recurrence and SPLC. We will also exclude case reports and prospective case series, defined here as studies including fewer than 20 participants.

To our knowledge, there are no eligible RCTs. If we do identify any, we will consider them observational studies and treat recurrence and SPLC as events for subgroup analysis. In the same way, if we identify studies where only a subset of participants are eligible for inclusion, we will consider these as observational studies and treat recurrence and SPLC as events for subgroup analyses.

Given the prognostic nature of our objective, we will include studies with any follow-up duration.

## Targeted population

Populations and cohorts of people aged 18 years or older who have undergone complete resection of a primary NSCLC and who have index lung cancer recurrence or an SPLC.

Histological proof of recurrence or SPLC is not an inclusion criterion for this review.

## Types of outcomes to be predicted Primary objectives

|              |  |
|--------------|--|
| Population   | People aged over 18 years who underwent complete resection of stage T1–3 N0–2 NSCLC according to the eighth edition of the TNM classification or equivalent (Goldstraw 2016), and who have a recurrence of the index lung cancer or an SPLC, regardless of perioperative treatment |
| Intervention | Not applicable   |
| Comparator   | Not applicable   |
| Outcome      | Overall survival (OS)  |
| Timing       | Prospective and retrospective longitudinal studies, reporting on index lung cancer recurrence, or SPLC or both after surgery for an index lung cancer. We will also include randomised controlled trials (RCTs).   |
| Setting      | No restrictions regarding setting  |

Overall survival (OS) of people diagnosed with index lung cancer recurrence or SPLC after complete resection for NSCLC. We will define OS as time between the diagnosis of recurrence or SPLC to death from any cause or to last follow-up (mean survival in months).

Overall mortality: proportion of mortality (percentage) from one to two years, from two to five years, and from five years (upper limits not inclusive).

## Secondary objectives

To assess the most discriminant definition for recurrence/SPLC in terms of OS.

Additionally, we will explore the following characteristics of the included studies.  
OS from surgery of the index lung cancer in the recurrence group and in the SPLC group

Detection method of index lung cancer recurrence or SPLC (scheduled or unscheduled procedure, symptomatic or not)

Extension (stages) at diagnosis of index lung cancer recurrence or SPLC  
Treatment of index lung cancer recurrence or SPLC

Health-related quality of life at one to two years, at two to five years, and from five years (upper limits not inclusive), measured with any generic or disease-specific quality of life instrument

## Search methods for identification of studies Electronic searches

We will search for relevant studies in the following databases with no restrictions based on language, publication date or publication status.

1. MEDLINE via PubMed (from 1951 to date of search)
2. Embase (from 1947 to date of search)

We will perform the electronic searches according to the recommendations of the Cochrane Methods Prognosis Group, using filters described by Ingui and colleagues in 2001 and updated by Haynes and colleagues in 2005 (Haynes 2005; Ingui 2001). Appendix 1 presents the search strategies for MEDLINE, and Appendix 2 presents the search strategies for Embase.

### Searching other resources

We will handsearch the references of eligible studies to identify additional studies for inclusion. We will search the meeting abstracts of conferences from the following sources (from 2020 to date of search).

American Society of Clinical Oncology (ASCO)  
European Society for Medical Oncology (ESMO)  
World Conference on Lung Cancer (WCLC)  
International Lung Cancer Research Association (IASLC)  
European Society for Medical Oncology (ESMO) Immuno-Oncology Congress  
European Lung Cancer Conference (ELCC)

American Association of Cancer Research (AACR)

We will collect clinical study reports about the checkpoint inhibitors from the websites of the US Food and Drug

Administration (FDA; [www.fda.gov](http://www.fda.gov)) and European Medicines Agency (EMA; [www.ema.europa.eu](http://www.ema.europa.eu)).

## Data collection

### Selection of studies

Using Covidence software (Covidence), two review authors (LL and CM) will independently screen the titles and abstracts of records retrieved by the searches, excluding those they consider clearly ineligible. We will retrieve the full-text articles of the remaining records, and two review authors (LL and GE) will assess them against our eligibility criteria. We will resolve any disagreements through discussion or by involving a third review author, if necessary.

We will present the process of study selection in a PRISMA study flow diagram (Rethlefsen 2021). **Data extraction and management**

We will base our data extraction form on the CHECKlist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS; Moons 2014). We will pilot our data extraction form on

---

several studies and make appropriate amendments.

We will extract the following information from each included study.

Study identification: author and year of publication Study design: cohort study, RCT  
Study setting: number of centres  
Study dates: study start and completion date Study eligibility criteria

Participants characteristics: number, age, sex, smoking status Study interventions (for RCTs)  
Study outcomes: primary and secondary outcomes (for RCTs) Prognostic factors (if analysed in the included study)

Number of prognostic factors Definition of prognostic factors

Methods for measuring prognostic factors (e.g. medical records, clinical diagnosis, pathological diagnosis)

Timing of measurement (before or after surgery)

Association measures for prognostic factors, reported as odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs). We will extract both unadjusted and adjusted data (detailing the adjustment variables).

Study analysis method: unadjusted and adjusted analysis and modelling method used (univariate, multivariate or other methods)

Other information: funding and conflicts of interest Information to assess risk of bias

We will conduct data management and analysis according to the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022).

Two review authors (LL and RM) will extract data to an Excel spreadsheet (Microsoft 2018). We will resolve any disagreements through discussion or by involving a third review author (GE), if necessary.

We will contact trial authors for missing information.

### **Assessment of risk of bias in included studies**

Two review authors (LL and RM) will evaluate risk of bias, resolving any discrepancies by including a third reviewer (GE). There is no available scale for assessing risk of bias in global prognostic studies. For this review, we will use the Quality In Prognosis Studies tool (QUIPS; Hayden 2013).

We will rate risk of bias in the following six domains :

- Outcome measurement
- Study confounding
- Statistical analysis and reporting
- Study participation
- Prognostic factor measurement
- Study attrition

For each domain we will assign an overall rating of 'low risk', 'moderate risk', or 'high risk' based on the signaling item.

### **Measures of association or predictive performance measures to be extracted**

We will assess OS for recurrence and SPLC as means or medians, with their corresponding variability estimators.

If included studies measure the prognostic value (degree of association) of recurrence compared with SPLC, we will use HRs with their CIs (where available) rather than medians and means to calculate OS. We will extract the unadjusted and adjusted measure of association for each study, if available.

The core set of adjustment factors are age, smoking status and the tumour-specific factors. If any studies provide adjusted estimates but do not adjust for the core set of adjustment factors, we will include data in the overall meta-analysis but exclude the studies in a sensitivity analysis.

We will use the HR as a common measure of association. We will meta-analyse HRs, RRs and ORs separately (Riley 2019).

### **Dealing with missing data**

We will not impute missing outcome data. We will consider the method utilised for dealing with missing data in relation to the outcome, and assess the associated risk of bias accordingly. If any studies use 'last diagnosis carried forward' when outcomes are unavailable, we will assign a high risk of bias. However, we will include studies with missing data in the analysis.

### **Assessment of heterogeneity**

If a meta-analysis is possible, we will use a random-effects model, as we expect the included studies to differ methodologically and clinically.

To address statistical heterogeneity, we will perform the Chi<sup>2</sup> test to identify variation in effect estimates beyond chance, considering a P value below 0.05 representative of a significant result, and we will calculate the I<sup>2</sup> statistic to describe the percentage of the variability in effect estimates owing to heterogeneity rather than sampling error. We will adopt the following standard thresholds for interpretation (Deeks 2011).

0% to 40%: might not be important

30% to 60%: may represent moderate heterogeneity 50% to 90%: may represent substantial heterogeneity 75%

to 100%: considerable heterogeneity

We will perform subgroup analyses to explore possible sources of heterogeneity (see 'Subgroup analyses' section below).

### **Assessment of reporting deficiencies**

We plan to investigate publication bias if we include 10 or more studies in any meta-analysis. We will visually examine any asymmetry in funnel plots, and test for asymmetry by applying Egger's test for HRs and Peters' test for ORs (Debray 2018; Sterne 2011).

### **Data synthesis Meta-analysis**

We will obtain pooled estimates of OS by meta-analysis, pooling data for recurrence and SPLC separately. We will conduct indirect comparison of the overall prognosis for both conditions by comparing estimates and their CIs. If trials present comparative HRs, we will pool them to allow for direct comparison of the prognosis of both conditions. We will use adjusted measures of effect, if available.

We plan to include all eligible studies in the review and, if possible, to restrict the results summary and any meta-analyses to results from multivariable analyses. Where this is not possible, we will include the results of univariable analyses, taking into account the phase of investigation in both the risk of bias assessment and GRADE rating on the certainty of the summary estimates.

Studies may measure the strength of association between prognostic factors (recurrence and SPLC) and the outcomes in different ways (using ORs, RRs or HRs) (Riley 2019). Where studies do not report the measure of association, we will try to calculate any unreported measures of association using a 2 × 2 frequency table, graphs



and figures. We hope to combine adjusted prognosis estimates from multivariable statistical models, including studies with similar participant populations and prognostic factor definitions. We will meta-analyse the following factors separately.

Unadjusted and adjusted measures of prognostic value of recurrence compared with SPLC

Ideally, prognostic estimates adjusted for different confounders. However, realistically, we will probably have to combine risk factors adjusted for different sets of confounders.

When meta-analysis is inappropriate, we will synthesise results narratively.

Where data are sufficiently similar to permit pooling, we will use a random-effects approach, given our expectation of high heterogeneity between studies. We will apply the Hartung-Knapp-Sidik-Jonkman method to obtain CIs ([IntHout 2014](#)). We will use RevMan Web ([RevMan Web 2020](#)) and Stata software ([StataCorp 2021](#)) to run our analyses.

## **Subgroup analysis**

When feasible, we will perform subgroups analysis by the following characteristics :

- Study design (prospective versus retrospective)
- Age
- Sex
- Stage at first surgery
- Smoking status
- Duration of follow-up
- Surgery type
- Experience of surgeon

We will distinguish prospective and retrospective studies because we suspect there will be an unequal loss of information between the two groups (recurrence versus SPLC). Indeed, one of our hypotheses is that these two events occur at differing delays after surgery, which is why we propose to create subgroups based on duration of follow-up.

Different factors may influence survival after resection of a primary NSCLC, including age, sex and smoking status. We hypothesise that risk of recurrence in relation to risk of SPLC increases with age, and we believe that female sex and smoking cessation are protective factors for risk of recurrence.

Finally, stage at first surgery, surgery types and experience of the surgeon are factors that can influence risk of recurrence.

## **Sensitivity analysis**

We will conduct sensitivity analyses by restricting the meta-analyses to data from studies with OS that are at low risk of bias.

## **Conclusions and summary of findings**

We will provide a summary of findings table with the following outcomes. OS for people with index lung cancer recurrence or SPLC

Percentage mortality from one to two years, from two to five years, and from five years after detection of recurrence or SPLC (upper limits not inclusive).

We will use the GRADE approach recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020) and modified for overall prognosis studies (Iorio 2015) to rate the certainty of the evidence.

In contrast to observational intervention studies, we will start with high certainty of evidence for cohort studies and low certainty of evidence for RCTs. Rating will result in a judgement of high, moderate, low, or very low certainty of the evidence.

We will interpret our judgements as follows (Iorio 2015).

High: we are very confident that the true prognosis (probability of future events) lies close to that of the estimate.

Moderate: we are moderately confident that the true prognosis (probability of future events) is likely to be close to the estimate, but there is a possibility that it is substantially different.

Low: our confidence in the estimate is limited; the true prognosis (probability of future events) may be substantially different from the estimate.

Very low: we have very little confidence in the estimate; the true prognosis (probability of future events) is likely to be substantially different from the estimate.

## Acknowledgements

We would like to acknowledge the Cochrane Lung Cancer Group and the Cochrane Prognosis Method Group for all their advice and support, particularly Prof. Dr Nicole Skoetz, University Hospital of Cologne, Cochrane Haematology, Germany,

We are grateful to the external peer reviewers for their time and comments. Martin J. Edelman, MD, FACP. Fox Chase Cancer Center, Philadelphia, PA

---

Kwun M Fong, University of Queensland Thoracic Research Centre, The Prince Charles Hospital, Brisbane, Queensland, Australia

Associate Professor RG Stirling, Monash University, Senior Specialist, Respiratory Medicine, Alfred Health, Melbourne, Australia.

We would also like to thank Julia Turner for copy-editing our manuscript.

## Contributions of authors

Draft protocol: LL, GE, FC, RM, MRF Design of the search strategies: FC

## Declarations of interest

LL: none known

GE: none known.

FC: none known

RM: none known

MRF: is Statistician for the Cochrane Lung Cancer Group and was not involved in the editorial process.

## Sources of support Internal sources

No sources of support provided

## External sources

INCa, France  
French Cancer National Institute (INCa n° 2022-047)

## Appendices

### Appendix 1. MEDLINE search strategy

1. lung neoplasms[MeSH Terms]
2. "Bronchopulmonary carcino\*" [Title/Abstract] OR "Cancer of Lung\*" [Title/Abstract] OR "Cancer of the Lung\*" [Title/Abstract] OR "Lung adenocarcinoma\*" [Title/Abstract] OR "Lung Cancer\*" [Title/Abstract] OR "Lung carcinoma\*" [Title/Abstract] OR "Lung malignan\*" [Title/Abstract] OR "Lung Neoplasm\*" [Title/Abstract] OR "Lung Tumo\*" [Title/Abstract] OR "Pulmonary adenocarcinoma\*" [Title/Abstract] OR "Pulmonary Cancer\*" [Title/Abstract] OR "pulmonary carcino\*" [Title/Abstract] OR "pulmonary malignan\*" [Title/Abstract] OR "Pulmonary Neoplasm\*" [Title/Abstract] OR "Pulmonary tumo\*" [Title/Abstract]
3. Carcinoma, Non-Small-Cell Lung[MeSH Terms] OR "Non-small Cell Lung Cancer\*" [Title/Abstract] OR "Non Small Cell Lung Cancer\*" [Title/Abstract] OR "Non-small Cell Lung Carcinoma\*" [Title/Abstract] OR "Non Small Cell Lung Carcinoma\*" [Title/Abstract] OR NSCLC[Title/Abstract]
4. Small Cell Lung Carcinoma[MeSH Terms] OR "Oat Cell Carcinoma\*" [Title/Abstract] OR "Oat Cell Lung Cancer\*" [Title/Abstract] OR SCLC[Title/Abstract] OR "Small Cell Lung Cancer\*" [Title/Abstract] OR "Small Cell Lung Carcinoma\*" [Title/Abstract]
5. #1 OR #2 OR #3 OR #4
6. Neoplasms, Second Primary[MeSH Terms] OR "Second Primary" [Title/Abstract] OR "Second lung" [Title/Abstract] OR "Second Cancer" [Title/Abstract] OR "second neoplasm" [Title/Abstract] OR Recurren\* [Title/Abstract]
7. #5 AND #6
8. Carcinoma, Non-Small-Cell Lung[MeSH Terms] OR nsclc[Title/Abstract]
9. "lung cancer\*" [Title/Abstract] OR "lung carcinom\*" [Title/Abstract] OR "lung neoplasm\*" [Title/Abstract] OR "lung tumor\*" [Title/Abstract] OR "lung tumour\*" [Title/Abstract]
10. "non small cell\*" [Title/Abstract] OR "nonsmall cell\*" [Title/Abstract]
- 
11. (#8 OR #9) AND #10
12. Neoplasm Recurrence, Local[MeSH Terms] OR recurren\* [Title/Abstract]
13. pneumonectomy[MeSH Terms] OR Pulmonary Surgical Procedures[MeSH Terms] OR lobectom\* [Title/Abstract] OR pneumonectom\* [Title/Abstract] OR resect\* [Title/Abstract] OR surgery [Title/Abstract] OR surgical [Title/Abstract] OR segmentectom\* [Title/Abstract]
14. (Small Cell Lung Carcinoma[MeSH Terms]) OR (SCLC[Title/Abstract])
15. (#11 AND #12 AND #13) NOT #14
16. #7 OR #15
17. Survival[MeSH Terms] OR Survival [Title/Abstract]

18. overall[Title/Abstract] OR risk[Title/Abstract] OR prognos\*[Title/Abstract] OR recurren\*[Title/Abstract] 19.  
#17 AND #18  
20. #16 AND #19

21. (Validat\* OR Predict\*[Title] OR Rule\*) OR (Predict\* AND (Outcome\* OR Risk\* OR Model\*)) OR ((History OR Variable\* OR Criteria OR Scor\* OR Characteristic\* OR Finding\* OR Factor\*) AND (Predict\* OR Model\* OR Decision\* OR Identif\* OR Prognos\*)) OR (Decision\* AND (Model\* OR Clinical\* OR Logistic Models[MeSH Terms])) OR (Prognostic AND (History OR Variable\* OR Criteria OR Scor\* OR Characteristic\* OR Finding\* OR Factor\* OR Model\*))

22. Stratification OR Roc Curve[MeSH Terms] OR Discrimination OR Discriminate OR "c-statistic" OR "c statistic" OR "Area under the curve" OR AUC OR Calibration OR Indices OR Algorithm OR Multivariable

23. #21 OR #22 24. #20 AND #23

## Appendix 2. Embase search strategy

#1,'bronchopulmonary carcino\*':ti,ab OR 'cancer of lung\*':ti,ab OR 'cancer of the lung\*':ti,ab OR 'lung adenocarcinoma\*':ti,ab OR 'lung cancer\*':ti,ab OR 'lung carcinoma\*':ti,ab OR 'lung malignan\*':ti,ab OR 'lung neoplasm\*':ti,ab OR 'lung tumo\*':ti,ab OR 'pulmonary adenocarcinoma\*':ti,ab OR 'pulmonary cancer\*':ti,ab OR 'pulmonary carcino\*':ti,ab OR 'pulmonary malignan\*':ti,ab OR 'pulmonary neoplasm\*':ti,ab OR 'pulmonary tumo\*':ti,ab' OR 'lung tumor'/exp OR 'lung tumor'

#2,'non small cell lung cancer'/exp OR 'nonsmall cell lung cancer\*':ti,ab OR 'non small cell lung cancer\*':ti,ab OR 'nonsmall cell lung carcinoma\*':ti,ab OR 'non small cell lung carcinoma\*':ti,ab OR 'nslc':ti,ab

#3,'small cell lung cancer'/exp OR 'oat cell carcinoma\*':ti,ab OR 'oat cell lung cancer\*':ti,ab OR 'sclc':ti,ab OR 'small cell lung cancer\*':ti,ab OR 'small cell lung carcinoma\*':ti,ab

#4,#1 OR #2 OR #3

#5,'second cancer'/exp OR 'second primary':ti,ab OR 'second lung':ti,ab OR 'second cancer':ti,ab OR 'second neoplasm':ti,ab OR 'recurren\*':ti,ab

#6,#4 AND #5

#7,'non small cell lung cancer'/exp OR 'nonsmall cell lung cancer\*':ti,ab OR 'non small cell lung cancer\*':ti,ab OR 'nonsmall cell lung carcinoma\*':ti,ab OR 'non small cell lung carcinoma\*':ti,ab OR 'nslc':ti,ab

#8,'cancer recurrence'/exp OR 'recurren\*':ti,ab

#9,'lung resection'/exp OR 'lobectom\*':ti,ab OR 'pneumonectom\*':ti,ab OR 'resect\*':ti,ab OR 'surgery':ti,ab OR 'surgical':ti,ab OR 'segmentectomy'/exp OR 'segmentectom\*':ti,ab

#10,'small cell lung cancer'/exp OR 'oat cell carcinoma\*':ti,ab OR 'oat cell lung cancer\*':ti,ab OR 'sclc':ti,ab #11,#7 AND #8 AND #9 NOT #10

#12,#6 OR #11

#13,'survival':ti,ab AND ('overall':ti,ab OR 'risk':ti,ab OR 'prognos\*':ti,ab OR 'recurrent':ti,ab)

#14,#12 AND #13

#15,'validat\*' OR 'predict\*':ti OR 'rule\*' OR ('predict\*' AND ('outcome\*' OR 'risk\*' OR 'model\*')) OR (('history' OR 'variable\*' OR 'criteria' OR 'scor\*' OR 'characteristic\*' OR 'finding\*' OR 'factor\*') AND ('predict\*' OR 'model\*' OR 'decision\*' OR 'identif\*' OR 'prognos\*')) OR ('decision\*' AND ('model\*' OR 'clinical\*' OR 'statistical model'/exp)) OR ('prognostic' AND ('history' OR 'variable\*' OR 'criteria' OR 'scor\*' OR 'characteristic\*' OR 'finding\*' OR 'factor\*' OR 'model\*'))

#16,'stratification' OR 'receiver operating characteristic'/exp OR 'discrimination' OR 'discriminate' OR 'c-statistic' OR 'c statistic' OR 'area under the curve' OR 'auc' OR 'calibration' OR 'indices' OR 'algorithm' OR 'multivariable'

#17,#15 OR #16 #18,#14 AND #17

### Appendix 3. Data collection form Datacollectionform

#### General information

#### Methods

|   |
|---|
| Study ID ( <i>surname of first author and year first full report of study was published e.g. Smith 2001</i> ) |
| Notes:  |
| Date form completed ( <i>dd/mm/yyyy</i> )   |
| Name/ID of person extracting data   |
| Study title   |
| Study author contact details  |
| Publication type ( <i>e.g. full report, abstract, letter</i> )  |
| Notes:  |

| Study Characteristics  | Eligibility criteria<br><br><i>(Insert inclusion criteria for each characteristic as defined in the Protocol)</i>  | Eligibility criteria met? |    |         | Location in text or source<br><i>(pg &amp; ¶/fig/table/other)</i> |
|--|--|---------------------------|----|---------|---|
|  |  | Ye s                      | No | Unclear |   |
| <b>Type of study</b>   | RCT, prospective or retrospective longitudinal studies, reporting on the recurrences of the index lung cancer or SPLC or both after surgery for an index lung cancer with more than 20 participants.   |                           |    |         |   |
| <b>Participants</b>  | Population and cohorts of people older than 18 years after complete resection of a primary NSCLC presenting a recurrence of the index lung cancer or a SPLC.   |                           |    |         |   |
| <b>Types of prognostic/ predictive factor(s) or model(s)</b> | The main aim is to assess overall prognosis of recurrence or SPLC.   |                           |    |         |   |
| <b>Types of outcome measures</b>                             | Overall survival for people with a recurrence of the index lung cancer or a SPLC in people with NSCLC after complete resection for NSCLC (time between the diagnosis of recurrence or SPLC to death from any cause or last follow-up).<br><br>Percentage of mortality at 1 year to < 2 years, at 2 years to < 5 years, and at > 5 years of recurrence and SPLC in people with NSCLC after complete resection for NSCLC will be collected or calculated if possible.<br><br>Secondary outcomes:<br><br>Overall survival from surgery of the index lung cancer for people with a recurrence of the index lung cancer |                           |    |         |   |

|                             |  |                |  |  |  |
|-----------------------------|--|----------------|--|--|--|
|                             | or a SPLC (time between the surgery to death from any cause or last follow-up) |                |  |  |  |
| <b>INCLUDE</b>              |  | <b>EXCLUDE</b> |  |  |  |
| <b>Reason for exclusion</b> |  |                |  |  |  |
| <b>Notes:</b>               |  |                |  |  |  |
|                             |  |                |  |  |  |
|                             |  |                |  |  |  |

**Characteristics of included studies Methods**

## References

### Additional references Antakli 1995

Antakli T, Schaefer RF, Rutherford JE, Read RC. Second primary lung cancer. *Annals of Thoracic Surgery* 1995;59(4):863-7.

### Colt 2013

Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5):E437S- E454S.

### Covidence [Computer program]

Veritas Health Innovation Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation, 2020.

### Debray2017

Debray TP, Damen JA, Snell KI, Ensor J, Hooft L, Reitsma JB, et al. A guide to systematic review and meta- analysis of prediction model performance. *BMJ* 2017;356:6460. [DOI: [10.1136/bmj.i6460](https://doi.org/10.1136/bmj.i6460)]

### Debray2018

Debray TP, Moons KG, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: a comparison of new and existing tests. *Research Synthesis Methods* 2018;9(1):41-50.

### Deeks 2011

Deeks JJ, Higgins JP, Altman DG. Chapter 9: analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [training.cochrane.org/handbook/archive/v5.1/](http://training.cochrane.org/handbook/archive/v5.1/).

### Deeks 2022

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.3 (updated February 2022). Cochrane, 2022. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

### Detterbeck 2003

Detterbeck FC, Jones DR, Kernstine KH, Naunheim KS, American College of Physicians. Lung cancer. Special treatment issues. *Chest* 2003;123(1):244S-258S.

### **Ettinger2020**

Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN clinical practice guidelines in oncology (NCCN guidelines). Non-small cell lung cancer. Version 3.2020. Available from [www.nccn.org](http://www.nccn.org).

### **Fink-Neuboeck 2020**

Fink-Neuboeck N, Lindenmann J, Porubsky C, Fediuk M, Anegg U, Maier A, et al. Hazards of recurrence, second primary, or other tumor at ten years after surgery for non-small-cell lung cancer. *Clinical Lung Cancer* 2020;21(4):333-40.

### **Goldstraw 2016**

Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology* 2016;11(1):39-51.

### **Hayden2013**

Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of Internal Medicine* 2013;158(4):280-6.

### **Haynes 2005**

Haynes RB, McKibbin KA, Wilczynski NL, Walter SD, Werre SR, Hedges Team. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ* 2005;330(7501):1179.

### **Howlader 2020**

Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER cancer statistics review, 1975–2017. National Cancer Institute, 2020. Available from [seer.cancer.gov/archive/csr/1975\\_2017](http://seer.cancer.gov/archive/csr/1975_2017).

### **Ingui 2001**

Ingui BJ, Rogers MA. Searching for clinical prediction rules in MEDLINE. *Journal of the American Medical Informatics Association* 2001;8(4):391-7.

### **IntHout 2014**

IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Medical Research Methodology* 2014;14:25.

### **Iorio 2015**

Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.

### **Johnson 1998**

Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. *Journal of the National Cancer Institute* 1998;90(18):1335-45.

### **Leroy 2019**

Leroy T, Monnet E, Guerzider S, Jacoulet P, De Bari B, Falcoz PE, et al. Let us not underestimate the long-term risk of SPLC after surgical resection of NSCLC. *Lung Cancer* 2019;137:23-30.

### **Lo 2014**

Lo C, Mertz D, Loeb M. Newcastle-Ottawa scale: comparing reviewers' to authors' assessments. *BMC Medical Research Methodology* 2014;14:45.

### **Lou 2013**

Lou F, Huang J, Sima CS, Dycoco J, Rusch V, Bach PB. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. *Journal of Thoracic and Cardiovascular Surgery* 2013;145(1):75-82.

### **Martini 1975**

Martini N, Melamed MR. Multiple primary lung cancers. *Journal of Thoracic and Cardiovascular Surgery* 1975;70(4):606-12.

### **Microso39 2018**

Microsoft Corporation. Microsoft Excel [Internet]. 2018. Available from office.microsoft.com/excel.

### **Moons 2014**

Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLOS Medicine* 2014;11(10):e1001744.

### **Postmus 2017**

Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2017;28((supplement 4)):iv1-iv21.

### **Rethlefsen 2021**

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al & PRISMA-S Group. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Systematic Reviews* 2021;10:39. [DOI: [10.1186/s13643-020-01542-z](https://doi.org/10.1186/s13643-020-01542-z)]

### **RevMan Web 2020 [Computer program]**

Review Manager Web (RevMan Web). Version 1.22.0. The Cochrane Collaboration, 2020. Available at revman.cochrane.org.

### **Riley 2019**

Riley RD, Moons KG, Snell KI, Ensor J, Hooft L, Altman DG, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019;364:k4597.

### **Ripley 2014**



Ripley RT, McMillan RR, Sima CS, Hasan SM, Ahmad U, Lou F, et al. Second primary lung cancers: smokers versus nonsmokers after resection of stage I lung adenocarcinoma. *Annals of Thoracic Surgery* 2014;98(3):968-74.

### **Schneider 2020**

Schneider BJ, Ismaila N, Aerts J, Chiles C, Daly ME, Detterbeck FC, et al. Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. *Journal of Clinical Oncology* 2020;38(7):753-66.

### **Schünemann 2020**

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.1 (updated September 2020). Available from [www.training.cochrane.org/handbook/archive/v6.1](http://www.training.cochrane.org/handbook/archive/v6.1).

### **StataCorp 2021 [Computer program]**

Stata Statistical Software: release 17. College Station, TX: StataCorp LLC, 2021.

### **Sterne 2011**

Sterne JA, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [training.cochrane.org/handbook/archive/v5.1/](http://training.cochrane.org/handbook/archive/v5.1/).

### **Sterne 2016**

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.

### **Stirling 2021**

Stirling RG, Chau C, Shareh A, Zalcborg J, Fischer BM. Effect of follow-up surveillance after curative-intent treatment of NSCLC on detection of new and recurrent disease, retreatment, and survival: a systematic review and meta-analysis. *Journal of Thoracic Oncology* 2021;16(5):784-97.

### **Sung 2021**

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 2021;71(3):209-49.

### **Wolff 2019**

Wolff RF, Moons KG, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. *Annals of Internal Medicine* 2019;170(1):51-8.

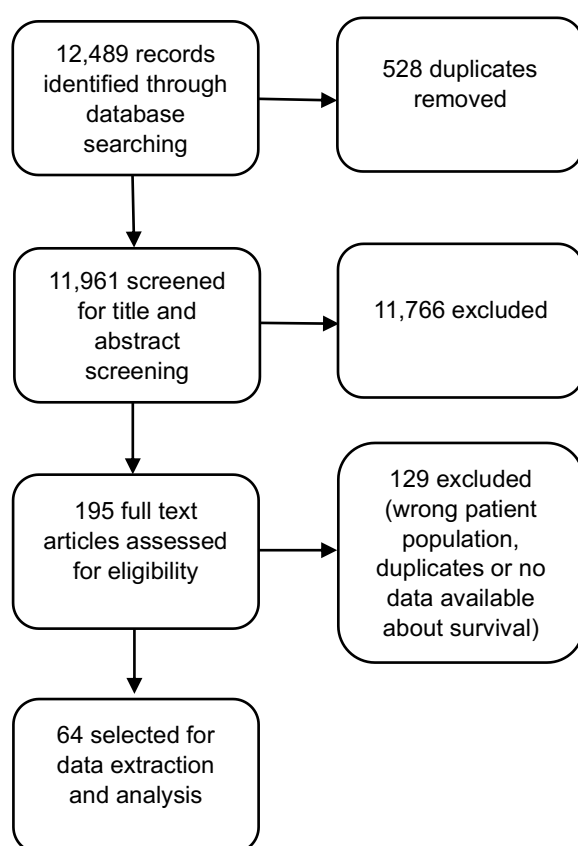
# Preliminary Results

## Description of studies

### Results of the search

The search identified 12,489 studies; 528 duplicates were removed. 11,961 were screened for title and abstract screening, 11,766 were excluded and 195 full text articles were assessed for eligibility. 86 were selected and 64 were included for data extraction after removal of duplicates or lack of data about survival.

Figure 1. Study flow diagram.



### Included studies

Fifty-five studies were conducted in a retrospective design. Five are prospective studies (Takenaka 2022, Rice 2003, Sugimura 2007, Westeel 2022, Zhang 2016), four others are literature review (Bowes 2023, Loukeri 2015, Johnson 1008, Fedor 2013).

Fifty-two were monocentric, one was conducted in two centers (Subotic 2018) and eight were multicenter studies (Takenaka 2022, Fu 2022, Wong 2016, Rice 2003, Taioli 2016, VanMeerBeeck 1996, Matsumura 2016, Wu 2020, Westeel 2022).

Study samples ranged from 23 to 9001 participants.

They were conducted in Europe, North America and Asia, specifically: twenty in Japan, eleven in the USA, nine in South Korea, three in Taiwan, three in China, and one each in Serbia, Austria, Germany, France, the Netherlands, Belgium and Scotland. They were conducted in Europe, North America and Asia, specifically: twenty in Japan, eleven in the USA, nine in South Korea, three in Taiwan, three in China, and one each in Serbia, Austria, Germany, France, the Netherlands, Belgium and Scotland.

## **Participant characteristics**

The review included 39536 older adults, women represent 8,7% (VanRens 2001) to 60% (Lee 2009), median age at first curative treatment range from 61 (Kim 2006) to 71,8 years (Ha 2015), and 60.2 (Subotic 2018) to 74,5 years (Saicho 2013) at recurrence or second primary lung cancer.

## **Outcome measures**

Seven studies compared outcomes concerning recurrences and SPLCs in which only 2 reported hazard ratios of overall survival between recurrences and SPLC. The other 5 only offer a descriptive, non-comparative analysis by presenting median survival and survival rates at 3, 5, 10 years.

For the other 47 studies which only reported the prognosis of an entity (recurrences or SPLC), the outcomes used were the median survival and the survival rates at 1, 2, 3, 5 and 10 years.

## **Definitions used**

In the majority of cases, to distinguish between a new primary lung cancer and a recurrence, the distinction was primarily based on histology if a biopsy had been performed. However, since most studies are retrospective, few biopsies are conducted when a new lesion appears. Therefore, differentiation between those two could be done in several ways.

### **Definitions of SPLC:**

When studies address the prognosis after a second lung cancer, the Martini and Melamed definition was used in the vast majority of cases. Three studies employ the criteria defined by Antakli et al.

One considers a Synchronous Primary Lung Cancer (SPLC) after 4 years of progression-free survival (Ha 2015). In one study (Taioli 2016) which recruitment of SPLC was assessed with SEER database, they used the Multiple Primary dataset (MP dataset). Briefly, SEER takes into account histology, site, laterality, and time since initial diagnosis to identify multiple primary cancers. For the present analysis, only second primary lung cancers included in the MP data set that were pathologically-proven and developed at least six months after the diagnosis of the first cancer were extracted.

A study focusing on operated metachronous NSCLCs considers any new NSCLC appearing after surgery as a second cancer, without considering the tumor site, progression-free survival, or histological type.

### **Definitions of recurrence:**

The diagnosis of a recurrence is often made by elimination when a new lesion appears. If it is considered as a second cancer, it can be an exclusion criterion. The decision can be made using the same criteria mentioned above or sometimes solely based on clinical and radiological data, at the discretion of clinicians.

## **Risk of bias of included studies**

To evaluate the risk of bias (ROB), we used the Quality In Prognosis Studies tool (QUIPS; Hayden 2013).

We rated risk of bias in the following six domains :

- Outcome measurement
- Study confounding
- Statistical analysis and reporting
- Study participation

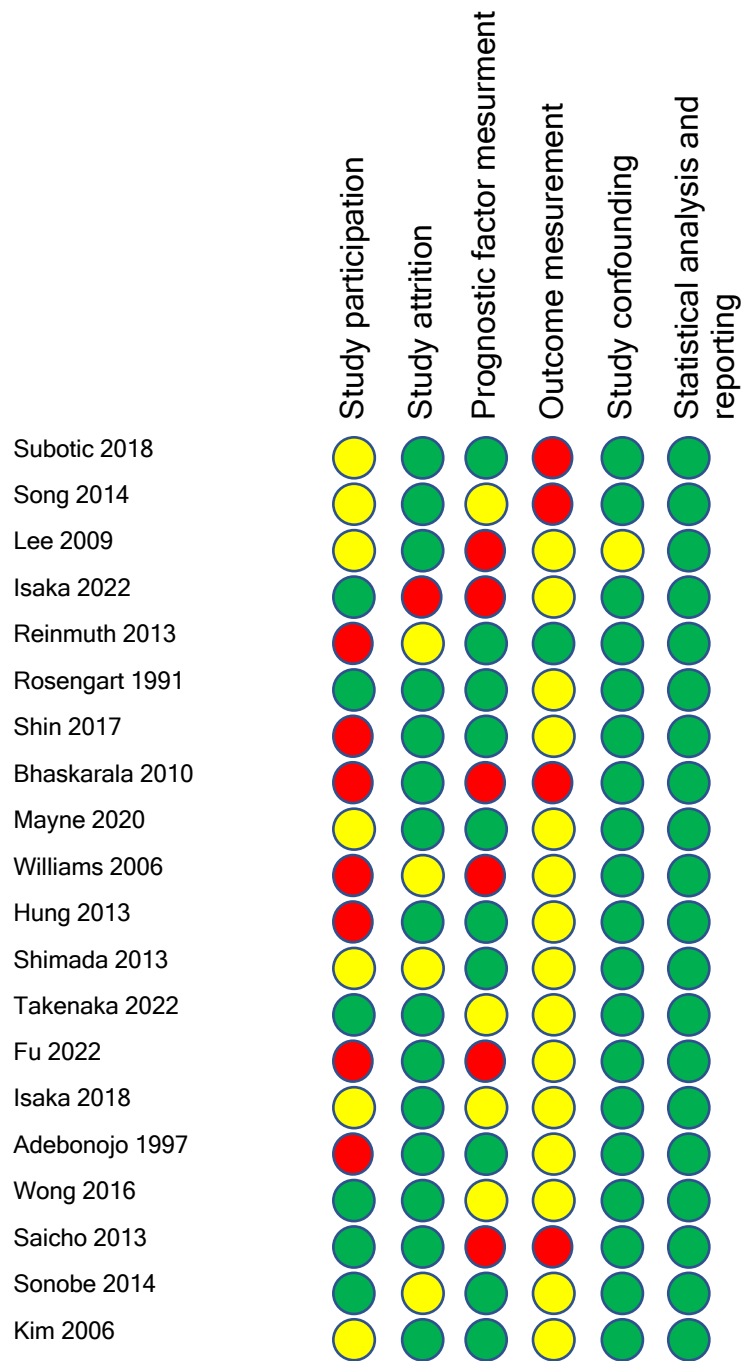
- Prognostic factor measurement
- Study attrition

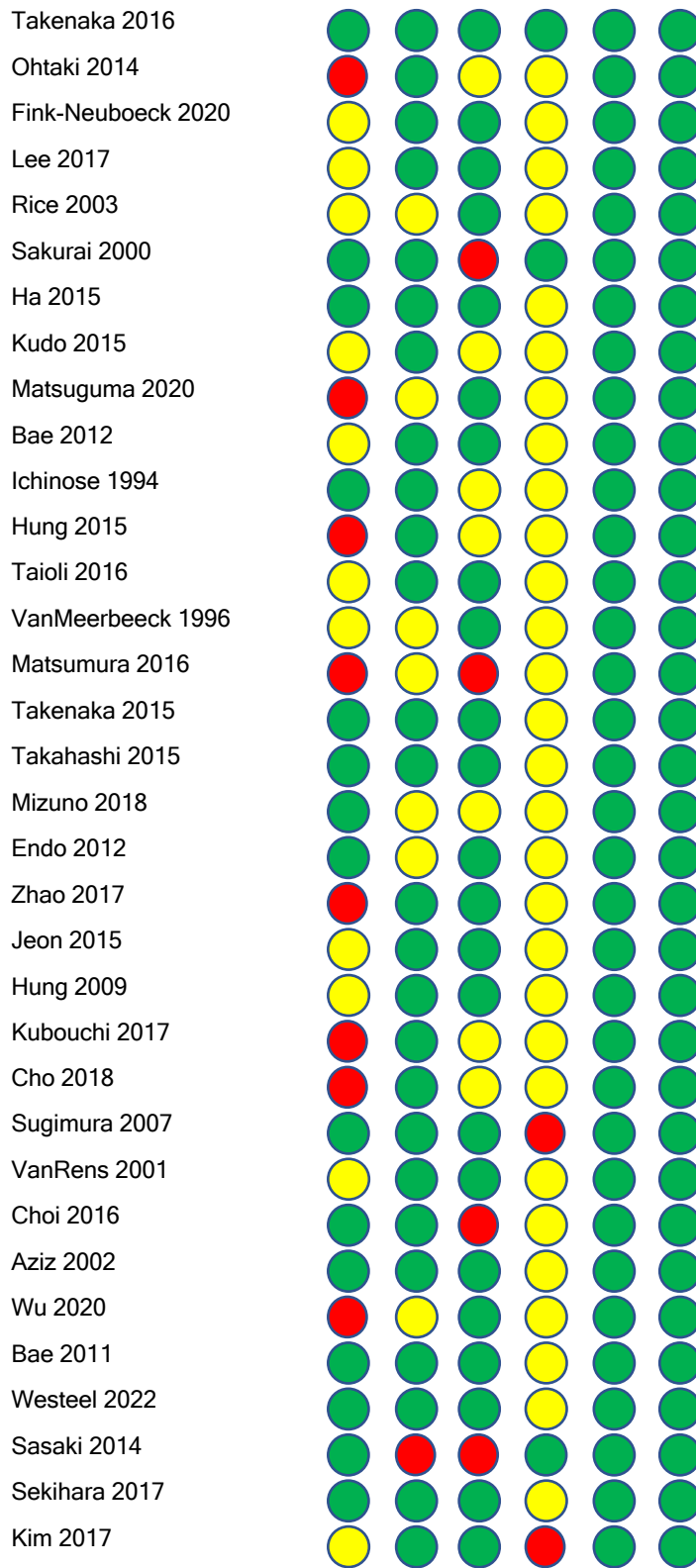
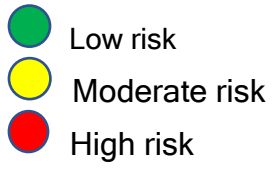
For each domain we assigned an overall rating of 'low risk', 'moderate risk', or 'high risk' based on the signaling item.

Thirty-four studies were at high risk of bias in at least one domain. Two studies were at low risk of bias in every domain (Choi 2022, Takenaka 2016). Twenty-five studies were at high risk of bias in at least one domain. No studies were at low risk of bias in every domain.

Most common issues were around study population (ten studies) because sometimes the initial lung cancer included small cell lung cancers, or a metastatic lung tumor and some patients didn't undergo curative surgery but they received other cancer specific treatments. For study attrition bias (two studies) or bias in definitions (ten studies) of a recurrence or a SPLC were not always detailed, some studies which evaluate outcomes after recurrence didn't explain if they excluded SPLC. It was heterogeneity in the follow-up (because of a majority of retrospective studies). In the majority of studies, death from all causes was considered instead of lung cancer specific related death, and some studies include initial stage IIIIB or/and stage IV and/or small cell lung cancers.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**





## Overall survival between people diagnosed with index lung cancer recurrence or SPLC after complete resection for NSCLC

Seven studies compared outcomes concerning recurrences and SPLCs:

- Two out of 7 studies (Subotic 2018, Kim 2006) demonstrate a survival advantage post-recurrence of the index lung cancer compared to post-second primary lung cancer.

Subotic and coll. evaluated post completion pneumonectomy outcomes, post-recurrence survival (PRS) = 48 months, post-SPLC = 7.7 months.

Kim and coll shown prognosis after surgical resection of a recurrence or a SPLC, median survival after surgery was 78.5 months and 70% at 5 years vs 62,4 months and 69% for SPLCs.

However, the main limitation lies in the fact that they involve very small sample sizes (respectively 24 and 9 recurrences, 4 and 20 second primary lung cancers). These studies only presented recurrences or SPLC accessible to curative, surgical treatment.

- Five of 7 studies (Martini 1999, Mayne 2020, Fink-Neuboeck 2020, Endo 2012, Westeel 2022) show an advantage in terms of survival after a second primary lung cancer. They involve larger sample sizes (respectively for recurrences: n=36, 46, 175, 102, 536 and for second primary cancers: n=26, 45, 25, 13, 67).

- Martini 1999 : survival after surgical resection of recurrences or SPLC : 10 years survival = 7%, and 36% after resection of a SPLC.
- Mayne 2020 : outcomes after lobectomy for stage IA NSCLC : for recurrences, PRS at 5 years = 2,3% vs 57,5% for SPLC.
- Fink-Neuboeck 2020 : survival after surgical resection of recurrences or SPLC : 10 years survival = 10%, and 52% after resection of a SPLC.
- Endo 2012 : Outcomes after curative surgical resection of NSCLC : SPLC : PRS = 63.3 months, recurrences : PRS = 18 months.
- Westeel 2022 : Post curative surgical resection of NSCLC : SPLC : PRS = 2,4 years, survival = 74% at 1 year and 30% at 5 years. For recurrences, PRS = 1,1 years, survival = 55% and 17% at 1 and 5 years respectively.

Nineteen studies assessed prognostic of recurrences after complete surgical resection of initial stage I to IIIA NSCLC (Isaka 2022, Williams 2006, Takenaka 2022, Saicho 2013, Sonobe 2014, Takenaka 2016, Sakurai 2000, Ichinose 2014, Takenaka 2015, Takashi 2015, Mizuno 2018, Sugimura 2007, Sasaki 2014, Sekihara 2017, Wang 2014, Hashimoto 2022, Zhang 2016, Choi 2016, Wong 2016). Post recurrence survival range from 218 days (7,3 months) to 30 months.

Thirteen studies evaluated survival post SPLC after complete surgical resection of initial stage I to IIIA NSCLC. PRS range from 11,8 months to 4,8 years (Lee 2009, Reinmuth 2013, Rosengrat 1991, Bhaskarala 2010, Ha 2015, Aziz 2002, Wu 2020, Bae 2011, Loukeri 2015, Fischer 2021, Johnson 1998, Choi 2022, Mousset 1989, Roeslin 1989).

Table 1 show the results summary of the included studies about recurrence prognosis.

**Table 1: results summary of the included studies about recurrence prognosis**

| ID study | comparison                | N  | Recurrence free interval | Survival : start at the diagnosis of recurrence |                |         |         |         |        |
|----------|---------------------------|--|--------------------------|---|----------------|---------|---------|---------|--------|
|          |                           |  |                          | Median OS                                       | 1 year         | 2 years | 3 years | 5 years |        |
| 4        | Isaka 2022                | recurrences                                      | 358                      | 16,3 months                                     | 27,3 months    |         |         |         | 29,8%  |
| 10       | Williams 2006             | recurrences                                      | 390                      | 11,5 months                                     | 8,1 months     | 37,00%  |         |         |        |
| 13       | Takenaka 2022             | recurrences                                      | 495                      | 14 months                                       | 30 months      |         |         |         | 31,9%  |
| 18       | Saisho 2013               | recurrences                                      | 76                       | 12,7 months                                     | 17,7 months    | 68,30%  | 45,80%  |         |        |
| 19       | Sonobe 2014               | recurrences                                      | 234                      |   | 21 months      |         |         | 33,00%  | 19,90% |
| 21       | Takenaka 2016             | recurrences (overall)                            | 280                      |   | 25 months      |         |         |         | 20,30% |
|          |                           | recurrences (75+years patients)                  | 65                       |   | 17 months      |         |         |         |        |
|          |                           | recurrences (younger patients)                   | 215                      |   | 26 months      |         |         |         |        |
| 26       | Sakurai 2000              | recurrences                                      | 123                      |   | 18,2 months    | 30,80%  | 13,80%  |         | 3,30%  |
| 31       | Ichinose 1994             | recurrences                                      | 215                      |   | 11,5 months    | 49,30%  | 25,60%  |         | 11,40% |
| 36       | Takenaka 2015             | NSCLC recurrences (overall)                      | 280                      | 12 months                                       | 25 months      |         |         |         | 20,30% |
|          |                           | NSCLC recurrences (EGFR Mt + TKI)                |                          |   | 49 months      |         |         |         |        |
|          |                           | recurrences (EGFR wild and unkown + TKI)         |                          |   | 20 months      |         |         |         |        |
|          |                           | recurrences (patients non treated by TKI)        |                          |   | 17 months      |         |         |         |        |
|          |                           | recurrences (EGFR Mt+)                           |                          |   | 44 months      |         |         |         |        |
|          |                           | recurrences (Wt)                                 |                          |   | 21 months      |         |         |         |        |
| 37       | Takahashi 2015            | recurrences                                      | 138                      | 21 months                                       | 22,5 months    |         | 44,60%  |         | 25,90% |
| 38       | Mizuno 2018               | recurrences (overall)                            | 281                      |   | 21,6 months    |         |         | 55,70%  | 34,80% |
|          |                           | recurrences (EGFR Mt+)                           | 135                      |   | 36,1 months    |         |         | 68,00%  | 41,9%  |
|          |                           | recurrences (KRAS Mt+)                           | 33                       |   | 18,2 months    |         |         | 34,10%  | 27,3%  |
|          |                           | recurrences (ALK rearrangements)                 | 13                       |   | 35,8 months    |         |         | 60,60%  | 60,6%  |
|          |                           | recurrences (no mutation)                        | 100                      |   | 16,5 months    |         |         | 44,50%  | 24,3%  |
| 45       | Sugimura 2007             | recurrences                                      | 390                      | 11,5 months                                     | 8,1 months     | 37,00%  | 17,00%  |         |        |
| 52       | Sasaki 2014               | recurrences                                      | 127                      |   | 21,9 months    | 69,80%  | 44,40%  |         |        |
| 53       | Sekihara 2017             | recurrences                                      | 635                      | 24 months                                       | 9 months       |         |         | 23,00%  | 13,00% |
| 62       | Wang 2014 (abstract)      | recurrences                                      | 235                      |   | 13 months      | 54,8%   | 32,6%   |         |        |
| 63       | Hashimoto 2022 (abstract) | recurrences                                      | 443                      | 13,2 months                                     |                | 74,00%  | 55,00%  |         | 16,00% |
|          |                           | EGFR or ALK mutated                              |                          |   |                | 86,00%  | 71,00%  |         | 24,00% |
|          |                           | EGFR or ALK- or unkown                           |                          |   |                | 64,00%  | 40,00%  |         | 10,00% |
| 65       | Zhang 2016 (abstract)     | recurrences                                      | 160                      |   | 20 months      |         |         |         |        |
| 47       | Choi 2016                 | recurrences                                      | 141                      | 14,2 months                                     | 10,8 months    | 50,70%  |         | 28,40%  |        |
| 17       | Wong 2016                 | recurrences : overall                            | 3043                     | 15,9 months                                     | <b>NO DATA</b> |         |         |         |        |
|          |                           | loco-regional recurrences + active treatment     |                          |   | 19,9 months    |         |         |         | 11,40% |
|          |                           | loco-regional recurrences + supportive care only |                          |   | 4,0 months     |         |         |         | 4,80%  |
|          |                           | distant recurrences + active treatment           |                          |   | 11,6 months    |         |         |         | 6,90%  |
|          |                           | distant recurrences + supportive care only       |                          |   | 3,0 months     |         |         |         | 2,00%  |



## DISCUSSION 1<sup>er</sup> AXE THEMATIQUE :

### Caractérisation pronostique des patients après chirurgie, récurrences, SCBP

---

L'objectif premier de cette thèse était d'évaluer le devenir des patients après une chirurgie exérèse d'un cancer broncho-pulmonaire non à petites cellules. La première démarche a été de mieux définir le profil des patients opérés en distinguant 2 trajectoires pronostiques, les patients présentant une récurrence et ceux présentant un second cancer. Dans cette revue systématique pronostique, nous avons identifié 86 études sur 30252 patients. Sur ces 86 études, 6 proposaient une comparaison directe du pronostic entre les récurrences et les seconds cancers broncho-pulmonaires (SCBP). Le pronostic des récurrences ou des SCBP était influencé par le stade au diagnostic. Or les récurrences étaient plus fréquemment diagnostiquées à un stade métastatique, sans accès à un traitement curateur. Les définitions utilisées des SCBP vs récurrences, ne différaient quasi exclusivement que sur le délai à utiliser pour séparer ces 2 entités (2 ans vs 4 ans). Cette différence n'impactait pas sur le pronostic des 2 entités. L'information à retenir de cette analyse est à notre sens l'évolution de l'incidence après chirurgie des SCBP et récurrences. Les récurrences, surviennent essentiellement dans les 2 ans, avec une incidence forte pendant les 6 premiers mois de surveillance puis une baisse rapide. A l'inverse, l'incidence des SCBP est constante, allant de 2% à 5% d'incidence par an (44, 75, 76, 77). Aucun facteur de risque, clinique, biologique, radiologique, n'a permis de mieux caractériser les patients qui feront une récurrence ou un SCBP.

La production de revues systématiques par le groupe *Lung Cancer* de la collaboration Cochrane comporte essentiellement des synthèses d'essais cliniques randomisés d'intervention. La présente revue pronostique sur la survie des récurrences ou seconds cancers pulmonaires a été la première de type pronostique, permettant au groupe de s'approprier la méthodologie Cochrane des revues systématiques pronostiques. Les limites méthodologiques et la plus grande hétérogénéité des études d'observation incluses dans cette revue ainsi que l'insuffisance des méthodes actuelles à contrôler tous les problèmes de leur agrégation méta-analytique constituent le défi principal à l'élaboration de ce type de revues. Il faudra dans un premier temps identifier tous les facteurs expliquant la survie des récurrences et des SCBP. Puis après leur identification, les prendre en compte dans l'analyse finale par une pondération par l'inverse de la probabilité d'être exposé ou l'utilisation d'un score de propension (78-80). Ceci sous-entend une méta-analyse sur données individuelles qui seront très complexes à obtenir.

Cette revue systématique pronostique a permis d'identifier plusieurs évolutions cliniques des patients opérés d'un CBNPC, indépendamment des définitions. La première évolution est celle de patients présentant une récurrence précoce, souvent symptomatique, au stade métastatique et de pronostic péjoratif. Cette récurrence concerne de 16% à 40% des patients selon les stades à la chirurgie du cas index. L'incidence de ces récurrences précoces diminue dans les 2 premières années post-chirurgie, en étant maximale dans les 3 premiers mois de

surveillance (44, 54, 75,76,77). D'autres patients vont présenter une récurrence indolente, jusqu'à 40% des récurrences et seront diagnostiqués plus tardivement à des stades au diagnostic de la récurrence plus précoce. A l'inverse, l'incidence des SCBP semble stable au cours du temps entre 1,5% et 4% selon les séries (55, 56, 57). Ceci même lorsque la surveillance se prolonge au décours des 5 ans souvent rapportés. Il est possible que le pronostic des récurrences indolentes soit comparable à celui des SCBP. Il y a peu d'analyse basée sur des preuves anatomopathologiques dans les études possiblement à l'origine d'un biais de classement entre les 2 entités. Seule une étude utilise des paramètres de biologie moléculaire pour différencier les 2 entités (52).

La survie globale des récurrences et des SCBP est corrélée au stade et donc à la possibilité d'un retraitement curateur au diagnostic de ces 2 entités. Ainsi la récurrence semble de moins bon pronostic car elle est diagnostiquée à des stades plus avancés. Notre revue a révélé des cas de récurrences de la maladie ou de seconds cancers chez 18 à 71 % des patients sous surveillance, avec des taux de récurrence plus élevés pour le stade IIIA (52 à 72 %) que pour ceux des stades I à II (11% à 22%). La plupart des récurrences ont été diagnostiquées dans les deux premières années suivant le traitement. Dès le diagnostic de récurrence, le taux de survie à 5 ans était estimé entre 16 et 23 % (1), avec une survie moyenne d'environ 25 à 30 mois (4, 54). Le taux de survie à 5 ans des patients atteints d'un deuxième cancer du poumon est estimé entre 23 et 77 % (60).

La récurrence est majoritairement diagnostiquée chez des patients symptomatiques (entre 51% à 82%) (58, 62). Celle-ci témoigne de maladies plutôt agressives, se développant à distance du poumon sur des sites symptomatiques (os, cerveau). Dans ces études, les auteurs présentaient des cohortes de patients opérés de cancer index au début des années 2000, avant que le PetScanner ne soit implémenté en routine (81) et recommandé en systématique du bilan d'extension pré-opératoire (82). L'on peut imaginer que le développement du PetScanner permettrait de reclasser ces tumeurs en métastatiques d'emblée et réduire le taux de récurrences métastatiques agressives (83). Les SCBP étaient majoritairement diagnostiqués par un suivi avec scanner, et ce plus souvent qu'en cas de récurrence (67 à 90%) (44, 84, 85). Les études incluses dans cette analyse ont été publiées entre 2000 et 2020. Il est vraisemblable que la précision diagnostique de l'imagerie par scanner ait évolué au cours de cette période, sans toutefois pouvoir affirmer que cela ait impacté la prise en charge et le pronostic de ces patients. Les symptômes ne motivaient en général pas de consultation non programmée par le suivi.

On pourrait discuter un faible rendement à l'imagerie répétée par scanner au décours immédiat de la chirurgie car la récurrence, souvent diagnostiquée par les symptômes, souvent agressive et peu accessible à un traitement curateur ne voit que peu son histoire naturelle modifiée par une détection précoce. Mais les traitements actuels sont plus efficaces en situation même avancée, notamment chez les patients peu symptomatiques et donc il a peut-être un intérêt à un diagnostic avant que la récurrence soit trop évoluée (86). Néanmoins, selon les recommandations actuelles, une proportion de plus en plus importante des opérés aura déjà reçu un traitement par chimio-IO péri-opératoire et si le patient récurrence, cela veut dire que la maladie est non sensible à l'immunothérapie et donc peu d'options thérapeutiques permettront d'espérer inverser la progression tumorale.

A l'inverse, prolonger les scanners thoraciques de surveillance pour poser plus précocement le diagnostic de SCBP, dont l'incidence est constante et persistante au cours du temps, semble se justifier davantage.

Il existait des limites à cette revue. L'utilisation d'analyses issues de données rétrospectives constitue la limite principale. Ces études ont généralement des données manquantes, des biais d'inclusion, d'échantillonnage, d'information et de non-randomisation. Il y avait une certaine hétérogénéité entre les études incluses. Par exemple, la cohorte décrite par Subotic *et al.* (87) s'intéressait à des récidives ou SCBP de stade opérable, alors que la cohorte décrite par Fink-Neuboeck *et al* analysait tous les stades (75). Les études, issues de cohorte ancienne, ne présentaient pas d'étude ancillaire biologique comme celle publiée par Girard *et al.* Pourtant dans l'étude biomarker France, 20% des patients aux stades précoces présentaient des mutations EGFR (88). Une piste d'exploration future serait d'utiliser les techniques actuelles de séquençage de l'ADN tumoral après biopsies des suspicions de récidives ou SCBP pour mieux les caractériser.

Conclusions : Cette revue de la littérature pronostique a permis d'étendre l'expertise du groupe *lung cancer* de la collaboration Cochrane, notamment sur la synthèse d'essais non randomisés, sur la prise en compte de l'hétérogénéité des études observationnelles. Ce travail se poursuit pour aboutir à la présentation complète des résultats et à la publication de la revue sur le site Cochrane.

La définition la plus utilisée et donc celle retenue après analyse de la littérature reste celle de Martini et Melamed (45) notamment par le choix du délai de 2 ans pour définir la période de récurrence. Cette définition est à placer dans le contexte des études analysées, essentiellement publiées avant l'avènement des techniques de biologie moléculaire. La perspective serait de moderniser cette définition par l'utilisation de ces techniques. Une étude ancillaire sur les patients de l'étude IFCT-0302 de surveillance des opérés pourrait être proposée avec analyse ou relecture histo-morphologique des prélèvements faits sur les récidives ou SCBP. Pour mémoire, dans cette étude, les récidives et SCBP étaient classées par l'investigateur utilisant la définition de Martini et Melamed sans relecture indépendante ni obligation de preuve histologique. Enfin cette revue serait à refaire en bornant la date d'inclusion des études à l'avènement des traitements d'immunothérapie soit en situation métastatique pour évaluer l'impact sur un diagnostic précoce des récidives mêmes métastatiques soit en situation péri-opératoire pour en voir les effets sur l'incidence des récidives et/ou SCBP ainsi que leur pronostic.

## *Axe Thérapeutique*

*Revue systématique avec méta-analyse en réseaux des traitements péri-opératoire d'immunothérapie dans le cancer bronchique non à petites cellules, protocole*

### **Résumé**

Jusqu'à récemment, il n'y a eu aucune avancée dans les stratégies thérapeutiques systémiques périopératoires (néoadjuvante ou adjuvante) depuis près d'une décennie chez les patients opérés d'un CBNPC. Parallèlement, l'utilisation généralisée de l'immunothérapie a transformé le traitement du CBNPC métastatique ou non résécable. Ces succès ont motivé le développement de l'immunothérapie dans le CBNPC résécable. L'association d'une chimiothérapie et d'une immunothérapie préopératoire est depuis peu le nouveau standard dans le traitement d'un cancer bronchique non à petites cellules résécable à haut risque de récurrence, dont les tumeurs expriment PD-L1 au seuil  $\geq 1\%$  (8, 9).

Il existe actuellement plusieurs schémas thérapeutiques péri-opératoires en développement en termes d'immunothérapie, d'association à d'autres immunothérapies, de chimiothérapie et en termes de timing d'administration (néoadjuvant, adjuvant).

Le groupe *Lung cancer* de la collaboration Cochrane souhaitait développer son expertise dans la méthodologie des revues systématiques avec méta-analyse en réseaux. Il a donc été proposé de réaliser ce type de méthodologie appliquée à la thématique des traitements péri-opératoires d'immunothérapie.

### **Objectifs**

L'objectif de cette revue systématique est de réaliser une méta-analyse en réseaux afin de comparer les effets des stratégies périopératoires d'administration d'immunothérapie sur la survie globale chez les patients opérables atteints d'un CBNPC résécable.

### **Modèle de recherche**

Nous incluons des essais contrôlés randomisés (ECR) en groupes parallèles. Nous excluons les essais croisés et en grappes, car ces modèles d'étude ne sont pas pertinents dans ce contexte. Nous excluons les études à un seul bras. Nous incluons les ECR quel que soit leur statut de publication ou leur langue de publication. Nous

inclurons l'immunothérapie périopératoire (néo-adjuvante, adjuvante, les deux), avec ou sans chimiothérapie, quel que soit le protocole de chimiothérapie.

Nous rechercherons des études pertinentes dans les bases de données suivantes :

- MEDLINE (accessible via Pubmed) de 2018 à aujourd'hui
- Embase de 2014 à aujourd'hui
- Registre Cochrane des essais contrôlés (CENTRAL) de 2014 à aujourd'hui
- et le Web de la Science.

Nous commencerons intentionnellement à partir de 2018 car c'est la date à laquelle le premier essai sur l'immunothérapie a été publié (Forde PM. NEJM, 2018). Nous n'appliquerons aucune rétractation aux stratégies de recherche. Nous effectuerons les recherches électroniques selon les recommandations du Cochrane Intervention Group (Higgins JPT. Cochrane, 2022).

Conclusion : Nous espérons pouvoir proposer une analyse hiérarchique des stratégies thérapeutiques périopératoires d'immunothérapie avec analyse de leur profil de tolérance. Cette revue sera proposée sur un mode « living » avec une actualisation bi-annuelle jusqu'à ce que les auteurs jugent la réponse comme acquise.

# Peri-operative immunotherapy for resectable non-small cell lung cancer, a living mapping of research and a living systematic review

## Table of contents

### Abstract

#### Background

- Description of the condition
- Description of the intervention
- How the intervention might work
- Why it is important to do this review

#### Objectives

#### Methods

- Criteria for considering studies for this review
- Search methods for identification of studies
- Data collection and analysis

#### Acknowledgements

#### Contributions of authors

#### Declarations of interest

#### Sources of support

- Internal sources
- External sources

#### Appendices

- Appendix 1. The Eighth Edition of TNM Staging of Lung Cancer
- Appendix 2. MEDLINE search strategy accessed via PubMed
- Appendix 3. EMBASE search strategy accessed via Elsevier
- Appendix 4. CENTRAL search strategy

#### References

- Additional references

Editors: Cochrane Lung Cancer Group

Contact Person: Corynne Marchal (lungcancergroup@chu-besancon.fr)

Department of Thoracic Oncology, University Hospital of Besançon, Besançon, France

Corynne Marchal [1] Guillaume Eberst [2] François Calais [3] Reem Malouf [4] Virginie Westeel [5] Anna Chaimani [6]

[1] Department of Thoracic Oncology, University Hospital of Besançon, Besançon, France

[2] Besançon, France

[3] Bibliothèque universitaire de Santé, Université de Franche-Comté, Besançon, France

[4] National Perinatal Epidemiology Unit (NPEU), University of Oxford, Oxford, UK

[5] Thoracic Oncology, University Hospital of Besançon, Besançon, France

[6] Research Center in Epidemiology and Statistics Sorbonne Paris Cité (CRESS-UMR1153), METHODS Team, Paris, France

#### Citation

Marchal C, Eberst G, Calais F, Malouf R, Westeel V, Chaimani A. Peri-operative immunotherapy for resectable non-small cell lung cancer, a living mapping of research and a living systematic review (Protocol).

Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: CD015819. DOI:

10.1002/14651858.CD015819.

#### Dates

Revision published: Issue TBD, TBD (TBD)  
Version published (citation changed): Issue TBD, TBD (TBD)  
Review first published: N/A  
Protocol first published: Issue TBD, TBD

---

## Abstract

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

#### First objective

To perform indirect comparisons in order to generate a clinically meaningful hierarchy of perioperative strategies of immunotherapy administration on overall survival in operable people with resectable non small cell lung cancer.

#### Second objective

To compare the effectiveness and safety of different immunotherapy agents that are administrated peri-operation among people with inresectable non small cell lung cancer via a network meta-analysis.

#### Third objective

To maintain the currency of evidence by taking a living systematic review approach.

---

## Background

### Description of the condition

Lung cancer remains the leading cause of cancer-related death worldwide, accounting for 18% of the total cancer deaths in 2020 ([GLOBOCAN 2020](#)). Lung cancers represent a group of heterogeneous entities both in terms of histology and molecular profile ([Herbst 2008](#)). Histologically, they are categorized into two types: non-small cell lung cancer (NSCLC) and small cell lung carcinoma (SCLC). NSCLCs are typically subdivided into adenocarcinoma, squamous cell carcinoma (SqCC), and large-cell carcinoma.

Non-small cell lung cancer is the most common type of lung cancer, accounting for 80 to 85% of all lung cancers ([Herbst 2008](#)). Both NSCLC and SCLC have very low survival rates. However, the outcomes differ according to stage at diagnosis, with a 24-month survival rate of 87 to 97% for stage I NSCLC and of 10 to 23% for stage IV. Stage I to IIIA NSCLC (classified as early stages in the TNM classification, eighth edition - see [Appendix 1](#)) accounts for 40% to 45% of all cases of lung cancer ([Goldstraw 2016](#)). This number is likely to grow with increased adoption of low-dose computed tomography screening leading to increased identification of early-stage NSCLC.

Surgery with or without perioperative chemotherapy (around the time of surgery) remains the treatment cornerstone of early stage lung cancer ([Ettinger 2022](#)).

For stage I to IIIA NSCLC, despite surgical resection, relapses and mortality are common. The five-year survival rate of people with lung cancer treated with curative intent ranges from 36% to 92% according to stage ([Goldstraw 2016](#)).

### Description of the intervention

The aim of perioperative chemotherapy is to reduce mortality by reducing the risk of recurrence. For decades, platinum-based adjuvant chemotherapy was the standard of care for patients with resectable stage II-IIIa disease, although the survival benefits were modest, with an increase in overall survival (OS) of approximately 5% ([Lim 2009](#)). Efforts to improve outcomes by adding antiangiogenics (e.g. bevacizumab) ([Wakelee 2017](#)) or adjuvant postoperative radiation therapy failed to confer a survival benefit ([Le Pechoux 2022](#)), underscoring the ongoing need for better outcomes in this setting.

Recently, immunotherapy has been incorporated into neo-adjuvant and adjuvant regimens on the basis of data demonstrating improvement in event-free survival (EFS) and disease free survival (DFS), respectively, for early-stage, resectable NSCLC without a driver mutation. IMpower-010 was the first phase III trial that demonstrated a DFS benefit with immunotherapy, following complete surgical resection, adjuvant chemotherapy, and then up to a year of adjuvant atezolizumab in patients with PD-L1-positive, stage II-IIIa disease ([Felip 2021](#)), leading the FDA to approve atezolizumab for this population. Of note, although the study demonstrated DFS benefit in patients with PD-L1-positive stage II-IIIa (stratified hazard ratio [HR], 0.66; 95% CI, 0.50 to 0.88), a post hoc analysis

indicated that the benefit was driven overwhelmingly by patients with tumor PD-L1 expression  $\geq 50\%$ . The hazard ratio was 0.87 and 0.43 for patients with PD-L1 1%-49% and  $\geq 50\%$ , respectively. Given the lack of benefit for PD-L1 of 1%-49%, the European Commission has approved atezolizumab only for patients with PD-L1  $\geq 50\%$ .

KEYNOTE-091 (PEARLS) trial also demonstrated improvement in DFS for patients with stage IB ( $\geq 4$  cm) to IIIA NSCLC who received up to a year of adjuvant pembrolizumab, and now has received FDA approval in this setting irrespective of PD-L1 expression. Interestingly, there was no association of greater or lesser efficacy in the KEYNOTE-091 trial by PD-L1 expression: The HR for DFS with PD-L1  $\geq 50\%$  was 0.82 (0.57-1.18) versus 0.76 (0.63- 0.91) in the overall trial population (O'Brien 2022).

In the neoadjuvant setting, the CheckMate-816 trial demonstrated an improvement in EFS with nivolumab plus chemotherapy for three cycles when compared with chemotherapy alone for patients with resectable stage IB to IIIA EGFR and ALK wild-type NSCLC (Forde 2022) and also has received FDA and European Commission approval. Similar to the findings in IMpower010, the HR for EFS in CheckMate-816 was 0.85 (0.54-1.32), 0.58 (0.30-1.12), and 0.24 (0.10-0.61) for patients with PD-L1 expression  $<1\%$ , 1%-49%, and  $\geq 50\%$ , respectively, although the differences here were not enough to lead to changes in regulatory approval on the basis of tumor PD-L1 expression. Notably, improved EFS with chemotherapy/nivolumab was highly associated with the achievement of a pathologic complete response (pCR) (HR, 0.13 vs no pCR).

AGEAN was a phase III, study assessing the activity of durvalumab and chemotherapy administered prior to surgery compared with placebo and chemotherapy administered in a neoadjuvant and adjuvant setting for patients with resectable early-stage (IIA-III B) NSCLC. After a median follow-up of 11.7 months, median EFS was not reached in the durvalumab-based regimen arm versus 25.9 months in the chemotherapy-alone arm. People in the durvalumab-based regimen arm showed a 32% reduction in the risk of disease progression precluding definitive surgery, disease recurrence, or death compared with those in the chemotherapy-alone arm (Heymach 2023).

## How the intervention might work

Most people with advanced NSCLC will not be cured, so cancer prevention and effective treatment of early-stage disease are the cornerstones of reducing mortality. Mounting evidence suggests that the incorporation of neoadjuvant immunotherapy may lead to:

- tumour regression and long-lasting anti-tumour immune responses in people with resectable NSCLC ,
- early eradication of micrometastases,
- a higher treatment initiation rate as well as higher people adherence,
- the possibility of surgical downstaging,
- a potential decrease in need for more extensive procedures (such as pneumonectomy or open thoracotomy),
- and the ability to assess pathologic responses, which may serve as a predictor of survival and inform decisions about future treatment immunotherapy (Conroy 2023).

Adjuvant immunotherapy can allow fastest time to surgery, eliminate undetectable residual "micrometastatic" tumour cells that may exist in lymph nodes, blood vessels, or lymphatic vessels, delaying or reducing postoperative recurrence and metastasis, prolonging PFS and OS, and improving people quality of life (Peng 2023).

## Why it is important to do this review

Until recently, there were no guidelines modifications in perioperative systemic therapy (neoadjuvant or adjuvant) but the widespread use of immunotherapy has transformed the treatment of metastatic or unresectable NSCLC. These successes have motivated research into using these treatment modalities for curable early-stage NSCLC.

There are currently several perioperative treatment regimens available in terms of immunotherapy: association with other immunotherapy agents, with chemotherapy, timing of administration (neoadjuvant, adjuvant). The strategies being tested are also different. Therefore, in the absence of a large number of randomised controlled trials comparing all perioperative treatment regimens, uncertainty remains as to the best option for operable people with resectable NSCLC. Specifically, many questions remain unanswered in the use of immunotherapy in the perioperative setting:

- Which people could benefit most from immunotherapy? Evidence regarding the therapeutic benefit of immunotherapy as perioperative treatments for early-stage NSCLC (stage I-II) is limited. Biomarkers, such as PD-1/PD-L1, T cell infiltration, tumor mutation burden (TMB), and others, are helpful for the selection of non-operable people who benefit most from immunotherapy (Herath 2022). However, studies that examined immunotherapy as perioperative treatments usually do not use biomarkers for participants selection. It has not yet been determined whether it is necessary to consider PD-1/PD-L1 expression to apply immunotherapy as perioperative treatments. Alternative biomarkers, such as imaging data, liquid biopsies, and even some clinical characteristics, could have the potential to predict the efficacy of neoadjuvant immunotherapy. A gap remains in the knowledge of the effects of perioperative



immunotherapy in the elderly. We know that perioperative chemotherapy is not effective above the age of 75 (Früh 2008), is this the case for immunotherapy?

- What is the optimal duration? Various treatment duration has been proposed with no real comparison to justify which one is more effective.
- What is the best timing and sequence of immunotherapy with other systemic therapies? The timing between adjuvant, neo-adjuvant or both prescriptions is not compared, making it impossible to recommend any strategy.

Stakeholders (patients, practitioners) have a constant need for relevant, accessible, up-to-date and reliable syntheses of high-quality evidences to inform their decisions.

Hundreds of randomised controlled trials (RCTs) have been launched on the use of immunotherapy in the perioperative setting and their results will be published gradually over the coming years. However, the vast majority of those trials are using placebo as a comparator because the pharmaceutical industry who is the main sponsors of large RCTs does not want to take the risk of a comparison that would not be in favour of their product and block the approval process.

### **Living systematic review approach**

After the first publication of this review, we are planning to maintain it as a living systematic review (LSR) with a yearly update. This means that we will search the literature continually and will incorporate any new evidence on a regular basis (Elliott 2017). A living systematic review approach is appropriate for this review because the topic is important for clinical decision-making; current evidence is unlikely to provide certainty; and a very active research programme is ongoing. Indeed, the review authors are aware of several ongoing trials and believe that incorporating results from these trials in a timely manner is crucial, as these findings may have an impact on review conclusions.

## **Objectives**

### **First objective**

To perform indirect comparisons in order to generate a clinically meaningful hierarchy of perioperative strategies of immunotherapy administration on overall survival in operable people with resectable non small cell lung cancer.

### **Second objective**

To compare the effectiveness and safety of different immunotherapy agents that are administrated peri-operation among people with irresectable non small cell lung cancer via a network meta-analysis.

### **Third objective**

To maintain the currency of evidence by taking a living systematic review approach.

## **Methods**

### **Criteria for considering studies for this review**

#### **Types of studies**

We will include parallel-group randomised controlled trials (RCTs). We will exclude cross-over and cluster trials, as these study designs are not relevant in this setting. We will exclude single-armed studies.

We will include RCTs regardless of their publication status or language of publication.

#### **Types of participants**

People aged 18 years or older, with pathologically confirmed NSCLC (any histology) of stage I to IIIA according to the AJCC staging system (8th edition - see Appendix 1) with an indication of resection or operated. People must not have any contraindication to immunotherapy and/or standard of care (chemotherapy)

#### **Types of interventions**

We will include perioperative immunotherapy (neo-adjuvant, adjuvant, both), with or without chemotherapy, whatever the chemotherapy protocol.

Chemotherapy regimens are usually composed of doublet platine, with docetaxel, etoposide, paclitaxel, vinorelbine neoadjuvant, adjuvant, both, with no limit on the number of cycles.

For immunotherapy, we will consider the following interventions:

- Neoadjuvant immunotherapy as monotherapy
- Neoadjuvant immunotherapy in combination with chemotherapy

- Adjuvant immunotherapy as monotherapy
- Adjuvant immunotherapy in combination with chemotherapy
- Neoadjuvant and adjuvant immunotherapy as monotherapy
- Neoadjuvant and adjuvant immunotherapy in combination with chemotherapy

At any time points, at any dose and at any frequency.

Currently, the main immunotherapy drugs are atezolizumab, cemiplimab, durvalumab, nivolumab, pembrolizumab, sintilimab or other PD-1, PD-L1 inhibitors.

### **Types of outcome measures**

We will estimate the hierarchy of evidence for the following outcome:

#### **Primary outcomes**

- Overall survival (OS) from the randomisation or allocation to death or last follow up, at any time points.

#### **Secondary outcomes**

- Disease free survival (DFS) from the randomisation or allocation to the first sign or symptom of cancer or death, at any time points.
- Relapse-free survival (RFS) from the surgery to the first sign or symptom of cancer or death, at any time points.
- Time to recurrence (TTR) from the surgery to disease recurrence, where deaths without recurrence were censored at the time of death, at any time points.
- Cancer specific survival (CSS) from the randomisation or allocation to the date of death from the disease, at any time points.
- Safety, toxicity profile, assessed according to NCI-CTCAE guidelines.
- Patient reported outcomes include instruments or tools that measure functional status, health-related quality of life, symptom and symptom burden, personal experience of care, and health-related behaviours such as anxiety and depression

### **Search methods for identification of studies**

We will perform a comprehensive search with no restrictions on language of publication or publication status.

#### **Electronic searches**

We will search for relevant studies in the following databases:

- MEDLINE (accessed via Pubmed) from 2018 to present
- Embase via Elsevier from 2018 to present
- Cochrane Central Register of Controlled Trials (CENTRAL) from 2018 to present
- and Web of Science.

We will intentionally start from 2018 onwards as it is the date the first trial on immunotherapy was published (Forde 2018). We will perform the electronic searches according to the recommendations of the Cochrane Intervention Group (Higgins 2022). The search strategy will combine relevant medical subject headings (MeSH) and keywords. The search strategies for MEDLINE via PubMed, Embase and CENTRAL are shown in Appendix 2, Appendix 3 and Appendix 4, respectively, and was designed with the help of the Lung Cancer Group Information Specialist.

#### **Living systematic review approach**

As this is a living systematic review, we will search the following databases twice a year, using auto-alerts when possible:

- Cochrane Lung Cancer Group Trials Register.
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library.
- MEDLINE, accessed via PubMed.
- Embase.

For other electronic databases and electronic sources (including trials registries), we will also set up auto-alerts (when possible) to deliver biannually search yield by email. When auto-alerts are not possible, we will manually search these electronic databases and electronic sources each 6 months.

We will review search methods and strategies yearly, to ensure that they reflect any terminology changes in the topic area or in the databases.

- Adjuvant immunotherapy as monotherapy
- Adjuvant immunotherapy in combination with chemotherapy
- Neoadjuvant and adjuvant immunotherapy as monotherapy
- Neoadjuvant and adjuvant immunotherapy in combination with chemotherapy

At any time points, at any dose and at any frequency.

Currently, the main immunotherapy drugs are atezolizumab, cemiplimab, durvalumab, nivolumab, pembrolizumab, sintilimab or other PD-1, PD-L1 inhibitors.

### **Types of outcome measures**

We will estimate the hierarchy of evidence for the following outcome:

#### **Primary outcomes**

- Overall survival (OS) from the randomisation or allocation to death or last follow up, at any time points.

#### **Secondary outcomes**

- Disease free survival (DFS) from the randomisation or allocation to the first sign or symptom of cancer or death, at any time points.
- Relapse-free survival (RFS) from the surgery to the first sign or symptom of cancer or death, at any time points.
- Time to recurrence (TTR) from the surgery to disease recurrence, where deaths without recurrence were censored at the time of death, at any time points.
- Cancer specific survival (CSS) from the randomisation or allocation to the date of death from the disease, at any time points.
- Safety, toxicity profile, assessed according to NCI-CTCAE guidelines.
- Patient reported outcomes include instruments or tools that measure functional status, health-related quality of life, symptom and symptom burden, personal experience of care, and health-related behaviours such as anxiety and depression

### **Search methods for identification of studies**

We will perform a comprehensive search with no restrictions on language of publication or publication status.

#### **Electronic searches**

We will search for relevant studies in the following databases:

- MEDLINE (accessed via Pubmed) from 2018 to present
- Embase via Elsevier from 2018 to present
- Cochrane Central Register of Controlled Trials (CENTRAL) from 2018 to present
- and Web of Science.

We will intentionally start from 2018 onwards as it is the date the first trial on immunotherapy was published (Forde 2018). We will perform the electronic searches according to the recommendations of the Cochrane Intervention Group (Higgins 2022). The search strategy will combine relevant medical subject headings (MeSH) and keywords. The search strategies for MEDLINE via PubMed, Embase and CENTRAL are shown in Appendix 2, Appendix 3 and Appendix 4, respectively, and was designed with the help of the Lung Cancer Group Information Specialist.

#### **Living systematic review approach**

As this is a living systematic review, we will search the following databases twice a year, using auto-alerts when possible:

- Cochrane Lung Cancer Group Trials Register.
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library.
- MEDLINE, accessed via PubMed.
- Embase.

For other electronic databases and electronic sources (including trials registries), we will also set up auto-alerts (when possible) to deliver biannually search yield by email. When auto-alerts are not possible, we will manually search these electronic databases and electronic sources each 6 months.

We will review search methods and strategies yearly, to ensure that they reflect any terminology changes in the topic area or in the databases.

## Living systematic review considerations

In developing this living systematic review, we will note when these key conferences are to be held and will search conference proceedings when published:

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- American Association for Cancer Research (AACR)
- World Conference on Lung Cancer (WCLC)

We will contact corresponding authors of ongoing studies as we identify them and will ask them to advise when study results are available, or to share early or unpublished data. We will contact the corresponding authors of any newly included studies for advice regarding other relevant studies.

We will manually search the reference lists of all newly included studies.

## Data collection and analysis

### Selection of studies

We will use [Covidence \(Covidence\)](#) to identify and remove potential duplicate records. Two review authors (CM, GE) will blindly review titles, abstracts or both to determine which studies should be assessed further using the same software. The same two review authors will investigate independently all potentially relevant records as full text, mapped records to studies, and will classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies following the criteria for each provided in chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019). We will resolve any discrepancies through consensus or recourse to a third review author (VW).

#### Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximise the yield of information by mapping all publications to unique studies and collating all available data. We will use the most complete data set aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

### Data extraction and management

We will develop a dedicated data extraction excel sheet form ([Microsoft Excel](#)) that we pilot-tested ahead of time. For studies that fulfil our inclusion criteria, two review authors (CM, GE) will independently extract the following information:

- Study design
- Study dates
- Study settings and country
- Participant inclusion and exclusion criteria (e.g. age, TNM stage)
- Participant details, baseline demographics (e.g. age, sex, smoking status, performance status)
- Numbers of participants by study and by study arm
- Details of relevant experimental intervention (type of immunotherapy, chronology and duration of administration) and comparator intervention (e.g. type of chemotherapy, chronology and duration of administration)
- Definitions of relevant outcomes and timing of outcome measurement (e.g. in months), as well as relevant subgroups (e.g. based on age, TNM stage, sex, smoking status, Performance status)
- Study funding sources
- Declarations of interest by primary investigators

In case of disagreement we will consult a third author (VW). The same review authors will also extract all data relevant to the review outcomes. For dichotomous outcomes, we will obtain numbers of events and totals for populations as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will obtain the means and standard deviations or data necessary to calculate this information.

In tables, we will provide information about potentially relevant studies, including the trial identifiers.

We will conduct data management and analysis according to the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

We will contact the authors of included studies to obtain key missing data as needed.

### Assessment of risk of bias in included studies

Two review authors (GE and RM) will independently assess the risk of bias of each included study using the Cochrane 'Risk of bias' tool (RoB1) as per Chapter 8 of the *Cochrane Handbook for Systematic Reviews of*

*Interventions* (Higgins 2011).

We will consider the following domains:

Selection bias: random sequence generation.

Selection bias: allocation concealment.

Performance bias: blinding of participants and personnel.

Detection bias: blinding of outcome assessment.

Attrition bias: incomplete outcome data for outcomes related to efficacy and safety.

Reporting bias: selective reporting of outcomes.

Other bias, such as inclusion of participants discordant to prespecified number of participants needed for calculation, unplanned interim analyses, and unbalanced baseline characteristics across study arms.

We will rate each domain of the tool as having 'low', 'high', or 'unclear' risk of bias at study level and for each outcome we will support the rating of each domain with a brief description. We will summarise risk of bias for each outcome within a study by considering all domains relevant to the outcome (i.e. both study-level entries, such as allocation sequence concealment, and outcome-specific entries, such as blinding).

We will resolve disagreements by consensus or by consultation with a third review author (CM).

We will identify the impact of bias on the results by performing a sensitivity analysis.

## Measures of treatment effect

### Characteristics of included studies and information flow in the network

We will generate descriptive statistics for the trial, and study population characteristics across all eligible trials, describing the types of comparisons and some important variables, either clinical or methodological (such as year of publication, age, severity of illness, sponsorship and clinical setting). The available evidence will be presented in the network diagram. The size of the nodes will reflect the amount of evidence accumulated for each treatment (total number of patients), the breadth of each edge will be proportional to the inverse of the variance of the summary effect of each direct treatment comparison, and the colour of each edge will represent risk of bias (refer Risk of bias assessment section). To understand which are the most influential comparisons in the network and how direct and indirect evidence influences the final summary data, we will use the contribution matrix that describes the percentage contribution of each direct meta-analysis to the entire body of evidence (Chaimani A 2013).

### Relative treatment effects

For overall survival outcome we will use the hazard ratio (HR) and 95%CI to combine data.

For dichotomous outcome such as adverse events, we will use a risk ratio (RR) with a 95%CI as a measure of an estimated effect.

For continuous data such as health-related quality of life measures we will use the mean difference (MD) to combine data across studies using the same measures and the standardised mean difference (SMD) when studies used different scales to measure the same outcome.

We will apply a random effect model to combine data as we anticipate methodological and clinical heterogeneity across the included studies.

We will summarise results in forest plots in both pairwise comparison and network reanalysis for the different agents of immunotherapy.

We will estimate the pairwise relative treatment effects of the competing interventions using time-to-event data for survival outcomes and relative effect sizes (mean differences or risk ratio) for safety outcomes. We will present results from network meta-analysis as summary relative effect sizes (SMD or RR) for each possible pair of treatments. We will perform analyses according to recommendations provided in Chapter 9 of the Cochrane Handbook (McKenzie 2022), and use Cochrane's statistical software, RevMan Web (RevMan Web 2023), for analysis. When possible, we will perform these standard pair-wise meta-analyses using a random-effects model because we will anticipate methodological and clinical heterogeneity across studies. We will calculate corresponding 95% CIs for all analyses, and will graphically present the results using forest plots. When trials are clinically too heterogeneous to be combined, we will perform only subgroup analyses without calculating an overall estimate. In order to avoid duplication with the supporting reviews of this network meta-analysis, we will describe only the pairwise comparisons for the data that could not be included in the network due to concerns about transitivity.

### Relative treatment ranking

We will estimate the ranking probabilities that all immunotherapy treatments would be at each possible rank for each intervention. We used the surface under the cumulative ranking curve (SUCRA) to rank the effectiveness and safety of each treatment (Salanti 2011). SUCRA accounts for both effect size magnitude and uncertainty around the underlying effect size. When the SUCRA value is at 100%, this indicates the treatment is the best and most effective one and the value of 0% indicates the treatment to be the least effective in the network. We will

display results (network plot, SUCRA plots and league table) using the 'network graph package' in Stata (Stata 2023; Chaimani 2017).

### Unit of analysis issues

The participant will be the primary unit of analysis.

### Studies with multiple treatment groups

For studies with multiple comparison groups that compare two or more intervention groups versus the same control group, we will first attempt to combine groups to create a single pair-wise comparison. When this is not possible we will include the multi groups trials as a series of two groups comparison. We will calculate within-study correlation as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

### Dealing with missing data

#### *Dealing with missing data*

We will try to obtain any missing data relevant to the risk of bias assessment and the review outcomes from study authors. We will try and perform intention-to-treat analyses if data will be available. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals) and critically appraise issues of missing data. If studies have used single imputation techniques (such as last observation carried forward, mean imputation etc.) we will consider the study to be at high risk of bias. In such cases, we will conduct a sensitivity analysis using a pattern mixture model (White 2008; Mavridis 2015) to evaluate how robust results are and departures from missing at random assumption.

### Assessment of heterogeneity

#### **Assessment of clinical and methodological heterogeneity within treatment comparisons**

To evaluate the presence of clinical heterogeneity we will generate descriptive statistics for trial and study population characteristics (potential effect modifiers such as dose, frequency and duration of treatment) across all eligible trials that compare each pair of interventions. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics. We will assess the impact of these relevant modifiers by performing subgroups analysis and a sensitivity analysis.

#### **Assessment of the transitivity assumption**

Lack of transitivity in a network can threaten the validity of the consistency assumption, that is, the statistical agreement between direct and indirect evidence (Caldwell 2005; Lu 2004). Before conducting a network meta-analysis, we will assess the transitivity assumption. Network meta-analysis rests on the assumption of transitivity, that is, that effect modifiers have a comparable distribution across treatment comparisons in a network (Cipriani 2013; Jansen 2013). To assess the plausibility of this assumption, we will assess the similarity of inclusion and exclusion criteria of all studies, including participants, treatments, and outcomes, to evaluate whether they impacted treatment effects. In this context we expect that the transitivity assumption will hold assuming that:

The common treatment used to compare different strategies indirectly is similar when it appears in different trials (chemotherapy product in standard of care is administered in a similar way).

All pair-wise comparisons do not differ with respect to the distribution of effect modifiers (the design and study characteristics of neoadjuvant versus chemotherapy alone trials are similar to adjuvant immunotherapy versus chemotherapy alone).

#### **Assessment of statistical heterogeneity**

We will explore whether treatment effects for our primary outcomes are robust in subgroup analyses and network meta-regression using the following characteristics: age, TNM stage, sex, smoking status, and *Performance status*. We will analyse each characteristic separately and finally include in a meta-regression those characteristics that were found to be statistically significant in the univariate analyses.

#### *Assumptions when estimating the heterogeneity*

In standard pairwise meta-analyses we will estimate different heterogeneity variances for each pairwise comparison within a random effects model framework.

#### *Measures and tests for heterogeneity*

We will assess the presence of heterogeneity within each pairwise comparison using the  $I^2$  (percentage of variability that is due to differences in the underlying effects across studies) and  $\tau^2$  statistics.

The assessment of statistical heterogeneity in the entire network will be based on the magnitude of  $\tau^2$  estimated from the network meta-analysis models. For dichotomous outcomes the magnitude of the heterogeneity variance will be compared with the empirical distribution (Turner 2012).

#### **Assessment of statistical consistency**

In network meta-analysis, results can be misleading in the presence of inconsistency. We will evaluate the presence of inconsistency both locally and globally. We will evaluate each network locally using the loop-specific method by generating an inconsistency factor along with a 95% CI for each closed-loop (Veroniki 2013). In this

way, we will identify which piece of evidence is responsible for inconsistency, and we will explore this further. We also will apply a global assessment for consistency in each network by applying the design-by-treatment interaction model (White 2012). It has been shown that inconsistency tests have low power to detect true inconsistency (Song 2003; Veroniki 2013). Hence, we will assess transitivity even in the absence of evidence for inconsistency. If inconsistency is found, we will follow the guidance provided in the *Cochrane Handbook for Systematic reviews of interventions* (Chaimani 2019).

### Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting. We will use comparison-adjusted funnel plots to assess small-study effects (Chaimani A 2013). There are different possible explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We, therefore, will interpret these results carefully. When there is a visual asymmetry of funnel plot we will perform an exploratory analysis for dichotomous data such as contour-enhanced funnel plots and trim and fill sensitivity analyses

### Data synthesis

#### Pairwise meta-analyses

For each pair-wise comparison, we will synthesise data to obtain summary standardised mean differences (SMD, Cohen's d) for continuous outcomes or relative risk (RR) for dichotomous outcomes, both with 95% Credible Intervals (CrI). We will use a random effects model (inverse variance weighting) to incorporate the assumption that the different studies are estimating different, yet related, treatment effects. For each outcome, we will first assume that each pairwise meta-analysis comparing treatments X and Y has its own heterogeneity variance parameter  $\tau^2_{XY}$  and then assume that there are two heterogeneity parameters; one common for all placebo-controlled trials and one for all active versus active comparisons. Visual inspection of the forest plots and monitoring of the posterior distributions of  $\tau^2_P$ ,  $\tau^2_{XY}$  and  $\tau^2$  will be used to investigate the possibility of statistical heterogeneity. We will compare the posterior distributions of the heterogeneity parameters to their predictive distributions, as described elsewhere (Turner 2012; Rhodes 2015). Finally, we will calculate the  $I^2$  statistic and its 95% CrI to convey the amount of heterogeneity. Initially, we will perform standard pairwise meta-analyses using a random effects model in RevMan Web (RevMan Web 2023), and we will perform all other analyses in Stata 14 using the 'network' (Stata 2023) and 'network graphs' packages (Stata 2023; White 2012; White 2015).

#### Methods for indirect and network comparisons

We will fit a random-effects network meta-analysis model because we anticipate methodological and clinical heterogeneity across studies. We will assume a common within-network heterogeneity estimate across comparisons, and we will estimate this using the restricted maximum likelihood (REML) method (Veroniki 2016). This is a reasonable assumption, given that all treatments included in the network are of the same nature. An advantage of this approach is that treatment comparisons informed by a single study can borrow strength from the rest of the studies in the network (Salanti 2008). If the collected studies appear to be sufficiently similar with respect to the distribution of effect modifiers (refer Assessment of transitivity assumption section), we will conduct a random effects NMA to synthesise all evidence for each outcome, and obtain a comprehensive ranking of all treatments. We will use arm-level data and the binomial likelihood for dichotomous outcomes. We will account for the correlations induced by multi-arm studies by employing multivariate distributions. We will assume a single heterogeneity parameter for each network. We will present the summary RR or SMD for all pairwise comparisons in a league table. We will also estimate the prediction intervals to assess how much the common heterogeneity affects the relative effect with respect to the extra uncertainty anticipated in a future study.

We will conduct a network meta-analysis using the network suite of commands in Stata (Stata 2023; White 2012; White 2015).

#### Methods for direct treatment comparisons

We will perform analyses according to recommendations provided in Chapter 9 of the *Cochrane Handbook of systematic review of interventions* (Deeks 2022), and use Cochrane's statistical software, RevMan web (RevMan Web 2023), for analysis. When possible, we will perform these standard pair-wise meta-analyses using a random-effects model because we will anticipate methodological and clinical heterogeneity across studies. We will calculate corresponding 95% CIs for all analyses, and will graphically present the results using forest plots. When trials are clinically too heterogeneous to be combined, we will perform only subgroup analyses without calculating an overall estimate. In order to avoid duplication with the supporting reviews of this network meta-analysis, we will describe only the pairwise comparisons for the data that could not be included in the network due to concerns about transitivity.

### Living systematic review considerations

Whenever we identify new evidence (meaning new studies, data, or information) that is relevant to the review, we will extract the data and assess risk of bias, as appropriate. We will not adjust meta-analyses to account for multiple testing, given that methods related to frequent updating of meta-analyses are under development (Simmonds 2017 [https://revman.cochrane.org/#/003418080817045395/dashboard/htmlView/1.0?revertEnabled=true#REF-Simmonds-2017]).

Our aim is to update the synthesis at least annually. For this purpose, we will search for, screen and extract data every six months. The updated synthesis will be reported online at least twice a year on a specific page that will be created on the Cochrane Lung Cancer Group website (<https://lungcancer.cochrane.or>). In addition, we will update this Cochrane Review at least once a year, or as soon as the certainty of evidence (assessed with the GRADE methodology) changes.

We will wait until the accumulating evidence changes one or more of the following aspects of the review, before incorporating it and re-publishing the Cochrane Review:

- the findings of one or more critical outcomes;
- the credibility (e.g. GRADE rating) of one or more critical outcomes;
- new settings, population, interventions, comparisons or outcomes studied; or
- new serious adverse events.

### **Subgroup analysis and investigation of heterogeneity**

When we will find important heterogeneity and/or inconsistency, we will explore possible sources for primary outcomes. When sufficient studies are available, we will perform subgroup analysis by using the following potential effect modifiers as possible sources of inconsistency and/or heterogeneity.

- Patient age (younger than 65 years versus 65 years and older).
- TNM stage (<IIA versus > or = to IIA).
- Performance Status (0-1 versus 2 or more)

These variables are chosen because they have been shown to impact the prognosis after resection of localised lung cancer ([Wei 2011](#)).

### **Sensitivity analysis**

We plan to perform sensitivity analyses limited to the primary outcome (OS) to explore the influence of the following factors (when applicable) on effect size:

- Restricting the analysis to RCTs with low risk of bias.
- Restricting the analysis to RCTs with adequately described inclusion criteria (age, TNM stage, sex, smoking status, performance status).

### **Summary of findings and assessment of the certainty of the evidence**

We will create a 'Summary of findings' table to summarise key results of the review, using the Confidence in Network Meta-analysis (CINeMA) framework and software ([Chaimani 2021](#); [CINeMA 2020](#); [Salanti 2014](#)). To evaluate the confidence in the results of the pairwise comparisons for the critical outcomes, we will rely on the GRADE approach ([Schünemann 2019](#)). We will include the following outcomes:

Primary outcome:

- OS

Secondary outcomes:

- DFS
- RFS
- TTR
- CSS
- Safety, toxicity profile with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 [CTCAE] grading scales ([CTCAE V4](#)).
- Patient reported outcomes.

All analyses of the primary outcome will be duplicated using the netmeta package in Stata ([Stata 2023](#)).

We will assess the quality of evidence will be assessed.

### **Methods for future updates**

We will review the scope and methods of this review yearly, in light of potential changes in the topic area or in evidence available for inclusion in the review (e.g. additional comparisons, interventions, or outcomes), or according to newly available review methods.

We will consider each year the necessity for the review to be living by assessing ongoing relevance of the question to decision-makers and by determining whether uncertainty is ongoing in the evidence and whether further relevant research is likely.



## Acknowledgements

We would like to thank....

## Contributions of authors

Writing of the protocol: CM, GE, FC, RM, VW, AC

Design of the search strategies: FC

## Declarations of interest

Corynne Marchal: none know. Managing Editor for the Cochrane Lung cancer Group not involved in the editorial process

Guillaume Eberst : to be reported after peer review by CM once the DoI are available in Convey

François Calais: none known

Virginie Westeel : to be reported after peer review by CM once the DoI are available in Convey

Reem Malouf: None known

Anna Chaimani: None known

## Sources of support

### Internal sources

- No sources of support provided

### External sources

- INCa (Institut National du Cancer), France  
COP Cochrane Groupe Cancer du Poumon n° 2022-047

## Appendices

### Appendix 1. The Eighth Edition of TNM Staging of Lung Cancer

|  |
|--|
| <b>T (primary tumor)</b>   |
| <b>T1 Tumor &lt;3 cm</b>   |
| T1s Carcinoma in situ (squamous or adenocarcinoma)   |
| T1mi Minimally invasive adenocarcinoma   |
| T1a Tumor 1 cm   |
| T1b Tumor >1 but 2 cm  |
| T1c Tumor >2 but 3 cm  |
| <b>T2 Tumor &gt;3 but 5 cm or tumor involving: visceral pleura, y main bronchus (not carina), atelectasis to hilum,</b>  |
| T2a Tumor >3 but <4 cm   |
| T2b Tumor >4 but <5 cm   |
| <b>T3 Tumor &gt;5 but &lt;7 cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe</b>  |
| <b>T4 Tumor &gt;7 cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe</b> |
| <b>N (regional lymph nodes)</b>  |
| N0 No regional node metastasis   |
| N1 Metastasis in ipsilateral pulmonary or hilar nodes  |
| N2 Metastasis in ipsilateral mediastinal or subcarinal nodes   |
| N3 Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes  |
| <b>M (distant metastasis)</b>  |
| M0 No distant metastasis   |
| M1a Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe  |
| M1b Single extrathoracic metastasis  |
| M1c Multiple extrathoracic metastases (1 or >1 organ)  |

### Appendix 2. MEDLINE search strategy accessed via PubMed

1 Carcinoma, Non-Small-Cell Lung[MeSH Terms]  
 2 NSCLC[Title/Abstract]  
 3 "lung cancer"[Title/Abstract]  
 4 "lung carcinom"[Title/Abstract]  
 5 "lung neoplasm"[Title/Abstract]  
 6 "lung tumor"[Title/Abstract]  
 7 "lung tumour"[Title/Abstract]  
 8 "non small cell"[Title/Abstract]  
 9 "nonsmall cell"[Title/Abstract]  
 10 (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)  
 11 #1 OR #2 OR #10  
 12 ((Pulmonary Surgical Procedures[MeSH Terms]) OR (pneumonectomy[MeSH Terms])) OR (thoracotomy[MeSH Terms])  
 13 (((((((((((lobectomy[Title/Abstract]) OR ("Lymph node sampl"[Title/Abstract])) OR (operable[Title/Abstract])) OR (perioperat\*[Title/Abstract])) OR (perioperat\*[Title/Abstract])) OR (postoperat\*[Title/Abstract])) OR (preoperat\*[Title/Abstract])) OR (resectable[Title/Abstract])) OR (resection\*[Title/Abstract])) OR (segmentectomy[Title/Abstract])) OR (surgery[Title/Abstract])) OR (surgical\*[Title/Abstract])) OR (thoracotomy[Title/Abstract])  
 14 (((Immunotherapy[MeSH Terms]) OR (Antineoplastic Agents, Immunological[Pharmacological Action])) OR (Immune Checkpoint Inhibitors[MeSH Terms])) OR (Immune Checkpoint Inhibitors[Pharmacological Action])  
 15 (((("Immune Checkpoint Inhibitor"[Title/Abstract]) OR ("PD L1 Inhibitor"[Title/Abstract])) OR ("PD 1 Inhibitor"[Title/Abstract])) OR ("CTLA 4 Inhibitor"[Title/Abstract])  
 16 (((((((nivolumab[MeSH Terms]) OR (nivolumab[Title/Abstract])) OR (Opdivo[Title/Abstract])) OR ("ONO 4538"[Title/Abstract])) OR (ONO4538[Title/Abstract])) OR ("MDX 1106"[Title/Abstract])) OR (MDX1106[Title/Abstract])) OR (BMS 936558[Title/Abstract])) OR (BMS936558[Title/Abstract])  
 17 (((((pembrolizumab[Supplementary Concept]) OR (pembrolizumab[Title/Abstract])) OR (lambrolizumab[Title/Abstract])) OR (Keytruda[Title/Abstract])) OR (SCH-900475[Title/Abstract])) OR (MK-3475[Title/Abstract])  
 18 (((durvalumab[Supplementary Concept]) OR (durvalumab[Title/Abstract])) OR (Imfinzi[Title/Abstract])) OR (MEDI-4736[Title/Abstract])) OR (MEDI4736[Title/Abstract])  
 19 (((((atezolizumab[Supplementary Concept]) OR (atezolizumab[Title/Abstract])) OR (Tecentriq[Title/Abstract])) OR (anti-PDL1[Title/Abstract])) OR (MPDL3280A[Title/Abstract])) OR (MPDL-3280A[Title/Abstract])  
 20 (((((avelumab[Supplementary Concept]) OR (avelumab[Title/Abstract])) OR (bavencio[Title/Abstract])) OR ("MSB 0010682"[Title/Abstract])) OR (MSB0010682[Title/Abstract])) OR (MSB0010718C[Title/Abstract])  
 21 #12 OR #13  
 22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20  
 23 #11 AND #21 AND #22  
 24 randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR drug therapy[MeSH Subheading] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]  
 25 animals[MeSH Terms] NOT humans[MeSH Terms]  
 26 #24 NOT #25  
 27 #23 AND #26

### Appendix 3. EMBASE search strategy accessed via Elsevier

|  |
|--|
| non small cell lung cancer'/exp  |
| NSCLC:ti,ab  |
| "lung cancer":ti,ab  |
| "lung carcinom":ti,ab  |
| "lung neoplasm":ti,ab  |
| "lung tumor":ti,ab   |
| "lung tumour":ti,ab  |
| "non small cell":ti,ab   |
| "nonsmall cell":ti,ab  |
| (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)  |
| #1 OR #2 OR #10  |
| lung surgery'/exp OR 'thoracotomy'/exp   |
| (lobectomy OR "Lymph node sampl" OR operable OR perioperat* OR perioperat* OR postoperat* OR preoperat* OR resectable OR resection* OR segmentectomy OR surgery OR surgical* OR thoracotomy):ti,ab |
| immunotherapy'/exp OR 'immunological antineoplastic agent'/exp OR 'immune checkpoint inhibitor'/exp  |
| ("Immune Checkpoint Inhibitor" OR "PD L1 Inhibitor" OR "PD 1 Inhibitor" OR "CTLA 4 Inhibitor"):ti,ab   |
| nivolumab'/exp OR (nivolumab OR Opdivo OR "ONO 4538" OR ONO4538 OR "MDX 1106" OR MDX1106 OR "BMS 936558" OR BMS936558):ti,ab   |
| pembrolizumab'/exp OR (pembrolizumab OR lambrolizumab OR Keytruda OR "SCH-900475" OR "MK-3475"):ti,ab  |
| durvalumab'/exp OR (durvalumab OR Imfinzi OR "MEDI-4736" OR MEDI4736):ti,ab  |
| atezolizumab'/exp OR (atezolizumab OR Tecentriq OR "anti-PDL1" OR MPDL3280A OR "MPDL-3280A"):ti,ab   |
| avelumab'/exp OR (avelumab OR bavencio OR "MSB 0010682" OR MSB0010682 OR MSB0010718C):ti,ab  |
| #12 OR #13   |

|   |
|---|
| #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20   |
| #11 AND #21 AND #22   |
| randomized controlled trial/exp OR (randomized OR placebo OR "drug therapy" OR randomly OR trial OR groups):ti,ab |
| animal/exp NOT 'human'/exp  |
| #24 NOT #25   |
| #23 AND #26   |

## Appendix 4. CENTRAL search strategy

### ID Search Hits

#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees 4896  
#2 nscic 11095  
#3 "lung cancer" 23446  
#4 "lung carcinom\*" 51  
#5 "lung neoplasm\*" 76  
#6 "lung tumor\*" 672  
#7 "lung tumour\*" 672  
#8 "non small cell\*" 15374  
#9 "nonsmall cell\*" 10462  
#10 (#3 or #4 or #5 or #6 or #7) and (#8 or #9) 14841  
#11 MeSH descriptor: [Pulmonary Surgical Procedures] explode all trees 1633  
#12 MeSH descriptor: [Pneumonectomy] explode all trees 607  
#13 MeSH descriptor: [Thoracotomy] explode all trees 616  
#14 lobectomy OR "Lymph node sampl\*" OR operable OR perioperat\* OR perioperat\* OR postoperat\* OR preoperat\* OR resectable OR resection\* OR segmentectomy OR surgery OR surgical\* OR thoracotomy 357817  
#15 #11 OR #12 OR #13 OR #14 358434  
#16 MeSH descriptor: [Immunotherapy] explode all trees 8819  
#17 MeSH descriptor: [Antineoplastic Agents, Immunological] explode all trees 538  
#18 MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees 95  
#19 "Immune Checkpoint Inhibitor\*" OR "PD L1 Inhibitor\*" OR "CTLA 4 Inhibitor\*" 974  
#20 MeSH descriptor: [Nivolumab] explode all trees 618  
#21 nivolumab OR Opdivo OR "ONO 4538" OR ONO4538 OR "MDX 1106" OR MDX1106 OR "BMS 936558" OR BMS936558 2655  
#22 pembrolizumab OR lambrolizumab OR Keytruda OR SCH-900475 OR MK-3475 2658  
#23 durvalumab OR Imfinzi OR MEDI-4736 OR MEDI4736 996  
#24 atezolizumab OR Tecentriq OR anti-PDL1 OR MPDL3280A OR MPDL-3280A 1296  
#25 avelumab OR bavencio OR "MSB 0010682" OR MSB0010682 OR MSB0010718C 356  
#26 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 372451  
#27 #10 AND #15 AND #26 3209

## References

### Additional references

#### Caldwell 2005

Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331(7521):897-900.

#### Chaimani 2017

Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Additional considerations are required when preparing a protocol for a systematic review with multiple interventions.. *Journal of Clinical Epidemiology* 2017;83:65-74.

#### Chaimani 2019

Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Undertaking network meta-analyses -. In: *Cochrane Handbook for systematic reviews of interventions*. The Cochrane Collaboration, 2019.

#### Chaimani 2021

Chaimani A, Porcher R, Sbidian É, Mavridis D. A Markov chain approach for ranking treatments in network meta-analysis. *Statistics in Medicine* 2021;40 (2):451-64.

#### Chaimani A 2013

Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS ONE* 2013;8 (10):e76654.

#### **CINeMA 2020 [Computer program]**

CINeMA: software for semi-automated assessment of the confidence in the results of network meta-analysis. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. *Campbell Systematic Reviews*, 2020.

#### **Cipriani 2013**

Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Annals of Internal Medicine* 2013;159 (2):130-7.

#### **Conroy 2023**

Conroy M, Forde PM. Advancing neoadjuvant immunotherapy for lung cancer. *Nature Medicine* 2023;29(3):533-4.

#### **Covidence [Computer program]**

Covidence. Melbourne: Veritas Health Innovation, Australia, 2020.

#### **CTCAE V4**

Common Terminology Criteria for Adverse Events (Version 4). U.S.Department of Health and Human Services - National Institutes of Health-National Cancer Institute 2009.

#### **Deeks 2022**

Deeks JJ, Higgins JPT, Altman DG, on behalf of the Cochrane Statistical Methods Group. Chapter 10: analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). The Cochrane collaboration, 2022.

#### **Elliott 2017**

Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, et al. Living systematic review: 1. Introduction—the why, what, when, and how. *Journal of Clinical Epidemiology* 2017;91:23-30.

#### **Ettinger 2022**

Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network* 2022;20 (5):497-530.

#### **Felip 2021**

Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *The Lancet* 2021;398:1344-57.

#### **Forde 2022**

Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *New England Journal of Medicine* 2022;386:1973-85.

#### **Forde 2018**

Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *New England Journal of Medicine* 2018;378:1976-86.

#### **Früh 2008**

Früh M, Rolland E, Pignon JP, Seymour L, Ding K, Tribodet H, et al. Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. *Journal of Clinical Oncology* 2008;26:3573-81.

#### **GLOBOCAN 2020**

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians* 2020;71(3):202-49.

#### **Goldstraw 2016**

Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology* 2016;11(1):39-51.

#### **Herath 2022**

Herath S, Sadeghi Rad H, Radfar P, Ladwa R, Warkiani M, O'Byrne K, et al. The role of circulating biomarkers in lung cancer. *Frontiers in Oncology* 2022;11:801269.

#### **Herbst 2008**

Herbst RS, JV Heymach, and SM Lippman. Lung Cancer. *New England Journal of Medicine* 2008;359(13):1367-80.

#### **Heymach 2023**

Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, et al. AEGEAN: a phase 3 trial of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC. In: Presented at: 2023 AACR Annual Meeting; April 14-19, 2023; Orlando, FL. Abstract CT005. 2023.

#### **Higgins 2011**

Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). In: Available from handbook.cochrane.org. The Cochrane Collaboration, 2011.

#### **Higgins 2022**

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane*. The Cochrane collaboration, 2022.

#### **Jansen 2013**

Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC medicine* 2013;11(1):1-8.

#### **Le Pechoux 2022**

Le Pechoux C, Pourel N, Barlesi F, Lerouge D, Antoni D, Lameze B, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial. *The Lancet Oncology* 2022;23:104-14.

#### **Lefebvre 2019**

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. Chapter 4: searching for and selecting studies. In: *Cochrane Handbook for Systematic Reviews of Interventions*, 2nd edition. Chichester (UK): John Wiley & sons, 2019:67-108.

#### **Lim 2009**

Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. *Journal of Thoracic Oncology* 2009;4 (11):1380-88.

#### **Lu 2004**

Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 2004;23(20):3105-24.

#### **Mavridis 2015**

Mavridis D, White IR, Higgins JP, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. *Statistics in Medicine* 2015;34 (5):721-41.

#### **McKenzie 2022**

McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV. Chapter 9: Summarizing study characteristics and preparing for synthesis. In: *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated ). The Cochrane collaboration, February 2022.

#### **Microsoft Excel [Computer program]**

Microsoft Excel. Microsoft Corporation, 2018.

### **O'Brien 2022**

O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *The Lancet Oncology* 2022;23:1274-86.

### **Peng 2023**

Peng Y, Li Z, Fu Y, Pan Y, Zeng Y, Liu J, et al. Progress and perspectives of perioperative immunotherapy in non-small cell lung cancer. *The Frontiers in Oncology* 2023;13:1011810.

### **RevMan Web 2023 [Computer program]**

*Review Manager (RevMan)*. Version 5.5. The cochrane Collaboration. Available at <https://revman.cochrane.org>, 2023.

### **Rhodes 2015**

Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *Journal of clinical epidemiology* 2015;68 (1):52-60.

### **Salanti 2008**

Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Statistical Methods in Medical Research* 2008;17 (3):279-301.

### **Salanti 2011**

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of clinical epidemiology* 2011;64 (2):163-71.

### **Salanti 2014**

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS one* 2014;9 (7):e99682.

### **Schünemann 2019**

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, on behalf of the Cochrane GRADEing Methods Group. Chapter 15: Interpreting results and drawing conclusions. In: *Cochrane handbook for systematic reviews of interventions*. The Cochrane collaboration, 2019:403-31.

### **Song 2003**

Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;326 (7387):472.

### **Stata 2023 [Computer program]**

*Stata Statistical Software: release 18*. TX: Statacorp LLC, 2023.

### **Turner 2012**

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International journal of epidemiology* 2012;41 (3):818-27.

### **Veroniki 2013**

Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. *International journal of epidemiology* 2013;42 (1):332-45.

### **Veroniki 2016**

Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Research synthesis methods* 2016;7 (1):55-79.

### **Wakelee 2017**

Wakelee HA, Dahlberg SE, Keller SM, Tester WJ, Gandara DR, Graziano SL, et al. Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. *The lancet oncology* 2017;18:1610-23.

**Wei 2011**

Wei S, Asamura H, Kawachi R, Sakurai H, Watanabe SI. Which is the better prognostic factor for resected non-small cell lung cancer: the number of metastatic lymph nodes or the currently used nodal stage classification? *Journal of Thoracic Oncology* 2011;6(2):310-8.

**White 2008**

White IR, Higgins JP, Wood AM. Allowing for uncertainty due to missing data in meta-analysis—part 1: two-stage methods. *Statistics in Medicine* 2008;27(5):711-27.

**White 2012**

White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research synthesis methods* 2012;3 (2):111-25.

**White 2015**

White IR. Network meta-analysis. *The Stata Journal* 2015;15 (4):951-85.

## DISCUSSION 2<sup>nd</sup> AXE THEMATIQUE :

### Stratégies péri-opératoires de réduction du risque de récurrence et SCBP

---

Nous avons entrepris une revue systématique dynamique d'essais interventionnels avec méta-analyse en réseaux sur les traitements péri-opératoires d'immunothérapie dans le CBNPC résecable. La méthode de méta-analyse en réseau avec comparaison indirecte permet de prendre en compte les différences dans les effets relatifs du traitement au fil du temps, les biais de sélection sur la différence de survie.

Plusieurs problématiques se posaient :

- l'hétérogénéité des études,
- le temps zéro différent entre les essais.

L'hétérogénéité est surtout le fait des différences dans les critères d'inclusion des études, des différences de produits d'immunothérapie utilisés, leur association ou non à d'autres molécules (immunothérapie, chimiothérapie, anti-angiogénique...). En cas de stratégie péri-opératoire, les études ne stratifiaient pas toutes sur la réponse pathologique. Il sera proposé des analyses en sous-groupe sur les facteurs identifiés comme source d'hétérogénéité.

La différence du temps zéro entre les études constitue le principal défi méthodologique à notre sens. En effet, les études qui randomisent les patients après la chirurgie et l'éventuelle chimiothérapie adjuvante n'ont pas les mêmes patients à risque que les études incluant avant la chirurgie. Il y a une proportion de patients non opérés après un schéma néo-adjuvant (jusqu'à 20% dans certaines études [8, 32, 33]) et ceux ne terminant pas une chimiothérapie adjuvante. Ces patients, ne sont pas pris en compte dans les analyses de survie des essais d'évaluation des traitements adjuvants.

Nous avons proposé des méthodes d'implémentation statistique avec un modèle mixte prenant en compte le risque relatif variable au cours du temps (89).

D'autres hypothèses sont spécifiques aux méta-analyses en réseaux et à vérifier: la transitivité et la cohérence. La méthode de Bucher *et al.* (90) repose sur l'hypothèse de transitivité qui ne peut être testée au niveau statistique. L'hypothèse de transitivité dans le cas de notre étude consiste dans le fait que les patients inclus dans le réseau auraient pu en principe être randomisés dans n'importe quelle situation de traitement : néo-adjuvant, adjuvant ou péri-opératoire. Or comme expliqué préalablement, cette hypothèse n'est pas respectée si l'on considère les études avec randomisation après chirurgie ou chimiothérapie adjuvante. Une analyse sera nécessaire soit par extrapolation si les données pré-chirurgie sont disponibles et permettent un appariement soit si des essais de stratégies adjuvantes ont inclus et randomisés des patients avant la chirurgie. Cette hypothèse est toutefois respectée dans la comparaison d'essai de stratégies néo-adjuvantes avec péri-opératoire



(néo-adjuvant et adjuvant). La cohérence est définie comme l'absence de discordance entre les résultats issus de comparaisons directes et ceux issus de comparaisons indirectes. Il n'y a, à notre connaissance, aucune comparaison directe entre les différentes stratégies de traitements d'immunothérapie péri-opératoires. Ces essais seront probablement mis en place prochainement ce qui nous a fait proposer d'actualiser les résultats de la revue systématique avec le concept de *living*.

Les analyses indirectes des méta-analyses en réseaux apportent un surplus d'information par rapport aux revues d'intervention directes. Par exemple, dans une étude de Blanchard P. *et al*, dont le but était d'identifier le meilleur traitement péri-opératoire pour les cancers de la tête et du cou localement avancés, l'analyse en réseaux a permis une hiérarchisation des stratégies de traitements que ne permettaient pas 2 revues systématiques d'intervention publiées antérieurement (91).

Notre revue systématique permettra d'apporter de la puissance à des analyses en générale réalisées en sous-groupe. La définition de la résécabilité est difficile avec un travail de consensus international en cours (11). Peut-être que l'analyse synthétique des données d'efficacité des traitements de chimiothérapie-immunothérapie néo-adjuvants chez les CBNPC de stades III, permettra une meilleure définition de la résécabilité. L'avènement du traitement néoadjuvant par immunothérapie a relancé le débat sur le traitement optimal des patients atteints d'un CBNPC de stade IIIB à la limite de la résécabilité (8, 92). Aucun essai n'a encore évalué le rôle de cette stratégie dans la conversion d'un CBNPC non résécable en CBNPC résécable. Dans l'essai CheckMate 816, des pourcentages plus faibles de pneumonectomies ont été réalisés dans le bras nivolumab néo-adjuvant (17 % contre 30 %) (8). En revanche, dans les essais Checkmate 77T, AGEAN et KEYNOTE-671, les pourcentages étaient similaires quel que soit le traitement néoadjuvant avec ou sans immunothérapie (93, 32, 33). Par conséquent, l'espérance d'un *downstaging* par l'association de l'immunothérapie à la chimiothérapie en situation néo-adjuvante n'est pas encore prouvée.

Enfin des données de sécurité pourront être étudiées. Par exemple, chez les patients sous immunothérapie néo-adjuvante, en raison de la réaction inflammatoire, les chirurgies thoraciques d'exérèse des CBNPC étaient décrites plus difficiles (94). L'essai IONESCO a été arrêté prématurément en raison d'un taux de mortalité postopératoire élevé de 9 % à 90 jours (95). Cependant, dans l'essai CheckMate 816, la durée médiane de l'intervention chirurgicale était de 186 minutes chez les patients recevant une chimio-immunothérapie néoadjuvante et de 210 minutes chez ceux recevant une chimiothérapie néoadjuvante seule (8). Une synthèse des données de tolérance semble pertinente pour l'analyse de ces stratégies.

En conclusion ce travail de revue systématique avec méta-analyse en réseaux laisse espérer de nombreuses réponses aux problématiques nouvelles des traitements d'immunothérapie péri-opératoires. Ce travail fait l'objet d'un échange avec l'équipe du groupe Cochrane France pour l'apport de leur expertise sur les méta-analyse en réseaux.

Le concept d'une revue systématique vivante, permettra d'agrémenter les résultats d'informations nouvelles au fil de leur publication. Par exemple, la découverte de nouveaux biomarqueurs, l'intérêt de l'analyse de la réponse pathologique dans la stratégie thérapeutique...

Enfin cette revue servira de base à la construction d'essai thérapeutique académique (Intergroupe Francophone de Cancérologie Thoracique) sur la stratégie de traitement péri-opératoire des CBNPC.

### *Axe Diagnostique*

*Impact sur la qualité de vie et sur la pénibilité ressentie par les patients d'un suivi basé sur le scanner thoraco-abdominal par rapport au suivi minimal chez les patients opérés d'un cancer du poumon non à petites cellules (CPNPC) de l'essai de phase III IFCT-0302*

L'essai IFCT-0302 était un essai multicentrique randomisé qui n'a pas retrouvé de bénéfice en survie globale à l'ajout d'un scanner thoraco-abdominal et d'une fibroscopie bronchique (facultatif pour les adénocarcinomes) à un suivi basé sur un examen physique et une radiographie pulmonaire dans le cancer bronchique réséqué. Nous présentons ici les résultats d'analyse de qualité de vie et de la pénibilité rapportés par les patients, un critère d'évaluation secondaire de l'essai.

#### Méthodes

La qualité de vie liée à la santé (QdV) était évaluée à l'aide du questionnaire *Short Form-12* (SF-12), et la pénibilité par une échelle visuelle analogique (entre 0 et 10) administrés lors de la randomisation, tous les 6 mois pendant 2 ans et annuellement jusqu'à 5 ans ou jusqu'à progression de la maladie, deuxième cancer primitif ou décès si l'un de ces événements survenait avant 5 ans. Le temps jusqu'à détérioration et un modèle mixte pour mesures répétées (MMRM) ont été utilisés pour analyser les données longitudinales.

#### Résultats

Entre janvier 2005 et novembre 2012, 1 775 patients ont été randomisés dans l'essai IFCT-0302. Au départ, 756 des 888 patients (85,1 %) du groupe de suivi minimal avaient au moins un score de QdV disponible, et 747 des 887 (84,2 %) du groupe de suivi basé sur la tomodensitométrie. Au total, 80,8 % des patients du groupe de suivi minimal et 75,6 % du groupe de suivi par tomodensitométrie ont rempli des questionnaires pendant une période allant jusqu'à un an. Il n'y avait aucune différence entre les groupes dans l'analyse du temps jusqu'à

détérioration pour les deux dimensions du questionnaire SF-12 : dimension mentale [RR (groupe de suivi basé sur CT vs groupe de suivi minimal) : 0,97 ; IC à 95 %, 0,82 à 1,15 ; p = 0,74] et dimension physique [RR (le groupe de suivi basé sur CT vs le groupe de suivi minimal) : 1,13 ; IC à 95 %, 0,92 à 1,38 ; p = 0,24)] et MMRM. La pénibilité était statistiquement plus élevée dans le groupe de suivi par tomodensitométrie (p < 0,0001) et était liée à la fibroscopie bronchique.

#### Interprétation

Aucun impact sur la QdV n'a été démontré en ajoutant le scanner thoraco-abdominal et la fibroscopie bronchique dans le suivi après résection du cancer pulmonaire, contrairement à la pénibilité impactée par la fibroscopie bronchique.

## Original article

# Impact of CT scan-based vs. minimal follow-up on patient-reported health-related quality-of-life outcomes for completely resected non-small cell lung cancer (NSCLC) in the phase III IFCT-0302 trial

Guillaume Eberst<sup>1, 2, 3, +</sup>, Julie Henriques<sup>2, 3</sup>, M. Monchatre<sup>4</sup>, E. Giroux-Leprieur<sup>5</sup>, E. Kelkel<sup>6</sup>, A.

Bizieux Thaminy<sup>7</sup>, P. Ravier<sup>8</sup>, S. Bayle<sup>9</sup>, C. Audigier Valette<sup>10</sup>, H. Berard<sup>11</sup>, F. Desliers<sup>12</sup>, A.

Lagrange<sup>13</sup>, P. Bonnefoy<sup>14</sup>, Alexandra Langlais<sup>15</sup>, Dewi Vernerey<sup>2, 3</sup>, Amélie Anota<sup>2, 3</sup>, Franck

Morin<sup>15</sup>, and Virginie Westeel<sup>1, 3</sup>, on behalf of the French Cooperative Thoracic Intergroup (IFCT)

<sup>1</sup> Chest Disease Department, University Hospital, Besançon, France

<sup>2</sup> Methodology and Quality of Life in Oncology Unit, University Hospital, Besançon, France

<sup>3</sup> Franche-Comté University, EFS, INSERM, UMR RIGHT, F-25000 Besançon, France

<sup>4</sup> Pneumology, Clinique Claude Bernard, Ermont, France,

<sup>5</sup> Department of Respiratory Diseases and Thoracic Oncology, University Paris-Saclay, UVSQ, APHP – Ambroise Paré Hospital, Boulogne-Billancourt, France,

<sup>6</sup> Pneumology, Centre Hospitalier Metropole Savoie - Chambéry, Chambéry, France,

<sup>7</sup> Pneumology, CHD Vendée, La Roche-sur-Yon, France,

<sup>8</sup> Cabinet de Pneumologie, Dijon, France,

<sup>9</sup> Pneumology, CHU Saint Etienne -Hopital Nord, Saint-Étienne, France,

<sup>10</sup> Pneumology, Hopital Sainte Musse, Toulon, France,

<sup>11</sup> Pneumology, Hôpital d'Instruction des Armées Sainte Anne Toulon, Toulon, Cedex, France,

<sup>12</sup> Cabinet de Pneumologie, Lens, France,

<sup>13</sup> Pneumology, Centre Hospitalier Louis Pasteur, Dôle, France,

<sup>14</sup> Pneumology, Hôpital de Jonzac, Jonzac, France,

<sup>15</sup> Clinical Research Unit, French Cooperative Thoracic Intergroup, Paris, France

<sup>+</sup>  
**Correspondence to:**

Guillaume EBERST, Chest Disease Department,

University Hospital of Besançon, 3 Boulevard Fleming, Besançon cedex, 25030, France

Email: [geberst@chu-besancon.fr](mailto:geberst@chu-besancon.fr)

## **Conflicts of interest**

### ***Evidence before this study***

Over the last decade, a tremendous growth in the incorporation of health-related quality of life (HRQoL) in cancer clinical trials has been observed. The US FDA considers HRQoL as an endpoint that assesses direct clinical benefit for the patient. To our knowledge, there is no study evaluating the relationship between follow-up procedures and HRQoL. The IFCT-0302 study is a randomised, controlled trial assessing the value of chest CT scans for the surveillance of patients with completely resected non-small cell lung cancer (NSCLC) in terms of overall survival. The results showed that the addition of chest CT scans to a follow-up including clinic visits and chest x-rays did not improve overall survival. CT scans were associated with the detection of more asymptomatic patients who had developed recurrence.

### ***Added value of this study***

To our knowledge, the IFCT-0302 trial is the first phase 3 study to evaluate the effect of chest CT scans on patient survival after complete resection of stage I–IIIA NSCLC.

The primary endpoint of overall survival was not met, therefore, HRQoL could be considered as an outcome to judge efficacy of each follow-up strategy.

The addition of chest CT scans (plus fibre-optic bronchoscopy in nonadenocarcinoma histology) to the follow up after surgery for NSCLC did not influence the HRQoL in the IFCT-0302 trial. The penibility assessed using a visual analogue scale graduated from 0 to 10, was significantly higher in the CT-based follow-up group due to the addition of fibre-optic bronchoscopy.

### ***Implications of all the available evidence***

The results of this large, randomised study provide guidance for clinicians and decision makers regarding the follow-up of patients who have undergone surgery for lung cancer. Overall survival was not significantly improved using a CT-based follow-up approach. However, the analysis of



HRQoL and penibility in the IFCT-0302 trial, showed no difference in HRQoL. Penibility was increased in patients who underwent fibre-optic bronchoscopy in the CT-based follow-up arm. These HRQoL and penibility results, along with the detection of more recurrences and second primary cancers with thoracic CT scans, which were more frequently asymptomatic, at an early stage and more frequently accessible to curative treatment, support its use for the follow-up of patients operated on for NSCLC.

## **Abstract**

### **Background**

The IFCT-0302 trial was a randomized multicenter trial that found no benefit to overall survival in adding chest CT-scan and fibre-optic bronchoscopy (optional for adenocarcinomas) to a follow-up based on physical examination and chest X-ray in resected NSCLC. We present the results of patient-reported outcomes (PROs), a secondary endpoint of the IFCT-0302 trial.

### **Methods**

PROs consisted of health-related quality-of-life (HRQoL), assessed using the Short Form-12 (SF-12) questionnaire, and a penibility visual analog scale (between 0 and 10) at randomization, administered every 6 months for 2 years and annually until 5 years or until disease progression or second primary cancer or death if any of these events occurred before 5 years. Time to deterioration and a mixed model for repeated measures (MMRM) were used to analyze longitudinal data.

### **Findings**

Between January 2005 and November 2012, 1775 patients were randomized in the IFCT-0302 trial. At baseline, 756 of the 888 patients (85.1%) in the minimal follow-up group had at least one HRQoL score available, and 747 of 887 (84.2%) in the CT-based follow-up group. A total of 80.8% of patients in the minimal follow-up group and 75.6% in the CT-based follow-up group completed questionnaires up to one year. There were no differences between groups in the time to deterioration for the two summary components of the SF-12 questionnaire: mental component summary [HR (the CT-based follow-up group vs. the minimal follow-up group): 0.97; 95% CI, 0.82–1.15;  $p = 0.74$ ] and physical component summary [HR (the CT-based follow-up group vs. the minimal follow-up group): 1.13; 95% CI, 0.92–1.38;  $p = 0.24$ ] and in MMRM. Penibility was statistically higher in the CT-based follow-up group ( $p < 0.0001$ ) and was related to fibre-optic bronchoscopy.

### **Interpretation**

No impact in HRQoL was demonstrated adding thoracic CT scans and fibre-optic bronchoscopy in the follow-up after resection of NSCLC, in contrast with penibility related to fibre-optic bronchoscopy.

**Key words:** Health-related quality of life – Time to deterioration HRQoL – Resected NSCLC – Surveillance – Follow-up

## **Introduction**

Lung cancer remains the leading cause of cancer-related deaths worldwide, accounting for 18% of total cancer deaths in 2020 (1). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80 to 85% of cases (2). In NSCLC, lung cancer outcomes differ according to the stage at diagnosis, with a 24-month survival rate of 87 to 97% for stage I and 10 to 23% for stage IV in 2017 (3).

Surgery with or without perioperative systemic treatment remains the cornerstone treatment of early-stage lung cancer (4). Most international recommendations suggest a follow-up for people after lung cancer surgery to detect treatment-related complications and/or recurrences of the index lung cancer or a new primary lung cancer. Radiological and clinical control twice a year for two years and once a year between 2 and 5 years after surgery is usually proposed (5, 6, 7).

Patient-reported outcomes (PROs), such as symptoms, function, and other health-related quality-of-life (HRQoL) aspects, are increasingly evaluated in cancer randomized controlled trials (RCTs) and required by regulatory authorities (8). While there are data demonstrating HRQoL evolution after NSCLC surgery (9, 10), the influence of follow-up strategies on HRQoL after surgery for lung cancer is unknown. Follow-up procedures might also be considered as having a negative impact on HRQoL (because they remind the patients of their disease or because of the invasiveness of these procedures) and as positively influencing HRQoL (when ruling out cancer recurrence).

The IFCT-0302 trial was a randomized multicenter trial that found no benefit in overall survival in adding chest CT scan and fibre-optic bronchoscopy (optional for adenocarcinomas) to a follow-up based on physical examination and chest X-ray in resected NSCLC (11). We present here the results of patient-reported outcomes (PROs), a secondary endpoint of the IFCT-0302 trial.

## **Methods**

### ***Patients and study design of the IFCT-0302 trial***

The IFCT-0302 trial was a randomized multicenter trial that compared two follow-up programs for completely resected stage pI, II, IIIA and T4 (pulmonary nodules in the same lobe) N0-2 NSCLC (TNM 6th edition) (11).

In the minimal follow-up group, the follow-up consisted of clinical examination and chest X-ray (CXR). In the CT-based follow-up group, patients underwent clinical examinations, CXR, and thoraco-abdominal contrast-enhanced CT scan plus fibre-optic bronchoscopy (optional for adenocarcinomas). In both arms, the procedures were repeated every 6 months after randomization during the first 2 years and yearly until 5 years. Supplementary procedures were allowed in cases with symptoms. The primary endpoint was overall survival (OS), defined as the time from randomization to death from all causes. Patients who survived were censored at the last follow-up (11). PROs were secondary endpoints. The study was conducted according to the Declaration of Helsinki of 1964 and Good Clinical Practice guidelines. All patients provided written consent to participate, and the research protocol was approved by a national ethics committee.

### ***Health-related quality of life***

HRQoL was assessed using the Short Form-12 (SF-12) questionnaire (12). Originally developed from the Medical Outcomes Study (MOS) 36-item Short-Form Health Survey SF-36 (13), the SF-12v2® covers the same eight health domains as the SF-36 with substantially fewer questions, making it a more practical research tool (14). Physical health-related domains include General Health (GH), Physical Functioning (PF), Role Physical (RP), and Body Pain (BP). Mental health-related scales include Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH) (15). The instrument has been validated across a number of chronic diseases and conditions (16) and used in lung cancer screening programs (17, 18).

The questionnaires were offered to the patient at randomization, before each patient visit every six

months during the first two years of follow-up, and every year until the end of the fifth postoperative year. All 12 questions were grouped into two global components: the physical component (Physical Component Summary or PCS) and the mental component (Mental Component Summary or MCS), as recommended by the authors (19). The score of the two components was obtained by weighting individual items and adding to a constant (57.65693 and 60.58847, respectively) for PCS and MCS in order to have a mean of 50 and a standard deviation of 10 in a general population. If one item is missing, the PCS and MSC are missing. Finally, high scale scores of the SF-12 physical and mental component summaries represent a good quality of life (20).

### ***Penibility evaluation***

The penibility of follow-up was assessed using a visual analogue scale graduated from 0 to 10 where 0 represents the absence of penibility and 10 a maximum. The penibility of the follow-up was assessed at the same time as the HRQoL.

### ***Statistical analysis***

The primary objective of IFCT-0302 was to demonstrate whether a surveillance program in resected NSCLC with chest CT scan and fibre-optic bronchoscopy can improve survival compared to a follow-up based only on physical examination and chest X-ray. The primary endpoint was not met (11). PROs were secondary endpoints of the trial. This was analyzed on the modified intent-to-treat (mITT) population, defined as all intent-to-treat patients for whom all SF-12 scores were available at baseline (mITT1 population) and all intent-to-treat patients for whom a penibility score was available at baseline (mITT2 population).

The analysis was conducted according to the patient-reported outcome CONSORT (Consolidated Standards of Reporting Trials) statement (21). For each evaluation time, the percentage of unanswered

or incomplete questionnaires, as well as the median scores and interquartile range (IQR) of the domains of the SF-12 and penibility scale, were described.

Baseline characteristics and OS were compared between the mITT1 population (resp. mITT2) and the non-mITT1 population (resp. non-mITT2). OS was estimated with the Kaplan–Meier method and compared with the log-rank test.

For the mITT1 and mITT2 populations, baseline characteristics, including the HRQoL scores of the patients, are described herein by treatment arms with frequencies and percentages for qualitative variables and with means, standard deviations (SDs), medians and interquartile ranges (IQRs) for quantitative variables. Qualitative variables were compared using a chi-square or a Fisher exact test, and quantitative variables were compared using a nonparametric Mann–Whitney test. OS was compared among arms in the mITT1 and mITT2 populations.

Longitudinal analyses of SF-12 score changes compared to baseline were performed with the mixed-model for repeated-measures (MMRM), including time effects as a categorical variable, treatment, and treatment by time interaction. They were adjusted in relation to the baseline score, with the consideration of an unstructured covariance matrix. The model also included random effects on the intercept to reflect any individual deviance from the mean intercept.

Time to deterioration HRQoL (TTD) of the SF-12 scores was also used as the modality of longitudinal analysis. It was defined as the interval between randomization and the occurrence of the first deterioration representing a minimal important difference (MID) of at least 5 points (22) compared to the HRQoL score at baseline for each component summary (23). Patients without deterioration detected were censored at the last HRQoL evaluation date. Patients with baseline scores but no follow-up score were censored immediately after baseline (Day 1). Only questionnaires completed at the planned measurement times according to the protocol were included in the analysis.

The TTD curves were calculated using the Kaplan–Meier estimation method, described using medians with 95% confidence intervals (Cis), and compared between treatment arms using log-rank

tests. Associations between TTD and the variables used as stratification factors for randomization (stage (cI–II vs. III), histology (adenocarcinomas vs. others), perioperative chemotherapy (yes vs. no), and perioperative radiotherapy (yes vs. no)) and variables known to be able to influence HRQoL evaluations (age, gender, smoking status) were assessed in univariate Cox proportional hazards regression models, and hazard ratios (HRs) with their 95% CIs provided (24). After consideration of collinearity between variables, all variables with a univariate p value <0.1 were eligible for a multivariate Cox regression model. The treatment arm variable was forced into the multivariate model.

For penibility score analysis, two MMRM analyses were performed, one considering the follow-up treatment group and the other considering the type of follow-up (fibre-optic bronchoscopy vs. CT scan) in the CT-based follow-up group following the same previous methodology.

A p value of 0.05 or lower was considered statistically significant. No adjustment for multiple testing was made since HRQoL was a secondary endpoint. The P value was interpreted for an exploratory purpose. All analyses were performed using SAS software, Version 9.4 (SAS Institute), and R software (Version 4.1).

## **Results**

### ***Patients and HRQoL scores at baseline***

Between January 2005 and November 2012, 1775 patients were randomized in the IFCT-0302 trial (minimal follow-up group: 888 patients; CT-based follow-up group: 887 patients) (11). Seventy-one patients were ineligible and included in the ITT population. At baseline, 756 of 888 patients (85.14%) in the minimal follow-up group arm answered the SF-12 questionnaire without any missing data at baseline, *versus* 747 of 887 (84.22%) in the CT-based follow-up group arm (Figure 1). The HRQoL analyses were carried out on this population of 1503 patients (mITT1 population). The baseline



characteristics and OS of these patients did not differ between the ITT and mITT1 populations (Supplementary Table 1, Supplementary Figure 1a) or between groups in the mITT1 population (Table 1, Supplementary Figure 2a). In the mITT1 population, the median age was 63 years (IQR=13.61). They comprised 1145 males (76.2%), 131 nonsmokers (8.72%), 1071 stage  $\leq$ IIA (71.3%), and 888 adenocarcinomas (59.1%) (Table 1). Postoperative chemotherapy, radiotherapy, or both was administered in 592 (39.4%) of 1503 patients, and postoperative radiotherapy was administered in 121 (8.1%) of 1503 patients. The mean score for the Physical Component Summary at baseline was 37.0 (SD=7.3) in the minimal follow-up group and 37.8 (SD=7.7) in the CT-based follow-up group ( $p=0.04$ ). The mean scores for the Mental Component Summary at baseline were 44.1 (SD=10.5) and 43.5 (SD=10.6), respectively ( $p=0.35$ ) (Supplementary Table 2).

### ***Compliance with the HRQoL questionnaires during follow-up***

Patient compliance with the HRQoL questionnaires over time is presented in Figure 1. The total numbers of questionnaires completed with at least one HRQoL score available among patients remaining in the study were 951 for 1215 patients (78.3%) at 1 year and 370 for 628 patients (58.9%) at 5 years. From months 6 and 12, the compliance was significantly higher in the minimal follow-up group ( $P$  value chi-square = 0.009 and  $P = 0.027$ , respectively).

### ***Longitudinal analyses of HRQoL***

In the prespecified MMRM analysis of mean change between baseline and each measurement time, we found that for Physical Component Summary and Mental Component Summary and for each group, patients reported an improvement in their HRQoL in 2 phases: a first phase of rapid improvement in HRQoL during the first year and then a second phase of overall stagnation after this first year (Figure 2). For the SF-12 physical component summary, the mean changes between baseline and 1 year were + 6.4 *versus* + 0.5 between 1 year and 5 years in the minimal follow-up group and +

5.4 *versus* - 0.01 in the CT-based follow-up group, respectively. We found no significant difference over time across groups in either component summary (p value for interaction term between time and group =0.6084 and 0.2370 for physical and mental component summary, respectively).

In the TTD analysis, there was no difference between follow-up groups for the SF-12 physical component summary (HR = 1.13; 95% CI, 0.92–1.38; log-rank p = 0.24) or for the SF-12 mental component summary (HR = 0.97; 95% CI, 0.82–1.15; log-rank p = 0.74) (Figure 3). There were no differences between arms in terms of TTD for any of the subgroups analyzed for the SF-12 physical component summary (Supplementary Figure 3) and for the SF-12 mental component summary (Supplementary Figure 4).

In the univariate Cox analyses, the only variable that was significantly associated with an increased SF-12 physical component summary was female sex (HR = 0.72; 95% CI, 0.56–0.93; p = 0.01) (Table 2). In a multivariate Cox analysis, in which sex, age and smoking status were entered, age < 65 years was the only variable independently associated with a longer TTD for the SF-12 physical component summary (HR = 0.81; 95% CI, 0.65–0.99; P = 0.037) (Table 2). In univariate and multivariate Cox analyses, no variable significantly influenced the TTD for the SF-12 mental component summary (Table 3).

### ***Penibility***

At baseline, 629 of 888 patients (70.83%) in the minimal follow-up group answered the penibility scale prompts without aberrant data, *versus* 635 of 887 (71.59%) in the CT-based follow-up group (Supplementary Figure 5). Penibility analyses were carried out on this population of 1264 patients (mITT2 population). No differences in terms of baseline characteristics or OS were observed between the non-mITT2 population (Supplementary Table 1, Supplementary Figure 1b) and the mITT2 population or between groups in the mITT2 population (Table 1, Supplementary Figure 2b). In this mITT2 population, the scores were not different at baseline between groups (Supplementary Table

3). In the MMRM analysis of mean changes between baseline and each measurement time, the penibility decreased faster in the minimal follow-up group (interaction term p value<0.0001; mean difference between 1 year and baseline: -0.87 (SD=2.4) and -0.26 (SD=3.0) for the minimal follow-up and CT-based follow-up groups, respectively) (Supplementary Figure 6). Fibre-optic bronchoscopy was found to be negatively associated with the CT-based follow-up group, influencing the penibility score (Supplementary Table 4) (at 2 years in the minimal follow-up group, mean difference between no fibre-optic bronchoscopy and fibre-optic bronchoscopy: 1.45; p < 0.0001). When we compared the scores of patients who received only a CT scan, the penibility of the no fibre-optic bronchoscopy group was closer to that of the minimal follow-up group (Supplementary Figure 7; mean change between 1 year and baseline =-0.87 (SD=2.4), -0.47 ((SD=2.9), 0.19 ((SD=3.2) in the minimal follow-up, no fibre-optic bronchoscopy and fibre-optic bronchoscopy groups, respectively).

## **Discussion**

The addition of chest CT scans (plus fibre-optic bronchoscopy in nonadenocarcinoma histology) to the follow up after surgery for NSCLC did not influence the HRQoL in the IFCT-0302 trial. The penibility was significantly higher in the CT-based follow-up group due to the addition of fibre-optic bronchoscopy. Although there are data reporting HRQoL after complete resection for NSCLC (25, 26), to our knowledge, there is no study evaluating the relationship between follow-up procedures and HRQoL.

Longitudinal analysis of HRQoL in the IFCT-0302 study showed a first phase of improvement in HRQoL during the first postoperative year, particularly during the first six months (Figure 2). For the SF-12 physical component summary, the mean changes between baseline and 6 months were + 4.7 in the minimal follow-up group and + 3.7 in the CT-based follow-up group, and the mean changes between 6 months and 12 months were + 2.4 in the minimal follow-up group and + 1.6 in the CT-

based follow-up group. The same improvement in HRQoL was observed in the systematic review by Gazala and colleagues in 393 patients undergoing thoracotomy in 5 mainly retrospective studies (27). They concluded that postoperatively, there was an initial decline in HRQoL (mainly in the physical component) followed by a return to preoperative HRQoL scores approximately three months after surgery evaluated using different HRQoL scales (European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (cancer core questionnaire), EORTC QLQ-LC13 lung cancer-specific module and SF-36). Even after bronchial sleeve lobectomy or pneumonectomy, as reported by Balduyck and colleagues in 100 consecutive patients with a diagnosis of NSCLC, the HRQoL (assessed using EORTC QLQ-C30 and the EORTC QLQ-LC13) improved during the first year, although this improvement was slow and did not return to the preoperative score (28). In the IFCT-0302 study, there was no evaluation of HRQoL before surgery, as patients were randomized postoperatively, but the HRQoL scores at one year were close to those of the general population (11). Szeliga and colleagues showed in a prospective cohort of 72 patients (52 men and 20 women) who underwent the surgical removal of lung cancer that the mental component summary of the HRQoL was only impaired during the first week after surgery (29). In the same cohort, surgery was found to have a major impact on physical functioning in the week after the operation, and a return to the preoperative score was observed six months after treatment. In the systematic review by Gazala and colleagues, 11.5% of patients underwent video-assisted thoracic surgery (VATS), which was associated with a more rapid improvement in HRQoL (27). In the IFCT-0302, fewer than 10 patients in each arm underwent VATS. We do not know whether the patient HRQoL returned to the preoperative scores, but the initial improvement in HRQoL is concordant with the literature, with the main improvement occurring during the first 6 months (29). The slope of HRQoL improvement over one year might be explained by the fact that most lung cancer resections in France were performed with open thoracotomy during the period of the study.

In the IFCT-0302 study, there was no significant difference in the HRQoL scores between the 2

follow-up groups. Based on screening studies (30, 31), patient perceptions of follow-up may include a fear of cancer recurrence or a second primary cancer diagnosis, penibility of procedures and patient concerns over radiation exposure (32). In the NLST, Nelson and PAN-CAN trials, no significant differences were found in HRQoL physical and mental components and state anxiety at 1 or 6 months by screening arm or after screening among participants who screened false-positive, positive for significant incidental findings, or negative. In the NLST, 2812 participants who had baseline HRQoL assessments were asked to complete the Short Form-36. The only significant difference in HRQoL scores during screening consisted of lower physical and mental health scores and higher state anxiety for those who screened true-positive and developed lung cancer within 1 year of their screening examination compared with all other screening groups (31). In the IFCT-0302 study, recurrence, as reported by the investigators, occurred in 246 patients (27.7%) in the minimal follow-up group and 289 (32.6%) in the CT-based follow-up group. Second primary lung cancers (SPLCs) were diagnosed in 102 patients (11.5%) in the minimal follow-up group and in 96 (10.8%) in the CT-based follow-up group. Therefore, the absence of a significant difference between the 2 follow-up groups in terms of diagnosis of recurrence or SPLC may explain the absence of a difference in the HRQoL results. Penibility was increased in the CT scan follow-up group because of fibre-optic bronchoscopy, which is more invasive than CT scans. Because it rarely leads to the detection of recurrence or second primary cancer in cases of normal thoracic CT scans, fibre-optic bronchoscopy is not recommended in guidelines for the follow-up of patients after curative-intent surgery for NSCLC (4, 5, and 6).

Multivariate Cox analysis in the present study revealed that only an age under 65 years was independently associated with a longer TTD for the physical component summary of the SF-12. In a study of 1718 (23.6%) patients who underwent curatively intended surgery, Brønserud MM et al showed that age under 70 years, along with earlier pathological cancer stage, nonsquamous histology, better forced expiratory volume, ECOG PS 0 or 1, a Charlson score of 0 or 1, high educational level, high disposable income, affiliation with the work market, and living with a partner, was only

associated with a better role functioning score using EORTC QLQ-C30 (24). Follow-up strategies were not analyzed in this study. Despite a thorough preoperative workup taking into account comorbidities, elderly patients remain at higher risk of morbi-mortality after lung cancer surgery, which can explain their impaired HRQoL (33).

In our trial, compliance levels were high at baseline, with approximately 12% missing data. Long-term compliance was good, with over 50% of patients answering the questionnaires at 5 years, which compares favorably with published compliance rates (31, 34). In another study evaluating compliance with HRQoL questionnaires published by Brønserud et al. and involving 7295 lung cancer patients, including 1718 operated patients, only 4229 (58%) completed at least one questionnaire (1315 [77%] of the operated patients). In this same cohort, the best response rates were achieved among patients treated with surgery and among patients who discussed their questionnaires with health care personnel. Responders had significantly better health and a higher socioeconomic position than nonresponders (34). In the NLST study, 1450 of the 11,581 screened patients responded to the HRQoL questionnaires at T1 of screening. To the best of our knowledge, imputation techniques for missing data are only exploratory and not validated and are not yet recommended for longitudinal HRQoL calculations using survival analyses such as TTD. There was no significant difference in HRQoL and penibility between compliant and noncompliant patients at baseline in either baseline characteristics or OS.

Certain other limitations of this analysis should be acknowledged. Since we randomly assigned patients after surgery, these HRQoL data did not fully evaluate the patient experience from the time of diagnosis. However, this delay is unlikely to have affected the results. Moreover, these prespecified and post hoc analyses remain exploratory and therefore lack formal statistical testing for some outcomes.

In conclusion, the analysis of HRQoL and penibility in the IFCT-0302 trial, which demonstrated no difference in survival between a follow-up with chest CT scan and fibre-optic bronchoscopy and a

follow-up based only on physical examination and chest X-ray after curative-intent surgery for lung cancer, showed no difference in HRQoL. Penibility was increased in patients who underwent fibre-optic bronchoscopy in the CT-based follow-up arm. These HRQoL and penibility results, along with the detection of more recurrences and SPLCs with thoracic CT scans, which were more frequently asymptomatic, at an early stage and more frequently accessible to curative treatment, support its use for the follow-up of patients operated on for NSCLC.

## **ACKNOWLEDGMENTS**

This study was supported by the French Health Ministry (PHRC 2003/2012), French National Cancer Institute (INCa–PNES Poumon), Weisbrem-Benenson Foundation, La Ligue Nationale Contre Le Cancer, and Lilly Oncology. We thank the trial participants and their families, all investigators, the staff of the Intergroupe Francophone de Cancérologie Thoracique, Alain Depierre, Silvy Laporte, Astrid Pozet, Mariette Mercier, Marie-Christine Woronoff-Lemsi, Franck Bonnetain, Brigitte Depierre, Alexandra Land and Marie Paule Lebitasy.

## **CONFLICT OF INTEREST STATEMENT**

The authors declare no conflicts of interest.

## **FUNDING SOURCES**

None

## **AUTHOR CONTRIBUTIONS**

The scientific guarantor of this publication is V.W.

J.H., D.V., A.L. and A.A. have significant statistical expertise.

The study protocol follows the ethical guidelines of the Helsinki Declaration and was approved by the institutional review board.

G.E., V.W., F.M. : Conceptualization, Methodology, Formal analysis, Investigation and Writing — Original Draft, Writing — Review & Editing — M.M., E.G-L., E.K., A.B-T., P.R., S.B., C.A-V.,

H.B., F.D., A.L., P.B. : Investigation, Writing — J.H., D.V., A.L. and A.A.: Methodology, Formal analysis, Writing.



## FIGURE and TABLE LEGENDS

Table 1: Baseline characteristics of the mITT1 and mITT2 populations by follow-up group.

Table 2: Univariate and multivariate Cox models for time to deterioration of the SF-12 physical component summary.

Table 3: Univariate Cox model for time to deterioration of the SF-12 mental component summary.

Figure 1: Flowchart for HRQoL data.

Figure 2: Changes in the SF-12 physical (A) and mental (B) summary components between baseline and each measurement time, presented as a plot of the least mean square change from baseline with 95% CI bars from the mixed model for repeated measures-adjusted scores.

Figure 3: Time to deterioration of the SF-12 (A) physical component summary and (B) mental component summary.

Supplementary Table 1: Patient characteristics between mITT populations (mITT1 and mITT2) and non-mITT populations.

Supplementary Table 2: Descriptive analysis of the HRQoL for two summary component of the SF-12 questionnaire at each measurement time

Supplementary Table 3: Descriptive analyze of penibility scale scores according to the randomization group at each measurement time

Supplementary Table 4: Penibility scale scores according to the randomization group and the performance of fibre-optic bronchoscopy

Supplementary Figure 1: Overall survival in the ITT population regarding completion of the SF-12 (A) and penibility scale (B) at baseline

Supplementary Figure 2: Overall survival in the mITT1 (A) and mITT2 (B) populations by follow-up group.

Supplementary Figure 3: Time to deterioration of symptoms, subgroup analysis, forest plot for the physical component summary.

Supplementary Figure 4: Time to deterioration of symptoms, subgroup analysis, forest plot, for the mental component summary.

Supplementary Figure 5: Flow chart for the penibility scale data

Supplementary Figure 6: Changes in penibility between baseline and each measurement time in the mITT2 population. Plot of the least mean square change from baseline with 95% CI bars from the mixed model for repeated measures-adjusted scores.

Supplementary Figure 7: Changes in penibility between baseline and each measurement time in the mITT2 population depending on having follow-up by CT scan alone, fibre-optic bronchoscopy and CT scan and neither (minimal follow-up). Plot of the least mean square change from baseline with 95% CI bars from the mixed model for repeated measures-adjusted scores.

## REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 2021; 71 (3): 209-249.
2. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *New England Journal of Medicine*, 2020; 383 (7): 640-649.
3. Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology*, 2016; 11 (1): 39-51.
4. Ettinger DS, Wood DE, Aisner DL, *et al.* Non–small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, 2022; 20 (5): 497-530.
5. Colt HG, Murgu SD, Korst RJ, *et al.* Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 2013; 143 (5): e437S-e454S.
6. Postmus PE, Kerr KM, Oudkerk M, *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology*, 2017; 28: iv1-iv21.
7. Schneider BJ, Ismaila N, Aerts J, *et al.* Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. *Journal of Clinical Oncology*, 2020; 38 (7): 753-766.
8. Beitz J, Gnecco C, Justice R. Quality-of-life end points in cancer clinical trials: The US food and drug administration perspective. *J Natl Cancer Inst Monogr* 1996; 20: 7–9.
9. Zheng L, Song P, Jiang Y, *et al.* Outcomes and quality of life after Robot-assisted lobectomy/segmentectomy for lung cancer compared to video-assisted thoracoscopic surgery: both

three-port procedures performed by a single surgeon. *J Thorac Dis.* 2022 Mar; 14 (3): 689-698.

10. Stamatis G, Leschber G, Schwarz B, Brintrup DL, Ose C. Perioperative course and quality of life in a prospective randomized multicenter phase III trial, comparing standard lobectomy versus anatomical segmentectomy in patients with non-small cell lung cancer up to 2 cm, stage IA (of TNM staging system). *Lung Cancer*, 2019; 138: 19-26.

11. Westeel V, Foucher P, Scherpereel A. Chest CT scan plus x-ray versus chest x-ray for the follow-up of completely resected non-small-cell lung cancer (IFCT-0302): a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*, 2022; 23 (9): 1180-1188.

12. Ware JE, Keller SD, & Kosinski M. SF-12: How to score the SF-12 physical and mental health summary scales. Health Institute, New England Medical Center, 1995. ISO 690

13. Ware Jr JE, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Lincoln, RI: QualityMetric, Inc., 2000.

14. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med* 1997; 19: 179–86.

15. Ware J Jr., Kosinski M, Keller SD. A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Medical care*. 1996; 34: 220–233

16. Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the medical expenditure panel survey. *Qual Life Res.* 2009; 18: 727–35.

17. Van den Bergh KA, Essink-Bot ML, Borsboom GJ, *et al.* Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *British journal of cancer*, 2010; 102 (1): 27-34.

18. Taghizadeh N, Tremblay A, Cressman S, *et al.* Health-related quality of life and anxiety in the PAN-CAN lung cancer screening cohort. *BMJ open*, 2019; 9 (1): e024719.

19. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. User's manual for the SF-12v2(R) health survey. Lincoln, Rhode Island: QualityMetric Inc., 2009.
20. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *International Quality of Life Assessment. J Clin Epidemiol*, 1998; 51 (11): 1171-8.
21. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013; 309: 814–22.
22. Osoba D, Rodrigues G, Myles J, *et al.* Interpreting the significance of changes in health-related quality-of-life scores. *Journal of clinical oncology*, 1998; 16 (1): 139-144.
23. Anota A, Hamidou Z, Paget-Bailly S *et al.* Time to health-related quality of life score deterioration as a modality of longitudinal analysis for health-related quality of life studies in oncology: do we need RECIST for quality of life to achieve standardization?. *Qual Life Res*, 2015; 24: 5–18
24. Brønserud MM, Iachina M, Green A, Groenvold M, & Jakobsen E. Patient reported outcome data as performance indicators in surgically treated lung cancer patients. *Lung Cancer*, 2019; 130: 143-148.
25. Brunelli A, Soggi L, Refai M, Salati M, Xiumé F, & Sabbatini A. Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis. *The Annals of thoracic surgery*, 2007; 84 (2): 410-416.
26. Win T, Sharples L, Wells FC, Ritchie AJ, Munday H, & Laroche CM. Effect of lung cancer surgery on quality of life. *Thorax*, 2005; 60 (3): 234-238.
27. Gazala S, Pelletier JS, Storie D, *et al.* A systematic review and meta-analysis to assess patient-reported outcomes after lung cancer surgery. *The Scientific World Journal*, 2013.

28. Balduyck B, Hendriks J, Lauwers P, *et al.* Quality of Life after Lung Cancer Surgery: A Prospective Pilot Study comparing Bronchial Sleeve Lobectomy with Pneumonectomy. *Journal of Thoracic Oncology*, 2008; 3 (6): 604-608.
29. Szeliga E, Czenczek-Lewandowska E, Kontek A, *et al.* Evaluation of the quality of life after surgical removal of lung cancer. *Advances in Respiratory Medicine*, 2019; 87 (1): 14-19.
30. Taghizadeh N, Tremblay A, Cressman S, *et al.* Health-related quality of life and anxiety in the PAN-CAN lung cancer screening cohort. *BMJ open*, 2019; 9 (1): e024719.
31. Gareen IF, Duan F, Greco EM, *et al.* Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. *Cancer*, 2014; 120 (21): 3401-3409.
32. Wang GX, Baggett TP, Pandharipande PV, Park ER, *et al.* Barriers to lung cancer screening engagement from the patient and provider perspective. *Radiology*, 2019; 290 (2): 278-287.
33. Pagès PB, Mariet AS, Madelaine L, Cottenet J, Abou Hana A, Quantin C, *et al.* Impact of video-assisted thoracic surgery approach on postoperative mortality after lobectomy in octogenarians. *J Thorac Cardiovasc Surg.* 2019; 157: 1660-7.
34. Brønserud MM, Iachina M, Green A, Groenvold M, Dørflinger L, & Jakobsen E. Patient-reported outcomes (PROs) in lung cancer: Experiences from a nationwide feasibility study. *Lung Cancer*, 2019; 128: 67-73.

**Table 1: Baseline characteristics of the mITT1 and mITT2 populations by follow-up group**

|  |                          | mITT1 population                 |       |                                   |       | p value | mITT2 population                 |       |                                   |       | p value |
|--|--------------------------|----------------------------------|-------|-----------------------------------|-------|---------|----------------------------------|-------|-----------------------------------|-------|---------|
|  |                          | Minimal follow-up group<br>n=756 |       | CT-based follow-up group<br>n=747 |       |         | Minimal follow-up group<br>n=629 |       | CT-based follow-up group<br>n=635 |       |         |
| <b>Sex</b>   |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | Male                     | 575                              | 76.06 | 570                               | 76.31 | 0.9105  | 481                              | 76.47 | 481                               | 75.75 | 0.7633  |
|  | Female                   | 181                              | 23.94 | 177                               | 23.69 |         | 148                              | 23.53 | 154                               | 24.25 |         |
| <b>Median age, years (IQR)</b>   |                          | median 63.34 (13.35)             |       | 62.8 (14.21)                      |       | 0.2110  | 63,16 (13,33)                    |       | 62,8 (14,59)                      |       | 0.3803  |
| <b>Smoking status</b>  |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | Former or current smoker | 693                              | 91.77 | 679                               | 90.90 | 0.6938  | 582                              | 92.53 | 579                               | 91.18 | 0.6938  |
|  | Never smoker             | 63                               | 8.33  | 68                                | 9.10  |         | 47                               | 7.47  | 56                                | 8.82  |         |
| <b>Fibre-optic bronchoscopy</b>  |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | No                       | 43                               | 5.69  | 36                                | 4.82  | 0.4506  | 34                               | 5.41  | 29                                | 4.57  | 0.4934  |
|  | Yes                      | 713                              | 94.31 | 711                               | 95.18 |         | 595                              | 94.59 | 606                               | 95.43 |         |
| <b>Clinical stage</b>  |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | I                        | 519                              | 68.65 | 506                               | 67.74 | 0.7664  | 427                              | 67.89 | 439                               | 69.13 | 0.8162  |
|  | II                       | 103                              | 13.62 | 103                               | 13.79 |         | 84                               | 13.35 | 85                                | 13.39 |         |
|  | III                      | 134                              | 17.72 | 137                               | 18.34 |         | 118                              | 18.76 | 110                               | 17.32 |         |
|  | IV                       | 0                                | 0     | 1                                 | 0.13  |         | 0                                | 0     | 1                                 | 0.16  |         |
| <b>Histological subtype</b>  |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | Adenocarcinoma           | 444                              | 58.73 | 444                               | 59.44 | 0.7583  | 376                              | 59.78 | 375                               | 59.06 | 0.8322  |
|  | Squamous                 | 267                              | 35.32 | 250                               | 33.47 |         | 215                              | 34.18 | 214                               | 33.70 |         |
|  | Large cell               | 32                               | 4.23  | 37                                | 4.95  |         | 25                               | 3.97  | 32                                | 5.04  |         |
|  | Others                   | 13                               | 1.72  | 16                                | 2.14  |         | 13                               | 2.07  | 14                                | 2.20  |         |
| <b>Surgery</b>   |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | Lobectomy or bilobectomy | 654                              | 86.51 | 653                               | 87.42 | 0.7933  | 544                              | 86.62 | 562                               | 88.64 | 0.5440  |
|  | Pneumonectomy            | 89                               | 11.77 | 80                                | 10.71 |         | 72                               | 11.46 | 61                                | 9.62  |         |
|  | Segmentectomy            | 13                               | 1.72  | 14                                | 1.87  |         | 12                               | 1.91  | 11                                | 1.74  |         |
| <b>Preoperative chemotherapy, or preoperative radiotherapy or both</b> |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | No                       | 671                              | 88.76 | 650                               | 87.02 | 0.3007  | 559                              | 88.87 | 557                               | 87.72 | 0.5232  |
|  | Yes                      | 85                               | 11.24 | 97                                | 12.98 |         | 70                               | 11.13 | 78                                | 12.28 |         |
| <b>Postoperative chemotherapy, radiotherapy, or both</b>               |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | No                       | 467                              | 61.77 | 444                               | 59.44 | 0.3543  | 392                              | 62.32 | 379                               | 59.69 | 0.3367  |
|  | Yes                      | 289                              | 38.23 | 303                               | 40.56 |         | 237                              | 37.68 | 256                               | 40.31 |         |
| <b>Preoperative or postoperative radiotherapy, or both</b>             |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | No                       | 689                              | 91.14 | 678                               | 90.76 | 0.8002  | 572                              | 90.94 | 578                               | 91.02 | 0.9576  |
|  | Yes                      | 67                               | 8.86  | 69                                | 9.24  |         | 57                               | 9.06  | 57                                | 8.98  |         |
| <b>Preoperative or postoperative chemotherapy, or both</b>             |                          |                                  |       |                                   |       |         |                                  |       |                                   |       |         |
|  | No                       | 427                              | 56.48 | 398                               | 53.28 | 0.2123  | 359                              | 57.07 | 345                               | 54.33 | 0.3261  |
|  | Yes                      | 329                              | 43.52 | 349                               | 46.72 |         | 270                              | 42.93 | 290                               | 45.67 |         |

Abbreviations: mITT, modified intent-to-treat population; IQR, interquartile range

**Table 2: Univariate and multivariate Cox model for time to deterioration of the Physical Component Summary**

|                  |                          | Univariate Cox Model |              |              |                | Multivariate Cox Model |           |               |
|------------------|--------------------------|----------------------|--------------|--------------|----------------|------------------------|-----------|---------------|
|                  |                          | n (events)           | Hazard Ratio | 95% CI       | p value        | Hazard Ratio           | 95% CI    | p value       |
| Group            | Minimal follow-up        | 756 (189)            | 1.000        |              | 0.23661        | 1.000                  |           | 0.2235        |
|                  | CT based follow-up       | 747 (188)            | 1.130        | 0.92 to 1.38 |                | 1.13                   | 0.93-1.39 |               |
| Sex              | Male                     | 1145 (302)           | 1.000        |              | <b>0.01223</b> | 1.000                  |           | 0.0712        |
|                  | Female                   | 358 (75)             | 0.723        | 0.56 to 0.93 |                | 0.77                   | 0.58-1.02 |               |
| Age              | <65                      | 861 (203)            | 1.000        |              | <b>0.06005</b> | 1.000                  |           | <b>0.0365</b> |
|                  | >=65                     | 642 (174)            | 1.215        | 0.99 to 1.49 |                | 1.24                   | 1.01-1.53 |               |
| Smoking status   | Former or current smoker | 1372 (350)           | 1            | 0.49 to 1.06 | 0.09875        |                        |           |               |
|                  | Never smoker             | 131 (27)             | 0.719        |              |                |                        |           |               |
| Surgery          | Lobectomy or bilobectomy | 1307 (330)           | 1.000        |              | 0.36374        |                        |           |               |
|                  | Pneumonectomy            | 169 (37)             | 0.993        | 0.71 to 1.39 |                |                        |           |               |
|                  | Segmentectomy            | 27 (10)              | 1.576        | 0.84 to 2.96 |                |                        |           |               |
| Histology        | Adenocarcinoma           | 888 (230)            | 1.000        |              | 0.45541        |                        |           |               |
|                  | Other                    | 615 (147)            | 0.924        | 0.75 to 1.14 |                |                        |           |               |
| Stage            | I/II                     | 1231 (320)           | 1.000        |              | 0.97161        |                        |           |               |
|                  | III                      | 271 (57)             | 1.005        | 0.76 to 1.33 |                |                        |           |               |
| Perioperative rt | No                       | 1367 (349)           | 1.000        |              | 0.64361        |                        |           |               |
|                  | Yes                      | 136 (28)             | 1.095        | 0.74 to 1.61 |                |                        |           |               |
| Perioperative ct | No                       | 825 (214)            | 1.000        |              | 0.41480        |                        |           |               |
|                  | Yes                      | 678 (163)            | 1.088        | 0.89 to 1.33 |                |                        |           |               |

**Table 3: Univariate Cox model for time to deterioration of the Mental Component Summary**

|       |                    | n (events) | Hazard Ratio | 95% CI       | p value |
|-------|--------------------|------------|--------------|--------------|---------|
| Group | Minimal follow-up  | 756 (288)  | 1.000        |              | 0.73260 |
|       | CT based follow-up | 747 (263)  | 0.971        | 0.82 to 1.15 |         |
| Sex   | Male               | 1145 (418) | 1.000        |              | 0.74790 |
|       | Female             | 358 (133)  | 0.969        | 0.80 to 1.18 |         |
| Age   | <65                | 861 (321)  | 1.000        |              | 0.83804 |
|       | >=65               | 642 (230)  | 0.982        | 0.83 to 1.16 |         |



|                  |                          |            |       |              |         |
|------------------|--------------------------|------------|-------|--------------|---------|
| Smoking status   | Former or current smoker | 1372 (501) | 1     |              | 0.90481 |
|                  | Never smoker             | 131 (50)   | 0.98  | 0.74 to 1.32 |         |
| Surgery          | Lobectomy or bilobectomy | 1307 (493) | 1.000 |              | 0.34633 |
|                  | Pneumonectomy            | 169 (49)   | 0.807 | 0.60 to 1.08 |         |
|                  | Segmentectomy            | 27 (9)     | 0.895 | 0.46 to 1.73 |         |
| Histology        | Adenocarcinoma           | 888 (333)  | 1.000 |              | 0.61494 |
|                  | Other                    | 615 (218)  | 0.957 | 0.81 to 1.14 |         |
| Stage            | I/II                     | 1231 (463) | 1.000 |              | 0.56709 |
|                  | III                      | 271 (88)   | 1.069 | 0.85 to 1.34 |         |
| Perioperative rt | No                       | 1367 (517) | 1.000 |              | 0.63821 |
|                  | Yes                      | 136 (34)   | 0.920 | 0.65 to 1.30 |         |
| Perioperative ct | No                       | 825 (321)  | 1.000 |              | 0.78980 |
|                  | Yes                      | 678 (230)  | 1.023 | 0.86 to 1.21 |         |

Figure 1: Flow chart for health-related quality of life data.

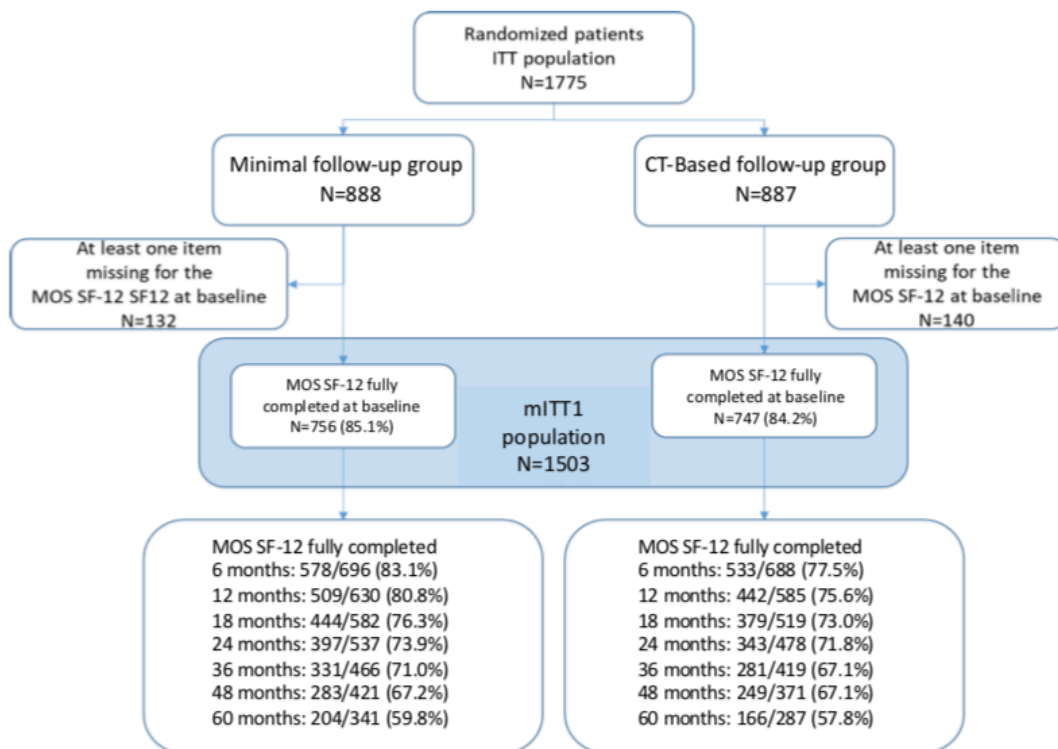


Figure 2: Plot of the least mean square change from baseline with 95% CI bars from MMRM for the physical component summary (A) and mental component summary (B)

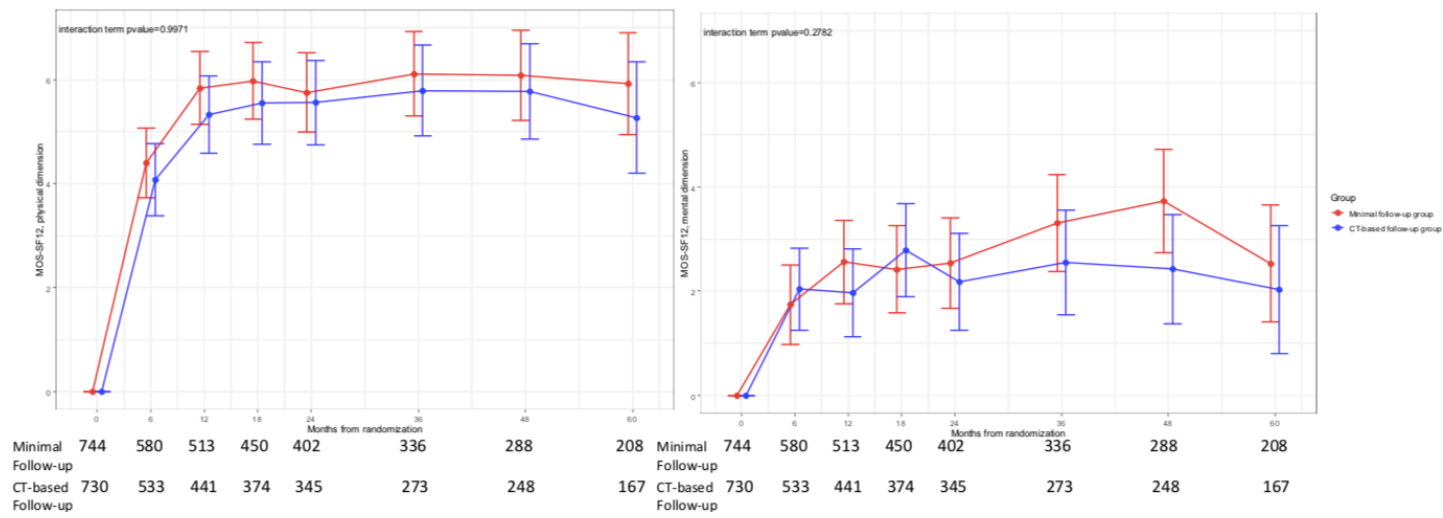
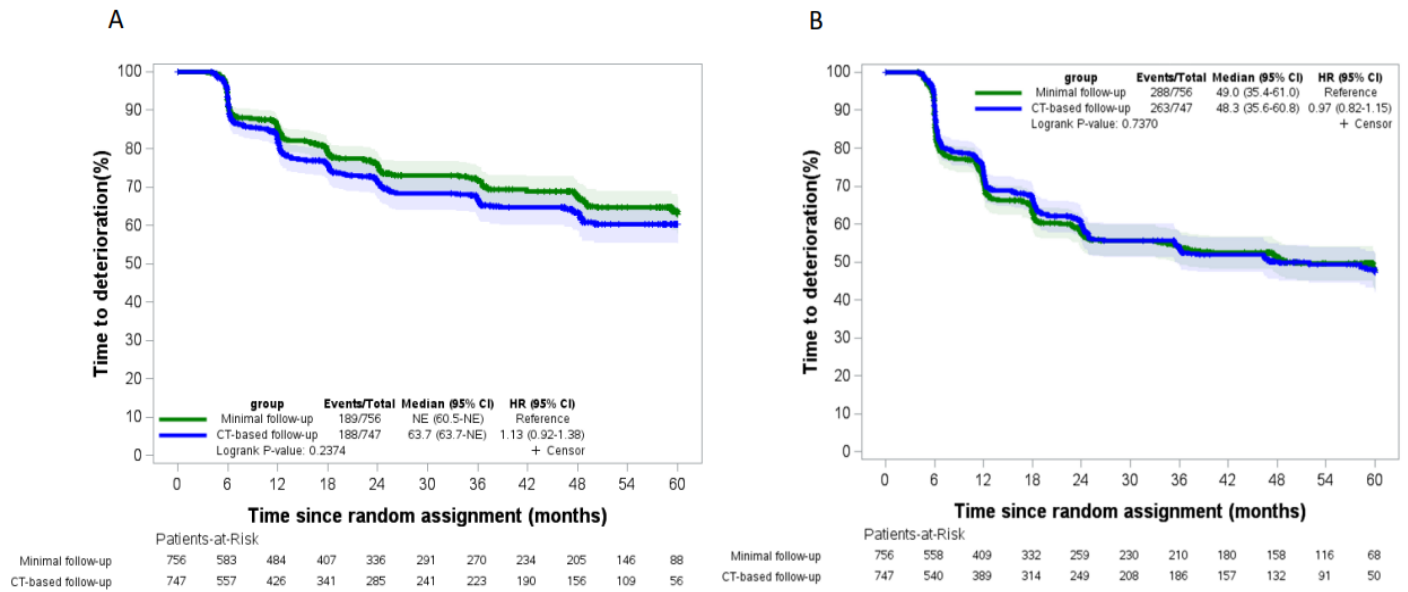


Figure 3: Time to deterioration of the SF-12 (A) Physical component summary and (B) Mental component summary in the mITT1 population.



Supplementary Table 1: Patient characteristics between mITT populations (mITT1 and mITT2) and non-mITT populations.

|  |                          | ITT<br>population<br>n=1775 |       | Non-mITT1<br>population<br>n=272 |       | mITT1<br>population<br>n=1503 |       | p value | Non-mITT2<br>population<br>n=272 |       | mITT2<br>population<br>n=1264 |       | p value |
|--|--------------------------|-----------------------------|-------|----------------------------------|-------|-------------------------------|-------|---------|----------------------------------|-------|-------------------------------|-------|---------|
|  |                          | n                           | %     |                                  |       |                               |       |         |                                  |       |                               |       |         |
| <b>Sex</b>   | Male                     | 1355                        | 76.34 | 210                              | 77.21 | 1145                          | 76.18 | 0.7144  | 393                              | 76.91 | 962                           | 76.11 | 0.7194  |
|  | Female                   | 420                         | 23.66 | 62                               | 22.79 | 358                           | 23.82 |         | 118                              | 23.09 | 302                           | 23.89 |         |
| <b>Median age, years (IQR)</b>   |                          | 62.96 (13.80)               |       | 62.53 (14.21)                    |       | 63.03 (13.61)                 |       | 0.6332  | 63.03 (13.58)                    |       | 62.95 (13.96)                 |       | 0.8642  |
| <b>Smoking status</b>  |                          |                             |       |                                  |       |                               |       | 0.4108  |                                  |       |                               |       | 0.8212  |
|  | Former or current smoker | 1627                        | 91.75 | 255                              | 93.68 | 1372                          | 91.28 |         | 227                              | 91.14 | 1161                          | 91.85 |         |
|  | Never smoker             | 148                         | 8.35  | 17                               | 6.32  | 131                           | 8.72  |         | 45                               | 8.86  | 103                           | 8.15  |         |
| <b>Fibre-optic bronchoscopy</b>  |                          |                             |       |                                  |       |                               |       | 0.4221  |                                  |       |                               |       | 0.7743  |
|  | No                       | 90                          | 5.08  | 11                               | 4.09  | 79                            | 5.26  |         | 27                               | 5.31  | 63                            | 4.98  |         |
|  | Yes                      | 1682                        | 94.92 | 258                              | 95.91 | 1424                          | 94.74 |         | 481                              | 94.69 | 1201                          | 95.02 |         |
|  | Unknown                  | 3                           |       | 3                                |       | 0                             |       |         | 3                                |       | 0                             |       |         |
| <b>Clinical stage</b>  |                          |                             |       |                                  |       |                               |       | 0.9035  |                                  |       |                               |       | 0.7796  |
|  | I                        | 1205                        | 68.00 | 180                              | 66.91 | 1025                          | 68.20 |         | 339                              | 66.73 | 866                           | 68.51 |         |
|  | II                       | 244                         | 13.77 | 38                               | 14.13 | 206                           | 13.71 |         | 75                               | 14.76 | 169                           | 13.37 |         |
|  | III                      | 322                         | 18.17 | 51                               | 18.96 | 271                           | 18.03 |         | 94                               | 18.50 | 228                           | 18.04 |         |
|  | IV                       | 1                           | 0.06  | 0                                | 0     | 1                             | 0.07  |         | 0                                | 0     | 1                             | 0.08  |         |
|  | Unknown                  | 3                           |       | 3                                |       | 0                             |       |         | 3                                |       | 0                             |       |         |
| <b>Histological subtype</b>  |                          |                             |       |                                  |       |                               |       | 0.2632  |                                  |       |                               |       | 0.7953  |
|  | Adenocarcinoma           | 1042                        | 58.74 | 154                              | 56.83 | 888                           | 59.08 |         | 291                              | 57.06 | 751                           | 59.41 |         |
|  | Squamous                 | 614                         | 34.61 | 97                               | 35.79 | 517                           | 34.40 |         | 185                              | 36.27 | 429                           | 33.94 |         |
|  | Large cell               | 79                          | 4.45  | 10                               | 3.69  | 69                            | 4.59  |         | 22                               | 4.31  | 57                            | 4.51  |         |
|  | Others                   | 39                          | 2.20  | 10                               | 3.69  | 29                            | 1.93  |         | 12                               | 2.35  | 27                            | 2.14  |         |
|  | Unknown                  | 1                           |       | 1                                |       | 0                             |       |         | 1                                |       | 0                             |       |         |
| <b>Pathological stage</b>  |                          |                             |       |                                  |       |                               |       | 0.2940  |                                  |       |                               |       | 0.2259  |
|  | I                        | 1120                        | 63.71 | 157                              | 59.47 | 963                           | 64.46 |         | 306                              | 60.59 | 814                           | 64.96 |         |
|  | II                       | 323                         | 18.37 | 55                               | 20.83 | 268                           | 17.94 |         | 101                              | 20.00 | 222                           | 17.72 |         |
|  | III                      | 315                         | 17.92 | 52                               | 19.70 | 263                           | 17.60 |         | 98                               | 19.41 | 217                           | 17.32 |         |
|  | Unknown                  | 17                          |       | 8                                |       | 9                             |       |         | 6                                | 0     | 11                            |       |         |
| <b>Surgery</b>   |                          |                             |       |                                  |       |                               |       | 0.4525  |                                  |       |                               |       | 0.0731  |
|  | Lobectomy or bilobectomy | 1533                        | 86.61 | 226                              | 84.64 | 1307                          | 86.96 |         | 427                              | 84.06 | 1106                          | 87.64 |         |
|  | Pneumonectomy            | 206                         | 11.64 | 37                               | 13.86 | 169                           | 11.24 |         | 73                               | 14.37 | 133                           | 10.54 |         |
|  | Segmentectomy            | 31                          | 1.75  | 4                                | 1.50  | 27                            | 1.80  |         | 8                                | 1.57  | 23                            | 1.82  |         |
|  | Unknown                  | 5                           |       | 5                                |       | 0                             |       |         | 3                                |       | 2                             |       |         |
| <b>Preoperative chemotherapy, or preoperative radiotherapy or both</b> |                          |                             |       |                                  |       |                               |       | 0.0575  |                                  |       |                               |       | 0.0389  |
|  | No                       | 1547                        | 87.25 | 226                              | 83.70 | 1321                          | 87.89 |         | 431                              | 84.68 | 1116                          | 88.29 |         |
|  | Yes                      | 226                         | 12.75 | 44                               | 16.30 | 182                           | 12.11 |         | 78                               | 15.32 | 148                           | 11.71 |         |
|  | Unknown                  | 2                           |       | 2                                |       | 0                             |       |         |                                  | 2     |                               | 0     |         |
| <b>Postoperative chemotherapy, radiotherapy, or both</b>               |                          |                             |       |                                  |       |                               |       | 0.4932  |                                  |       |                               |       | 0.9471  |
|  | Missing                  | 3                           |       | 3                                |       | 0                             |       |         | 3                                |       | 0                             |       |         |
|  | No                       | 1080                        | 60.95 | 169                              | 62.83 | 911                           | 60.61 |         | 309                              | 60.83 | 771                           | 61.00 |         |
|  | Yes                      | 692                         | 39.05 | 100                              | 37.17 | 592                           | 39.39 |         | 199                              | 39.17 | 493                           | 39.00 |         |
| <b>Preoperative or postoperative chemotherapy, or both</b>             |                          |                             |       |                                  |       |                               |       | 0.9411  |                                  |       |                               |       | 0.2607  |
|  | Missing                  | 3                           |       | 3                                |       | 0                             |       |         | 3                                |       | 0                             |       |         |
|  | No                       | 972                         | 54.85 | 147                              | 54.65 | 825                           | 54.89 |         | 268                              | 52.76 | 704                           | 55.70 |         |

|     |     |       |     |       |     |       |     |       |     |       |
|-----|-----|-------|-----|-------|-----|-------|-----|-------|-----|-------|
| Yes | 800 | 45.15 | 122 | 45.35 | 678 | 45.11 | 240 | 47.24 | 560 | 44.30 |
|-----|-----|-------|-----|-------|-----|-------|-----|-------|-----|-------|

Abbreviations: mITT, modified intent-to-treat population; IQR, interquartile range.

Supplementary Table 2: Descriptive analysis of HRQoL for two summary components of the SF-12 questionnaire, at each measurement time

|                 |              | mITT1 Population |               |        |       | Minimal Follow-up |               |        |       | CT-Scan Follow-up |               |        |       | p value |
|-----------------|--------------|------------------|---------------|--------|-------|-------------------|---------------|--------|-------|-------------------|---------------|--------|-------|---------|
|                 |              | n                | mean (SD)     | median | IQR   | n                 | mean (SD)     | median | IQR   | n                 | mean (SD)     | median | IQR   |         |
| <b>Baseline</b> | <i>PCS12</i> | 1503             | 37.35 (7.48)  | 37.11  | 9.81  | 756               | 36.95 (7.27)  | 36.7   | 9.93  | 747               | 37.75 (7.68)  | 37.69  | 9.70  | 0.04300 |
|                 | <i>MCS12</i> | 1503             | 43.80 (10.53) | 43.47  | 16.82 | 756               | 44.07 (10.51) | 43.95  | 17.10 | 747               | 43.52 (10.55) | 43.05  | 16.71 | 0.35229 |
| <b>M6</b>       | <i>PCS12</i> | 1111             | 41.55 (8.78)  | 41.18  | 14.03 | 578               | 41.64 (8.85)  | 41.31  | 14.36 | 533               | 41.46 (8.72)  | 41.08  | 13.42 | 0.72424 |
|                 | <i>MCS12</i> | 1111             | 45.80 (10.24) | 46.64  | 16.06 | 578               | 45.77 (10.35) | 46.45  | 17.10 | 533               | 45.84 (10.14) | 46.93  | 14.87 | 0.86138 |
| <b>M12</b>      | <i>PCS12</i> | 951              | 43.16 (8.81)  | 43.55  | 13.87 | 509               | 43.24 (8.98)  | 43.67  | 13.96 | 442               | 43.07 (8.62)  | 43.45  | 13.30 | 0.71467 |
|                 | <i>MCS12</i> | 951              | 46.55 (10.24) | 48.13  | 16.87 | 509               | 46.93 (10.33) | 48.46  | 17.41 | 442               | 46.11 (10.13) | 47.94  | 15.90 | 0.16998 |
| <b>M18</b>      | <i>PCS12</i> | 823              | 43.26 (8.92)  | 43.73  | 14.06 | 444               | 43.26 (9.03)  | 44.27  | 14.26 | 379               | 43.27 (8.80)  | 42.83  | 13.86 | 0.96691 |
|                 | <i>MCS12</i> | 823              | 46.75 (10.26) | 48.6   | 15.98 | 444               | 46.57 (10.31) | 48.38  | 16.56 | 379               | 46.95 (10.21) | 48.8   | 15.17 | 0.63304 |
| <b>M24</b>      | <i>PCS12</i> | 740              | 43.36 (8.80)  | 44.33  | 13.54 | 397               | 43.30 (8.75)  | 44.35  | 13.09 | 343               | 43.42 (8.88)  | 44.31  | 14.40 | 0.82653 |
|                 | <i>MCS12</i> | 740              | 46.78 (10.29) | 48.55  | 16    | 397               | 47.01 (10.16) | 48.63  | 15.49 | 343               | 46.51 (10.44) | 48.32  | 16.26 | 0.52990 |
| <b>M36</b>      | <i>PCS12</i> | 612              | 43.69 (8.77)  | 44.69  | 13.53 | 331               | 43.79 (8.88)  | 44.91  | 14.18 | 281               | 43.58 (8.65)  | 44.63  | 13.16 | 0.71720 |
|                 | <i>MCS12</i> | 612              | 47.50 (10.57) | 50.02  | 16.02 | 331               | 47.78 (10.26) | 50.13  | 16.56 | 281               | 47.19 (10.92) | 49.87  | 15.37 | 0.55752 |
| <b>M48</b>      | <i>PCS12</i> | 532              | 43.72 (9.07)  | 44.72  | 14.08 | 283               | 43.78 (9.03)  | 44.59  | 14.05 | 249               | 43.66 (9.14)  | 45.02  | 13.82 | 0.92188 |
|                 | <i>MCS12</i> | 532              | 47.74 (9.88)  | 49.68  | 14.39 | 283               | 48.54 (9.41)  | 50.49  | 13.43 | 249               | 46.84 (10.33) | 48.99  | 14.88 | 0.08415 |
| <b>M60</b>      | <i>PCS12</i> | 370              | 43.32 (8.88)  | 43.68  | 14.31 | 204               | 43.57 (9.20)  | 44.24  | 15.41 | 166               | 43.01 (8.47)  | 43.19  | 13.27 | 0.46059 |
|                 | <i>MCS12</i> | 370              | 47.01 (9.90)  | 49.56  | 15.28 | 204               | 47.33 (9.71)  | 49.78  | 15.77 | 166               | 46.61 (10.14) | 49.09  | 14.93 | 0.56949 |

Abbreviations: mITT1, modified intent-to-treat population; IQR, interquartile range; PCS12, SF-12 physical component summary; MCS12, SF-12 mental component summary; SD: standard deviation. P value, Mann–Whitney nonparametric test.

**Supplementary Table 3: Descriptive analysis of penibility scale scores according to the randomization group at each measurement time**

|          | miTT2 population |        |      | Minimal Follow-up |        |       | CT-Scan Follow-up |        |       | p value |
|----------|------------------|--------|------|-------------------|--------|-------|-------------------|--------|-------|---------|
|          | n                | median | IQR  | n                 | median | q1-q3 | n                 | median | q1-q3 |         |
| Baseline | 1264             | 0.94   | 2.94 | 610               | 0.96   | 2.81  | 605               | 0.87   | 2.98  | 0.46118 |
| M6       | 892              | 0.58   | 1.73 | 432               | 0.38   | 1.54  | 428               | 1.11   | 2.53  | 0.00000 |
| M12      | 768              | 0.49   | 1.65 | 380               | 0.29   | 1.34  | 356               | 1.11   | 2.05  | 0.00000 |
| M18      | 665              | 0.58   | 1.63 | 334               | 0.38   | 1.25  | 304               | 0.85   | 1.94  | 0.00001 |
| M24      | 613              | 0.56   | 1.55 | 306               | 0.39   | 1.15  | 281               | 0.78   | 2.04  | 0.00001 |
| M36      | 508              | 0.46   | 1.64 | 264               | 0.29   | 1.44  | 228               | 0.87   | 1.84  | 0.00034 |
| M48      | 449              | 0.58   | 1.74 | 228               | 0.38   | 1.58  | 202               | 0.92   | 1.93  | 0.00069 |
| M60      | 294              | 0.67   | 1.65 | 155               | 0.46   | 1.39  | 131               | 0.87   | 2.02  | 0.00115 |

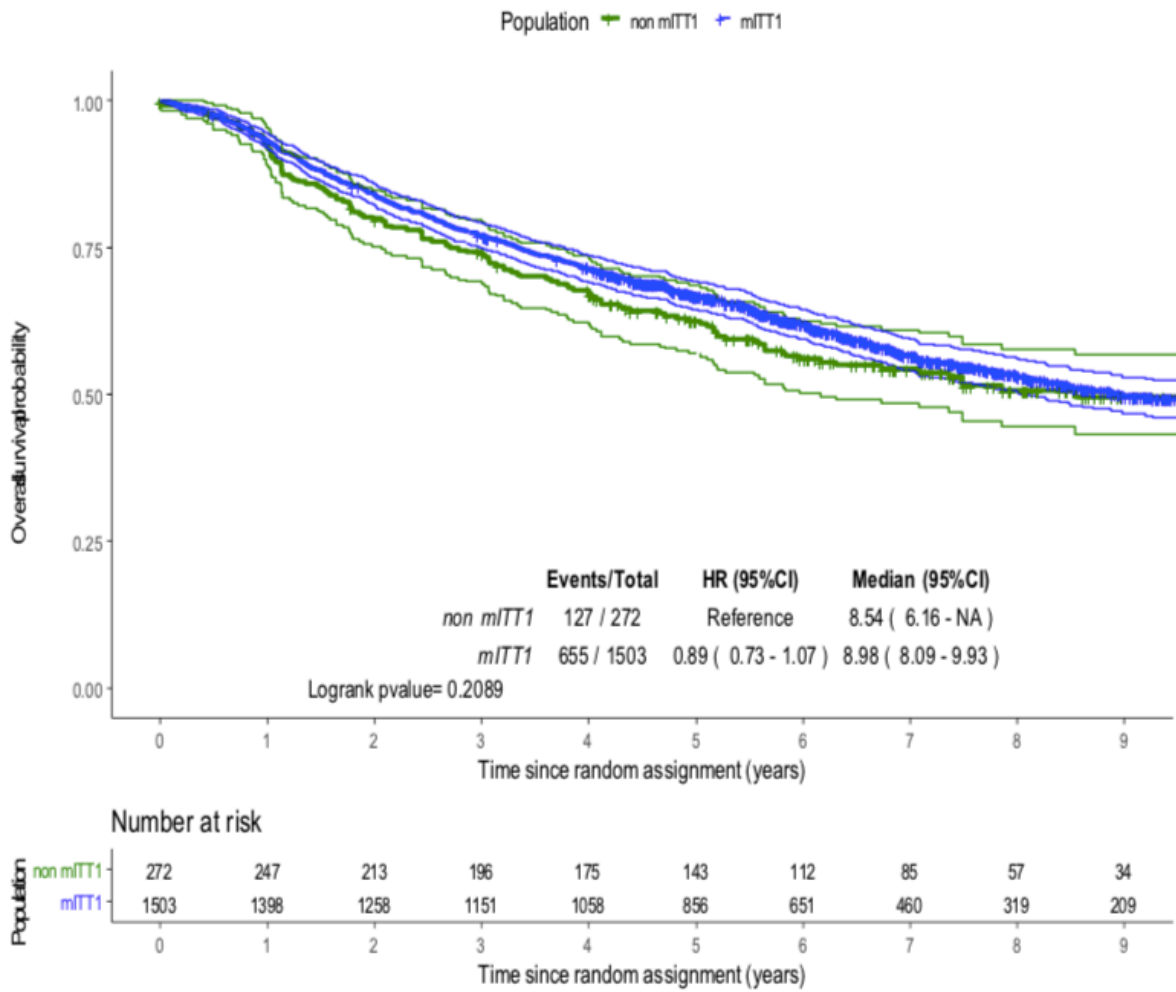


**Supplementary Table 4: Penibility scale scores according to the randomization group and the performance of a fibre-optic bronchoscopy**

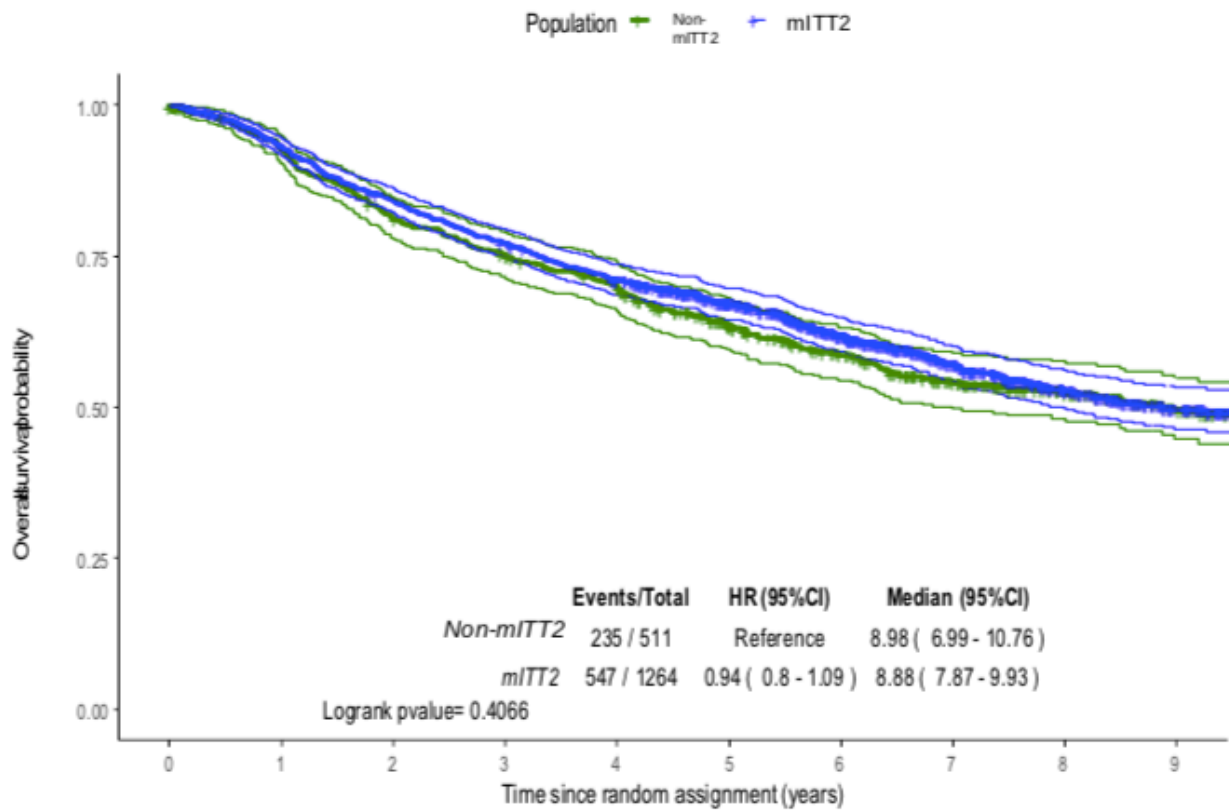
|            | Minimal Follow-up |        |      |                 |        |      | p value | CT-Scan Follow-up |        |       |                 |        |      | p value |
|------------|-------------------|--------|------|-----------------|--------|------|---------|-------------------|--------|-------|-----------------|--------|------|---------|
|            | Bronchoscopy      |        |      | No-bronchoscopy |        |      |         | Bronchoscopy      |        |       | No-bronchoscopy |        |      |         |
|            | n                 | median | IQR  | n               | median | IQR  |         | n                 | median | IQR   | n               | median | IQR  |         |
| <b>M6</b>  | 419               | 0.38   | 1.54 | 12              | 0.05   | 0.63 | 0.09830 | 213               | 0.58   | 1.53  | 215             | 1.73   | 3.74 | <0.0001 |
| <b>M12</b> | 363               | 0.29   | 1.25 | 12              | 1.62   | 3.18 | 0.04173 | 178               | 0.48   | 1.36  | 176             | 1.8    | 3.28 | <0.0001 |
| <b>M18</b> | 318               | 0.38   | 1.2  | 12              | 0.72   | 1.16 | 0.11225 | 174               | 0.58   | 1.49  | 126             | 1.63   | 3.08 | <0.0001 |
| <b>M24</b> | 294               | 0.38   | 1.15 | 10              | 0.43   | 0.67 | 0.45819 | 153               | 0.48   | 01.49 | 124             | 1.68   | 4.38 | <0.0001 |
| <b>M36</b> | 256               | 0.29   | 1.44 | 4               | 0.87   | 3.52 | 0.25506 | 121               | 0.38   | 1.37  | 105             | 1.44   | 2.91 | <0.0001 |
| <b>M48</b> | 216               | 0.38   | 1.56 | 10              | 0.77   | 1.83 | 0.82054 | 110               | 0.58   | 1.63  | 89              | 1.55   | 2.22 | <0.0001 |
| <b>M60</b> | 149               | 0.39   | 1.36 | 4               | 1.52   | 2.18 | 0.04241 | 76                | 0.43   | 1.02  | 52              | 2.02   | 2.75 | <0.0001 |

Supplementary Figure 1: Overall survival in the ITT population according to completion of SF-12 (A) and the penibility scale at baseline

A



B



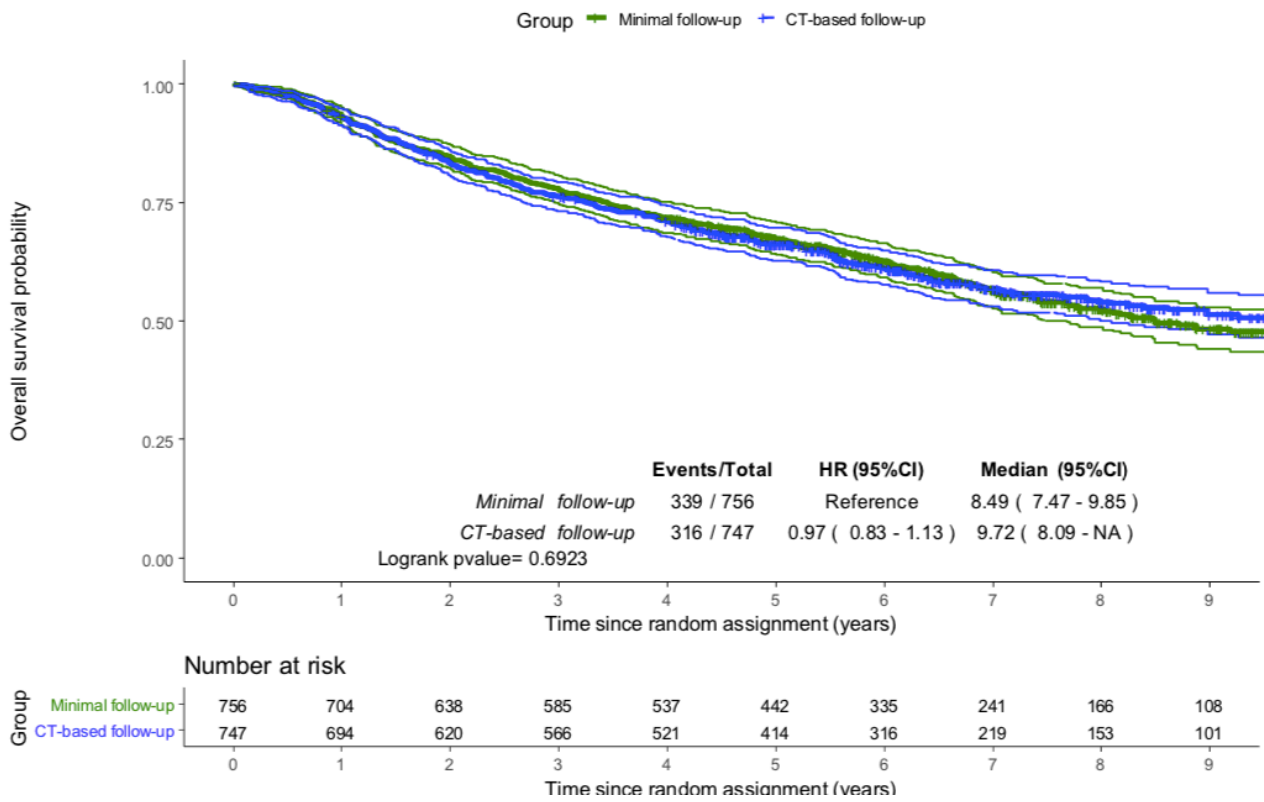
Number at risk

|           | 0    | 1    | 2    | 3   | 4   | 5   | 6   | 7   | 8   | 9   |
|-----------|------|------|------|-----|-----|-----|-----|-----|-----|-----|
| Non-mITT2 | 511  | 470  | 411  | 378 | 347 | 277 | 224 | 168 | 121 | 82  |
| mITT2     | 1264 | 1175 | 1060 | 969 | 886 | 722 | 539 | 377 | 255 | 161 |

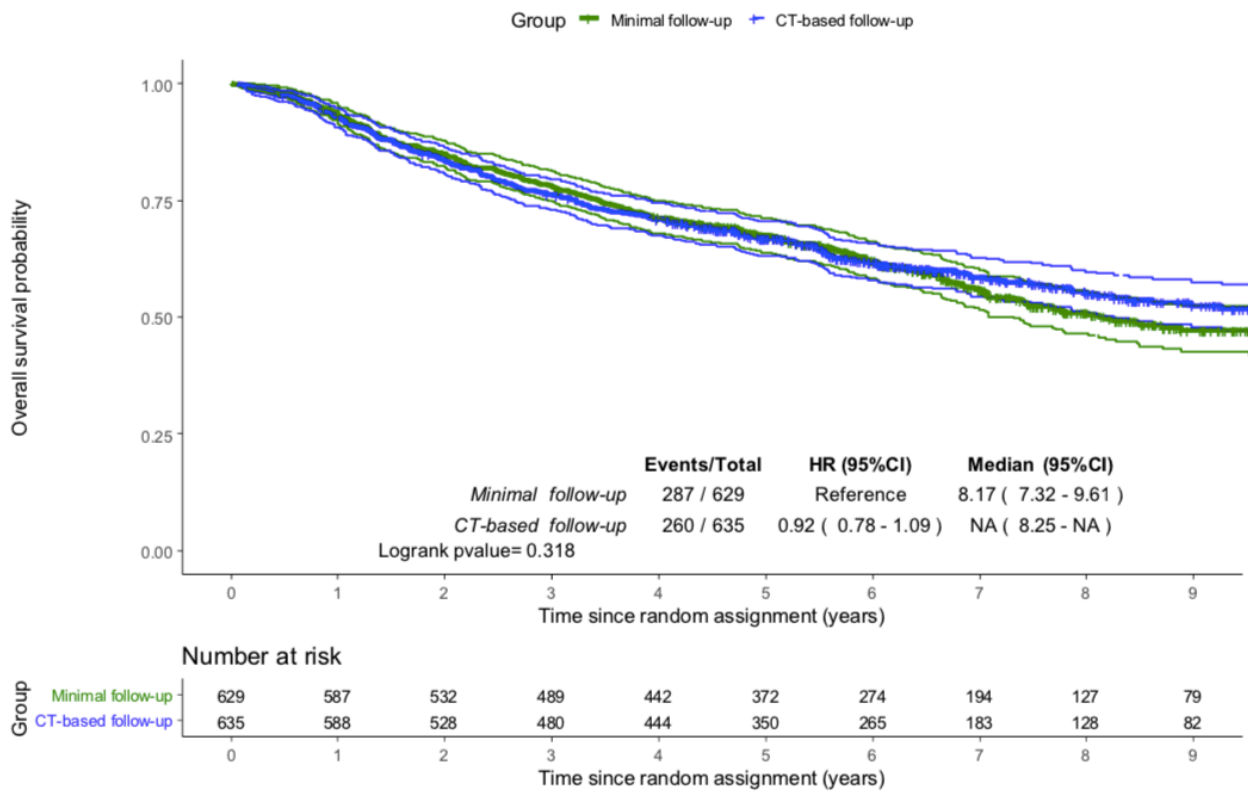
Time since random assignment (years)

Supplementary Figure 2: Overall survival in the mITT1 (A) and mITT2 (B) populations by follow-up group.

A

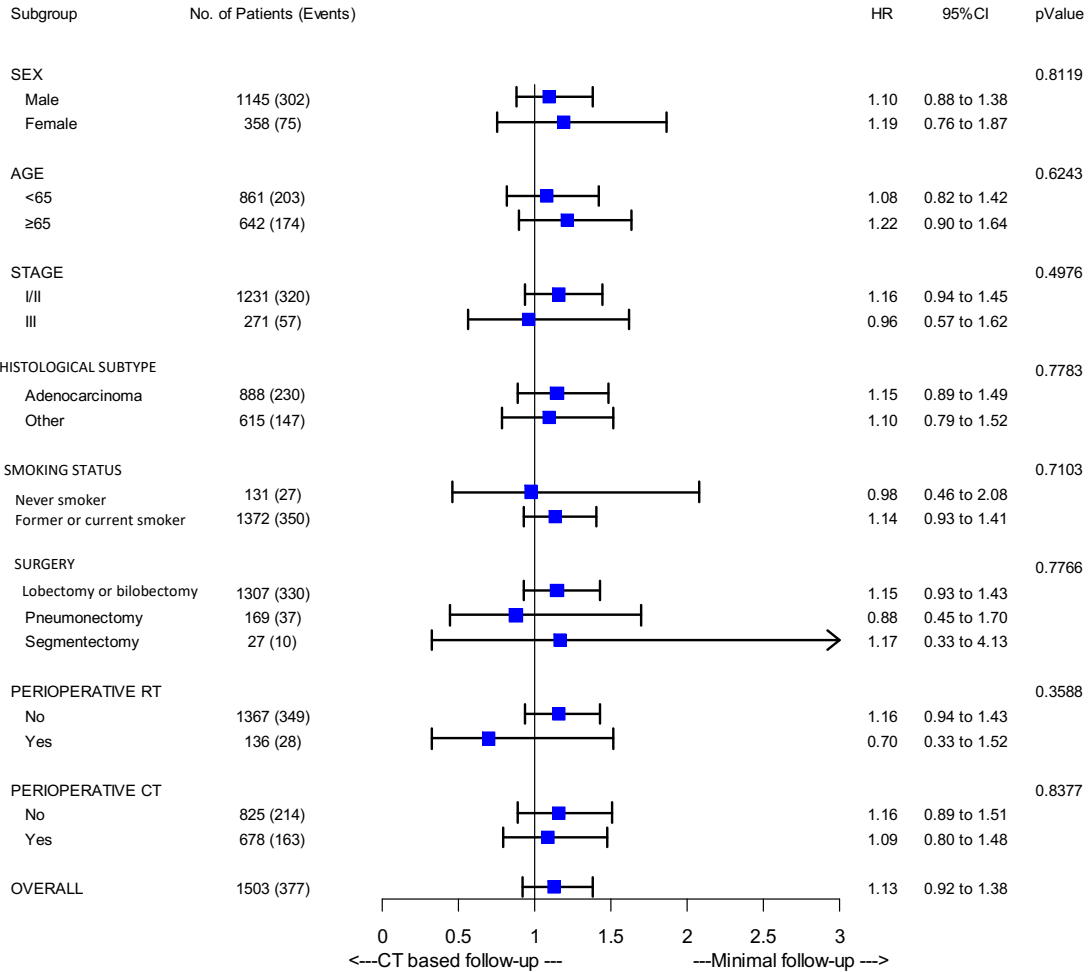


B

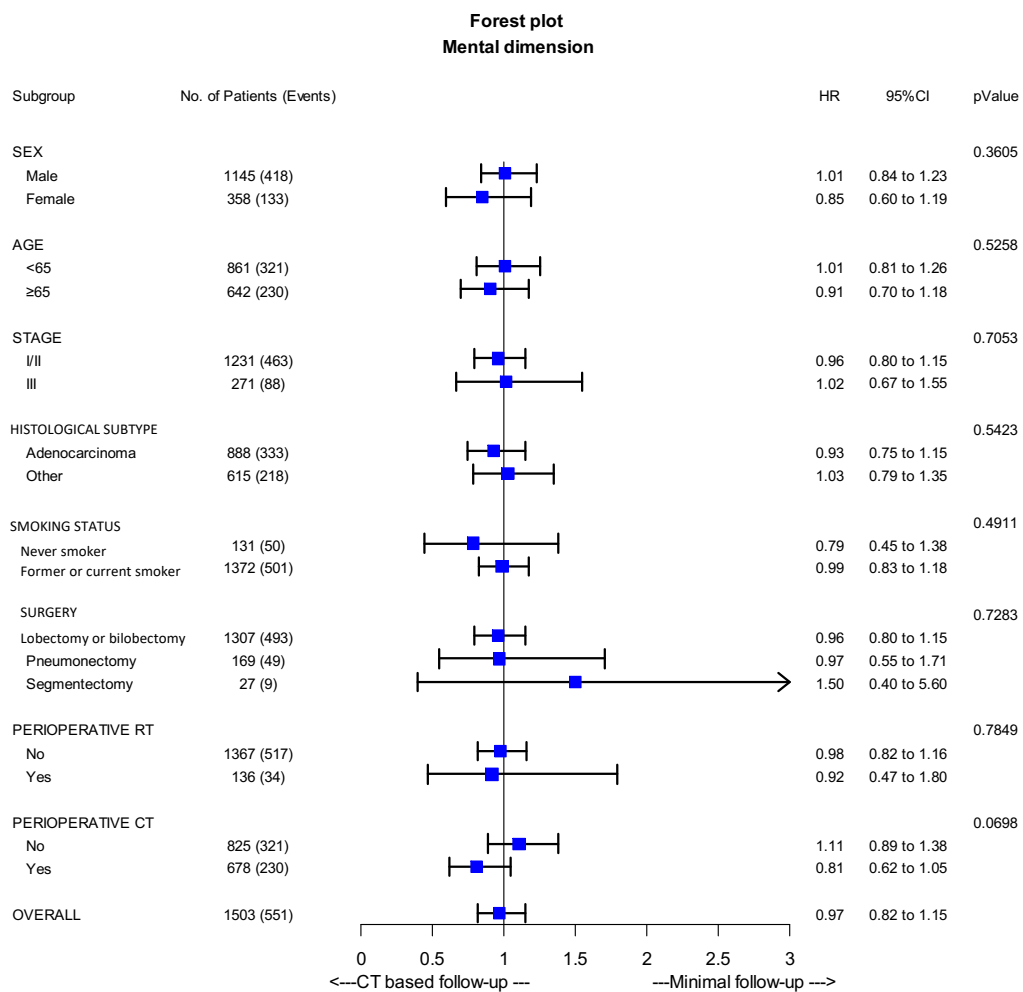


Supplementary Figure 3: Time to deterioration of symptoms, subgroup analysis, and forest plot for the physical component summary.

**Forest plot**  
**Physical dimension**

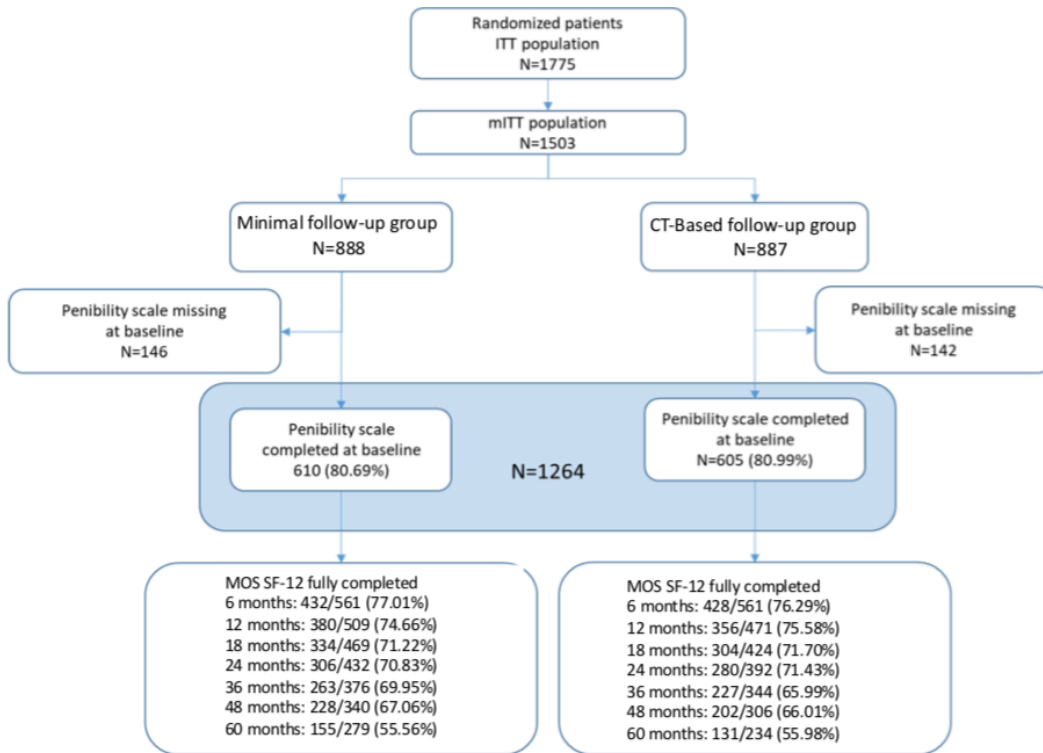


Supplementary Figure 4: Time to deterioration of symptoms, subgroup analysis, and forest plot for the mental component summary

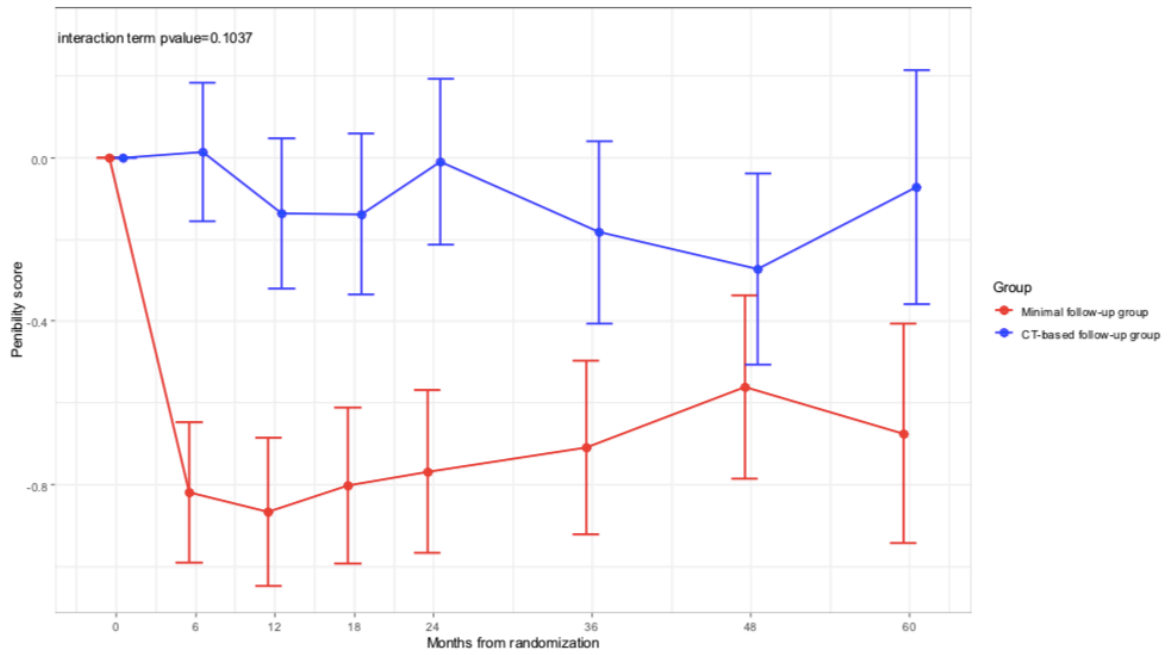


Supplementary Figure 5: Flow chart for the penibility scale data



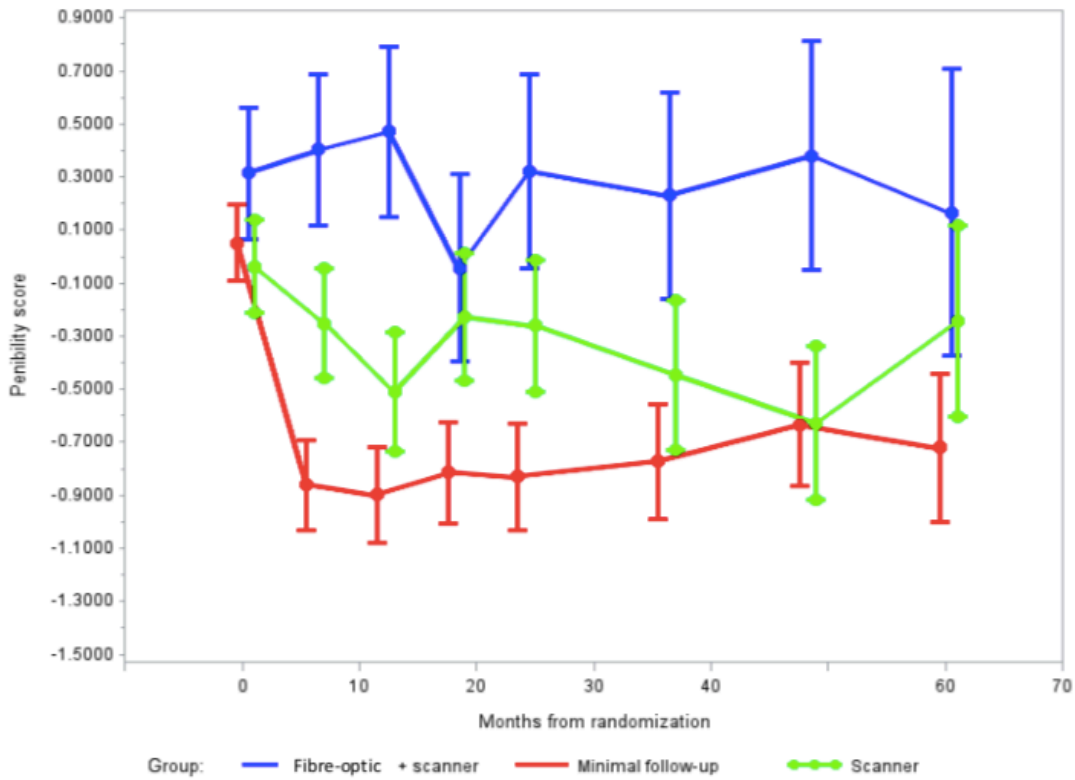


Supplementary Figure 6: Plot of the least mean square change from baseline with 95% CI bars from MMRM for the penibility scale



|                    |     |     |     |     |     |     |     |     |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Minimal follow-up  | 602 | 432 | 382 | 337 | 309 | 266 | 231 | 156 |
| CT-based follow-up | 593 | 431 | 358 | 302 | 286 | 223 | 203 | 135 |

Supplementary Figure 7: Changes in penibility between baseline and each measurement time in the mITT2 population depending on having follow-up by CT scan alone, fibre-optic bronchoscopy and CT scan and neither (minimal follow-up). Plot of the least mean square change from baseline with 95% CI bars from the mixed model for repeated measures-adjusted scores.





*Validation d'un score de risque de survenue de pneumothorax retardé après une ponction-biopsie pulmonaire transthoracique scano-guidée*

**Résumé :**

L'objectif principal de cette étude était d'identifier les facteurs de risque de pneumothorax post-biopsie pulmonaire transthoracique percutanée (BPTC) puis d'établir et de valider un score prédictif de survenue de pneumothorax afin d'identifier les patients éligibles aux soins ambulatoires.

**Matériel et méthodes :**

Les patients ayant subi une BPTC entre le 1er novembre 2012 et le 1er mars 2017 ont été évalués rétrospectivement pour déterminer les facteurs cliniques et radiologiques potentiellement liés à la survenue d'un pneumothorax. Une régression logistique multivariée a été utilisée pour identifier les facteurs de risque et le coefficient du modèle pour chaque facteur a été utilisé pour calculer un score. Ensuite, une cohorte de validation a permis d'évaluer prospectivement de mars 2018 à octobre 2019.

**Résultats :**

Parmi les 498 patients éligibles dans la cohorte de l'étude, un pneumothorax est survenu chez 124 patients (24,9 %) et a nécessité un drainage chez 34 patients (6,8 %). Les facteurs de risque de pneumothorax étaient la présence d'une broncho-pneumopathie chronique obstructive (OR 95 % IC 2,28 [1,18–4,43]), plusieurs passages à travers la plèvre (OR 95 % IC 7,71 [1,95–30,48]), une approche antérieure pour la biopsie (OR 95 % IC 6,36 [3,82–10,58]), distance peau-pleure  $\leq 30$  mm (OR 95 % IC 2,25 [1,09–6,65]) et épanchement pleural aérique  $> 10$  mm (OR 95 % IC 9,27 [5,16–16,65]). Parmi les 236 patients de la cohorte prospective de validation, un pneumothorax était survenu chez 18 % de ces patients et 8 % ont été drainés. Un score négatif ( $< 73$  points) prédisait une probabilité de survenue d'un pneumothorax de 7,4% et un drainage tardif de 2,5% (OR 95% IC respectivement 0,18[0,08–0,39] et 0,15[0,04–0,55]) et suggérait une durée d'hospitalisation réduite ( $P = 0,009$ ).

**Conclusion :**

Ce score prédictif du pneumothorax secondaire au BPTC présente des performances et une précision pronostiques élevées pour orienter les patients vers une prise en charge ambulatoire.

# Score to Predict the Occurrence of Pneumothorax After Computed Tomography-guided Percutaneous Transthoracic Lung Biopsy

Yassine Lamfichekh, MD,\* Valentin Lafay, MD,† Joffrey Hamam, MD,‡  
 Alicia Guillien, PhD,§ Marc Puyraveau, MSc,|| Julien Behr, MD,\*  
 Philippe Manzoni, MD,\* Paul Calame, MD,\*  
 Jean-Charles Dalphin, MD, PhD,†✱ Guillaume Eberst, MD,†¶#  
 Franck Grillet, MD,\*\*\* and Virginie Westeel, MD, PhD†¶#

**Purpose:** The main objective of this study was to identify risk factors for post-percutaneous transthoracic lung biopsy (PTLB) pneumothorax and to establish and validate a predictive score for pneumothorax occurrence to identify patients eligible for outpatient care.

**Material and Methods:** Patients who underwent PTLB between November 1, 2012 and March 1, 2017 were retrospectively evaluated for clinical and radiologic factors potentially related to pneumothorax occurrence. Multivariate logistic regression was used to identify risk factors, and the model coefficient for each factor was used to compute a score. Then, a validation cohort was prospectively evaluated from March 2018 to October 2019.

**Results:** Among the 498 eligible patients in the study cohort, pneumothorax occurred in 124 patients (24.9%) and required drainage in 34 patients (6.8%). Pneumothorax risk factors were chronic obstructive pulmonary disease (OR 95% CI 2.28 [1.18–4.43]), several passages through the pleura (OR 95% CI 7.71 [1.95–30.48]), an anterior biopsy approach (OR 95% CI 6.36 [3.82–10.58]), skin-to-pleura distance  $\leq 30$  mm (OR 95% CI 2.25 [1.09–6.65]), and arial effusion  $> 10$  mm (OR 95% CI 9.27 [5.16–16.65]). Among the 236 patients in the prospective validation cohort, pneumothorax occurred in 18% and 8% were drained. A negative score ( $< 73$  points) predicted a probability of

pneumothorax occurrence of 7.4% and late evacuation of 2.5% (OR 95% CI respectively 0.18[0.08–0.39] and 0.15[0.04–0.55]) and suggested a reduced length of hospital stay ( $P = 0.009$ ).

**Conclusion:** This predictive score for pneumothorax secondary to PTLB has high prognostic performance and accuracy to direct patients toward outpatient management.

**Clinical Trials:** NCT03488043

**Key Words:** Image-guided biopsy, lung cancer, pneumothorax, risk factors

(*J Thorac Imaging* 2023;38:315–324)

In the era of chest computed tomography (CT) screening for lung cancer screening,<sup>1</sup> the use of percutaneous CT-guided lung biopsy (PTLB) to assess evolving small lung lesions is steadily growing. PTLB makes it possible to obtain a histologic diagnosis of a pulmonary nodule or mass when bronchial endoscopy is impracticable, especially when lesions are too peripheral. This procedure has a substantial diagnostic yield in both sensitivity and specificity<sup>2</sup> with infrequent complications, which include pneumothorax, hemoptysis, hemothorax, infection, and air embolism.<sup>3,4</sup> Pneumothorax is the most frequent complication, occurring between 9% and 54%, with an average of 20%.<sup>5</sup> A meta-analysis including 8133 procedures reported a prevalence of pneumothorax of 25.3%, with 5.6% requiring intervention.<sup>4</sup>

Various studies have explored the risk factors for post-PTLB pneumothorax, and found that reduced lesion size, number of pleural needle passes, and length of intrapulmonary trajectory are significantly associated with an increased risk of pneumothorax.<sup>6–10</sup> The transfissural needle trajectory and the radiologist's experience are also related to the risk of pneumothorax.<sup>7,9</sup> However, some risk factors are controversial in the literature. Emphysema, patient age, lesion cavitation, location of lung lesion, presence of pleural effusion, number of samples, needle-pleural angle, and patient position after biopsy have no significant association with the risk of pneumothorax, according to Yeow et al.<sup>7</sup>

The development of a pneumothorax increases costs, as well as the need for hospitalization to manage the patient's symptoms, such as chest pain, shortness of breath, and hypoxia. In this perspective, the British Thoracic Society recommends patient monitoring followed by a control chest radiography 1 hour after biopsy and at 48 to 72 hours.<sup>11</sup> To

From the \*Department of Radiology; †Department of Chest Disease, University Hospital of Besançon, Besançon; ‡Department of Intensive Care Medicine, Hospital of Libourne, Libourne; §Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, IAB, Grenoble Alpes University, Inserm, CNRS, Grenoble; ||Methodology Unit, University Hospital of Besançon; ¶Methodology and Quality of Life in Oncology Unit, University Hospital, Besançon; #UMR: 1098, University of Franche-Comté, Besançon; and \*\*Department of Radiology, Centre Léon Berard, Lyon, France.

✱Deceased.

Y.L. and V.L. contributed equally to this study.

The scientific guarantor of this publication is P.V.W.

A.G., M.P., and P.C. have significant statistical expertise.

The study protocol follows the ethical guidelines of the Helsinki Declaration and was approved by the institutional review board.

Y.L.: Investigation, Writing, Original Draft—Writing. V.L.: Investigation, Writing, Original Draft—Writing. J.H.: Conceptualization, Methodology, and Investigation. A.G., M.P., and P.C.: Methodology and Formal analysis. J.B.: Methodology and Investigation. P.M.: Conceptualization. G.E.: Methodology, Writing—Review & Editing. F.G.: Conceptualization, Methodology, Investigation and Writing—Original Draft, Writing—Review & Editing. V.W.: Conceptualization, Validation, Writing—Original Draft, Writing—Review & Editing Supervision.

The authors declare no conflicts of interest.

Correspondence to: Franck Grillet, MD, Department of Radiology Centre Léon Bérard 28 Rue Laennec 69373 Lyon, France (e-mail: franck.grillet@lyon.unicancer.fr).

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/RTI.0000000000000729

this day, there is no clear consensus on patient management and surveillance following PTLB.

Patient management after PTLB used to be mainly hospitalization. However, a change of care is being seen in many centers, with increased outpatient management, but this strategy has pitfalls, and patients more suitable for in-patient care should be identified.

The objective of this study was to develop and validate a predictive score for pneumothorax based on patient, lesion, and procedure characteristics to classify patients according to their pneumothorax risk, and thereby select patients who could benefit from outpatient care.

## MATERIALS AND METHODS

### Ethical and Legal Considerations

This study followed the ethical guidelines of the Declaration of Helsinki and was approved by the local review board (approval number P/2018/372). All patients provided written informed consent.

### Study Design and Inclusion Criteria

This study was carried out at the University Hospital of Besancon, France, in 2 parts. After a retrospective analysis of all consecutive diagnostic CT-guided PTLB of a lung nodule or mass between November 1, 2012 and March 1, 2017 (study cohort), and then, prospective validation was conducted between March 30, 2018 and October 31, 2019 (validation cohort). All adult patients (older than 18 years of age) undergoing CT-guided PTLB for diagnostic purposes were eligible for the study. Ineligibility criteria were pulmonary lesions in contact with the pleura for which no ventilated pulmonary parenchyma was crossed; multiple sites of biopsy; preexisting pneumothorax; target lesion with alveolar or interstitial pattern; excavated lesions; and patients with missing or uninterpretable chest x-ray after PTLB.

### Study Variables

The following patient characteristics were retrieved from medical charts: height (m) and weight (kg); comorbidities (chronic obstructive pulmonary disease [COPD] documented in the patient's medical history, and/or any other respiratory disease); history of homolateral thoracic radiation therapy or surgery; smoking status (current smokers [ie, active or stopped <1 year before PTLB], former smokers [ie, stopped >1 year previously], and nonsmokers [ $<100$  cigarettes during their lifetime]).

### Percutaneous Transthoracic Lung Biopsy Procedure

PTLB was performed by 2 trained interventional radiologists (J.B. and P.M.) with 10 and 30 years of experience, respectively, on a Sensation 64 CT (Siemens Healthineers, Germany). The patient was placed on the CT table in a prone, supine, or lateral decubitus position, depending on the lesion's location, and a chest CT scan was performed. Local anesthesia was obtained using lidocaine chlorhydrate 1%. A 19 Gauge co-axial needle and a 20 G semi-automatic biopsy needle (Temno, Merit Medical, Utah, USA or Quick core, Cook Medical, IN) were used. One to 5 tissue samples were taken, depending on their macroscopic quality and patient tolerance of the procedure. After removing the needle, a CT scan was performed in search of pneumothorax. If positive, either the

pneumothorax was complete, and a chest tube was immediately inserted, and if incomplete, a second CT scan was performed at 5 minutes to monitor progress. In case of majoration, the pleural drain was inserted.

A chest x-ray was performed systematically between 4 and 24 hours after the biopsy on a DuraDiagnost Rel 4 table (Philips Healthcare, Netherlands). If the chest x-ray demonstrated complete pneumothorax, chest tube insertion or exsufflation was performed. In case of incomplete pneumothorax, and based on its tolerance, pneumothorax was either drained or monitored using chest x-rays until resolution or worsening, requiring pleural drainage.

### Imaging Analysis

Images were independently reviewed by 4 readers (retrospective phase: F.G., chest radiologist and J.H., pulmonologist; prospective phase: V.L., pulmonologist and Y.L., radiologist) on a PACS workstation (Carestream Health, Rochester, NY). In case of disagreement between readers, the consensus was achieved by simultaneous reading. Data relating to the target lesion, and the procedure were reported, namely: date, operator, procedure duration (time between needle insertion through the pleura and needle withdrawal), PTLB approach (anterior, lateral or posterior), number of biopsy samples, lesion location, size (in mm) and depth (from pleura to lesion, in mm), skin-to-pleura distance (in mm), presence of diffuse emphysema (defined when  $\geq 10\%$  of total lung parenchymal volume had a density lower than  $-940$  HU, obtained using automated lung segmentation software (Thoracic VCAR, Advantage Workstation platform, Version 3.2 Ext 3.3, GE Healthcare, Milwaukee, WI),<sup>12</sup> emphysema on the needle path, number of passages through the pleura, passage through a fissure, hemorrhage along the path after needle withdrawal (defined by ground glass opacity or consolidation along needle path) and distance between hemorrhage and pleural puncture point (in mm), and postprocedural aerial effusion (as the maximum distance of detachment of the visceral pleura from the parietal pleura measured in mm). All measures were done on an axial CT slice in a lung window set (1600;  $-600$  HU).

On frontal chest x-rays, pneumothorax was considered as complete if there was either pulmonary detachment over the entire axillary height and more than 2 cm at the pulmonary hilum or detachment of more than 3 cm at the pulmonary apex.<sup>13</sup>

### Statistical Analysis

Results are expressed as mean  $\pm$  SD for quantitative variables and as numbers and percentages for categorical variables. The  $\chi^2$  test was used to compare qualitative variables. For the comparison of means, Student *t*-test or the Wilcoxon test were used depending on the normality of the distribution. To develop the score, all quantitative variables were categorized, and bivariate logistic regression was used to identify factors associated with the occurrence of pneumothorax; *P* values  $<0.05$  were considered statistically significant. Multivariate logistic regression was performed, including the factors identified in the bivariate analyses that yielded a *P* value  $<0.20$ , with stepwise selection of variables to obtain the final multivariate model. The performance of the model was evaluated using the *C*-index (equivalent to the area under the ROC curve) and calibration by the Hosmer-Lemeshow test. The optimal cutoff to predict the occurrence of pneumothorax was identified using the

Downloaded from http://journals.lww.com/thoracicimaging by BMDMSEPHKAVTZEUMT1QON4a4kLLHEZPpshh0AXM  
IP: 091.091.100.100 on 09/21/2023

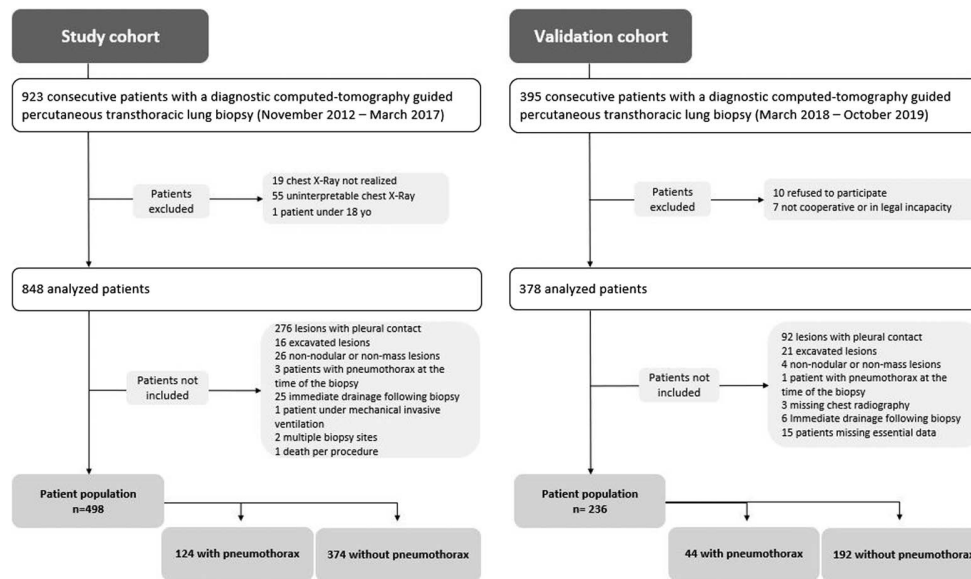


FIGURE 1. Flowchart of the study.

Youden index on the ROC curve to maximize both sensitivity and specificity. To overcome the statistical uncertainty due to the use of a limited sample size, a bootstrap technique was applied. Statistical indicators were calculated for each of the 5000 data sets. The mean and 95% confidence interval of the mean bounded by the 2.5% and 97.5% percentiles of the bootstrap distribution were calculated.

The model was transposed into a nomogram. First, the score was calculated by adding the points attributed to each identified factor; second, each value of the score was assigned a positive likelihood ratio. Finally, from Fagan's nomogram, by drawing a straight line through the pretest probability (prevalence of pneumothorax in our population) and the positive likelihood ratio found, we obtained the probability of the occurrence of pneumothorax after PTLB. We applied the same multivariate logistic model to the prospective validation cohort, and we assessed C-index,

probability of pneumothorax, sensitivity, specificity, and positive and negative predictive values with the same cutoff as that calculated in the development cohort. All statistical analyses were performed by the biostatistics unit of the University Hospital of Besançon using SAS version 9.4 (SAS Institute Inc., Cary, NC) with a significance level set at 0.05.

RESULTS

Retrospective Study Cohort

A flowchart of both cohorts is shown in Fig. 1. In all, 923 patients had CT-guided PTLB in the retrospective cohort. A total of 498 patients were included. Chest X-ray was noninterpretable or missing in 74 patients. Patients had a mean age of 67.3 (±11.2) years (Table 1). Sixty-two

TABLE 1. Patient Characteristics and Comparison Between Study and Validation Cohorts

|   | Study cohort<br>n = 498 | MD | Validation cohort<br>n = 236 | MD | P       |
|---|-------------------------|----|------------------------------|----|---------|
| Age (y), mean (SD)                              | 67.3 ± 11.2             |    | 67.9 ± 10.9                  |    | 0.56    |
| Male, n (%)                                     | 305 (61)                |    | 140 (59)                     |    | 0.80    |
| BMI <30 kg/m <sup>2</sup> , n (%)               | 375(75)                 | 60 | 197 (83)                     |    | 0.38    |
| Smoking status                                  |                         | 44 |                              |    |         |
| Non smokers, n (%)                              | 106 (23)                |    | 53 (22)                      |    | 0.77    |
| Former smokers, n (%)                           | 183 (40)                |    | 109 (46)                     |    | 0.11    |
| Current smokers, n (%)                          | 165 (36)                |    | 74 (31)                      |    | 0.73    |
| COPD, n (%)                                     | 62 (13)                 | 10 | 75 (32)                      |    | < 0.001 |
| History of homolateral chest irradiation, n (%) | 14 (3)                  | 10 | 16 (7)                       |    | 0.01    |
| History of homolateral chest surgery, n (%)     | 8 (2)                   | 10 | 19 (8)                       |    | < 0.001 |

BMI indicates body mass index (weight in kilograms/ the square of the height in meters); COPD, chronic obstructive pulmonary disease; MD, missing data.



TABLE 2. Results of the Bivariate Analysis in the Study Cohort

|   | Presence of pneumothorax |           | Absence of pneumothorax |         | P                             | OR [95% CI]        |
|---|--------------------------|-----------|-------------------------|---------|-------------------------------|--------------------|
|   | N = 124                  | N = 374   | N = 374                 | N = 124 |                               |                    |
| <b>Patient-related factors</b>                  |                          |           |                         |         |                               |                    |
| Age $\geq$ 70, n (%)                            | 64 (52)                  | 144 (39)  |                         |         | <b>0.01</b>                   | 1.70[1.13 2.57]    |
| Male, n (%)                                     | 77 (62)                  | 228 (61)  |                         |         | 0.82                          | 1.05[0.69 1.59]    |
| BMI $<$ 30 kg/m <sup>2</sup> , n (%)            | 99 (94)                  | 276 (83)  |                         |         | <b>0.003</b>                  | 3.41[1.42 8.15]    |
| <b>Smoking status</b>                           |                          |           |                         |         |                               |                    |
| Nonsmoker, n (%)                                | 28 (24)                  | 78 (23)   |                         |         | 0.93                          | 1.00               |
| Weaned $>$ 1 year, n (%)                        | 45 (39)                  | 138 (41)  |                         |         |                               | 0.98[0.56 1.71]    |
| Active or weaned $<$ 1 year, n (%)              | 43 (37)                  | 122 (36)  |                         |         |                               | 0.91[0.53 1.57]    |
| Presence of COPD, n (%)                         | 27 (22)                  | 35 (10)   |                         |         | <b><math>&lt;</math>0.001</b> | 2.66[1.53 4.62]    |
| History of respiratory disease, n (%)           | 13 (11)                  | 28 (8)    |                         |         | 0.31                          | 1.43[0.72 2.86]    |
| History of homolateral chest irradiation, n (%) | 4 (3)                    | 10 (3)    |                         |         | 0.76                          | 1.21[0.37 3.93]    |
| History of homolateral chest surgery, n (%)     | 0 (0)                    | 8 (2)     |                         |         | 0.21                          |                    |
| Diffuse emphysema, n (%)                        | 42 (34)                  | 93 (25)   |                         |         | <b>0.05</b>                   | 1.54[0.99 2.39]    |
| <b>Lesion-related factors</b>                   |                          |           |                         |         |                               |                    |
| Size of lesion $>$ 20 mm, n (%)                 | 95 (77)                  | 255 (68)  |                         |         | <b>0.08</b>                   | 1.53 [0.96 2.44]   |
| <b>Lesion side</b>                              |                          |           |                         |         |                               |                    |
| Left, n (%)                                     | 58 (47)                  | 153 (41)  |                         |         | 0.25                          | 1.27 [0.84 1.91]   |
| Right, n (%)                                    | 66 (53)                  | 221 (59)  |                         |         |                               | 1.00               |
| <b>Lesion location</b>                          |                          |           |                         |         |                               |                    |
| Lower lobe, n (%)                               | 24 (19)                  | 183 (49)  |                         |         | <b><math>&lt;</math>0.001</b> | 1.00               |
| Upper or medium lobe, n (%)                     | 100 (81)                 | 191 (51)  |                         |         |                               | 3.99 [2.45 6.51]   |
| <b>Procedure-related factors</b>                |                          |           |                         |         |                               |                    |
| <b>Operator experience</b>                      |                          |           |                         |         |                               |                    |
| $<$ 10 y  | 84 (68)                  | 242 (65)  |                         |         | 0.56                          | 1.14 [0.74 1.75]   |
| $>$ 10 y  | 40 (32)                  | 131 (35)  |                         |         |                               | 1.00               |
| <b>Approach</b>                                 |                          |           |                         |         |                               |                    |
| Anterior, n (%)                                 | 74 (60)                  | 87 (23)   |                         |         | <b>0.001</b>                  | 4.88 [3.17 7.52]   |
| Lateral and Posterior, n (%)                    | 50 (40)                  | 287 (77)  |                         |         |                               | 1.00               |
| <b>Several pleural passages</b>                 |                          |           |                         |         |                               |                    |
| No, n (%)                                       | 117 (94)                 | 369 (99)  |                         |         | <b>0.01</b>                   | 1.00               |
| Yes, n (%)                                      | 7 (6)                    | 5 (1)     |                         |         |                               | 4.42[1.38 14.17]   |
| Distance skin/pleural $\leq$ 30 mm, n (%)       | 19 (15)                  | 34 (9)    |                         |         | <b>0.05</b>                   | 1.81 [0.99 3.31]   |
| Angulation of the needle                        | 57.3 16.0                | 58.3 17.3 |                         |         | 0.55                          | 0.996 [0.98 1.008] |
| Parenchyma crossed $\geq$ 20 mm, n (%)          | 103 (83)                 | 276 (74)  |                         |         | <b>0.04</b>                   | 1.74 [1.03-2.94]   |
| Emphysema on needle path, n (%)                 | 19 (15)                  | 35 (9)    |                         |         | <b>0.07</b>                   | 1.75 [0.96 3.18]   |
| Passage through a fissure, n (%)                | 13 (10)                  | 23 (6)    |                         |         | <b>0.11</b>                   | 1.79 [0.88 3.65]   |
| No. samples                                     | 3.0 1.0                  | 3.0 1.0   |                         |         | 0.91                          | 1.01 [0.82 1.24]   |
| Procedure duration $\leq$ 12 min, n (%)         | 103 (83)                 | 283 (76)  |                         |         | <b>0.10</b>                   | 1.54 [0.91 2.61]   |
| Aerial effusion $\geq$ 10 mm                    | 53 (43)                  | 32 (9)    |                         |         | <b><math>&lt;</math>0.001</b> | 7.98 [4.80 13.26]  |
| <b>Hemorrhage-pleural contact*</b>              |                          |           |                         |         |                               |                    |
| Yes, n (%)                                      | 76 (72)                  | 311 (93)  |                         |         | <b><math>&lt;</math>0.001</b> | 1.00               |
| No, n (%)                                       | 30 (28)                  | 24 (7)    |                         |         |                               | 5.12 [2.83 9.25]   |

Analysis is not possible due to the small number of patients in both groups. P: significance threshold below 0.20.

\*Missing data regarding hemorrhage-pleural contact (n=18 for presence of pneumothorax, n=39 for absence of pneumothorax).

BMI indicates body mass index; COPD: chronic obstructive pulmonary disease; OR: odds ratio).

(12.4%) patients had COPD, 305 were males (61.2%), and 348 were smokers or ex-smokers (70%).

Pneumothorax occurred in 124 patients (24.9%) and was incomplete in 69% of cases and complete in 31%.

Pneumothorax drainage was required in 34 patients (27% of all pneumothorax, 6.8% of the 498 patients). In bivariate analysis, among patient characteristics, age  $>$  70 years ( $P=0.01$ ), BMI  $<$ 30 kg/m<sup>2</sup> ( $P=0.003$ ), and COPD ( $P<0.001$ ) were associated with a significantly higher risk of pneumothorax (Table 2). The risk of developing pneumothorax was significantly increased when the lesion was in the middle or upper lobes compared with the lower lobes ( $P<0.001$ ). Among the procedure-related factors, a significantly increased risk of pneumothorax was observed with the following variables: an anterior approach compared with lateral and posterior approaches ( $P<0.001$ ),  $>$  1 passage through the pleura

( $P=0.01$ ), and aerial effusion  $>$  10 mm ( $P<0.001$ ). Hemorrhage along the path after needle withdrawal was frequently seen (441 patients, 89%), and a significantly higher risk of pneumothorax was observed when there was no contact of the hemorrhage with the pleural puncture site ( $P<0.001$ ). Among the procedure-related factors, variables associated with a nonsignificant risk of pneumothorax ( $P<0.20$ ) were skin-to-pleura distance  $<$ 30 mm ( $P=0.05$ ) emphysema on the needle path ( $P=0.07$ ), and passage through a fissure (OR 1.79 [0.88 3.65],  $P=0.11$ ).

#### Multivariate Analysis and Score Definition

The multivariate model included the 498 patients, and 13 of the 15 variables identified in the bivariate analysis with a  $P<0.20$  (Table 2). Hemorrhage contact with the pleura and BMI were not included in the model because of missing data in 51 (10.2%) and 60 patients (12%), respectively. The

**TABLE 3.** Pneumothorax Risk Factors After Transthoracic Lung Biopsy: Results of Multivariate Analysis in the Study Cohort. Score Value in Points for Each Risk Factor as Determined From the Logistic Regression Coefficients

|                          | Beta    | AOR [95% CI]      | P      | Score value |
|--------------------------|---------|-------------------|--------|-------------|
| Intercept                | -1.8513 |                   | <0.001 |             |
| COPD                     |         |                   | 0.02   |             |
| No                       | 0       | 1.00              |        | 0 pt        |
| Yes                      | 0.8246  | 2.28 [1.18 4.43]  |        | 37 pts      |
| Approach                 |         |                   | <0.001 |             |
| Posterior/lateral        | 0       | 1.00              |        | 0 pt        |
| Anterior                 | 1.8498  | 6.36 [3.82 10.58] |        | 83 pts      |
| Several pleural passages |         |                   | 0.004  |             |
| No                       | 0       | 1.00              |        | 0 pt        |
| Yes                      | 2.0421  | 7.71 [1.95 30.48] |        | 92 pts      |
| Skin-pleura distance     |         |                   | 0.03   |             |
| > 30 mm                  | 0       | 1.00              |        | 0 pt        |
| ≤ 30 mm                  | 0.8123  | 2.25 [1.09 6.65]  |        | 36 pts      |
| Aerial effusion          |         |                   | <0.001 |             |
| < 10 mm                  | 0       | 1.00              |        | 0 pt        |
| ≥ 10 mm                  | 2.2266  | 9.27 [5.16 16.65] |        | 100 pts     |

AOR indicates adjusted odds ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Pearson correlation coefficient between BMI and skin-pleura distance was 0.43. Five variables were significantly associated with an increased risk of pneumothorax: COPD, anterior PTLB approach, > 1 passage through the pleura, distance skin-pleura <30 mm, and aerial effusion > 10 mm (Table 3). The *P* value from the Hosmer-Lemeshow test was 0.79, and the C-index was 0.81 (Fig. 2).

By assigning a value to each variable in the multivariate analysis based on the logistic regression coefficient, we obtained an overall score ranging from 0 to 348. The best cutoff value based on the Youden index was a score of 73 points, which made it possible to discriminate, with the best ratio in terms of sensitivity and specificity, patients who would present a pneumothorax from those who would not. Different score cutoffs are shown in Fig. 2. A Fagan nomogram was built based on each variable's value after indexation (Fig. 3).

**Score Validation in the Prospective Validation Cohort**

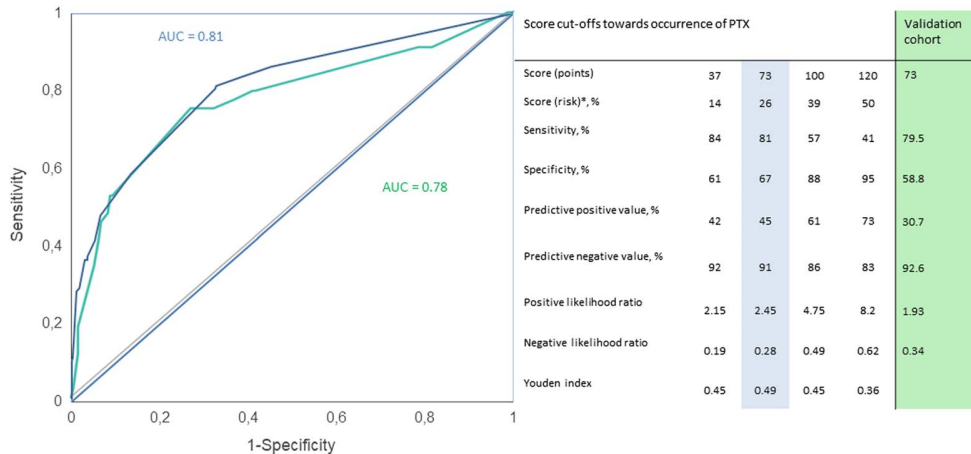
The characteristics of the 236 patients included in the validation cohort differed from the development cohort in terms of the history of COPD (*P*<0.001) and history of homolateral chest surgery and irradiation (*P*=0.01 and <0.001, respectively) (Table 1). Pneumothorax occurred in 44 patients (18.6%). Chest tube insertion was necessary for 19 patients (43% of all pneumothorax, 8% of the 236 patients).

Using the score, with a cutoff value of 73 points, the C-index was 0.78, and sensitivity and specificity were 79.5% and 58.8%, respectively. The negative and positive predictive values were 92.6% and 30.7%, respectively. (Fig. 2). A score <73 points was significantly associated with reduced pneumothorax occurrence (7.4%, OR 0.18, 95% CI [0.08 0.39]), chest tube insertion (2.5%, OR 0.15, 95% CI [0.04 0.55]) and length of hospital stay (1.1 vs. 1.6 d, *P*=0.009) (Table 4).

Procedures examples with score utilization are depicted in Figs. 4, 5, and 6.

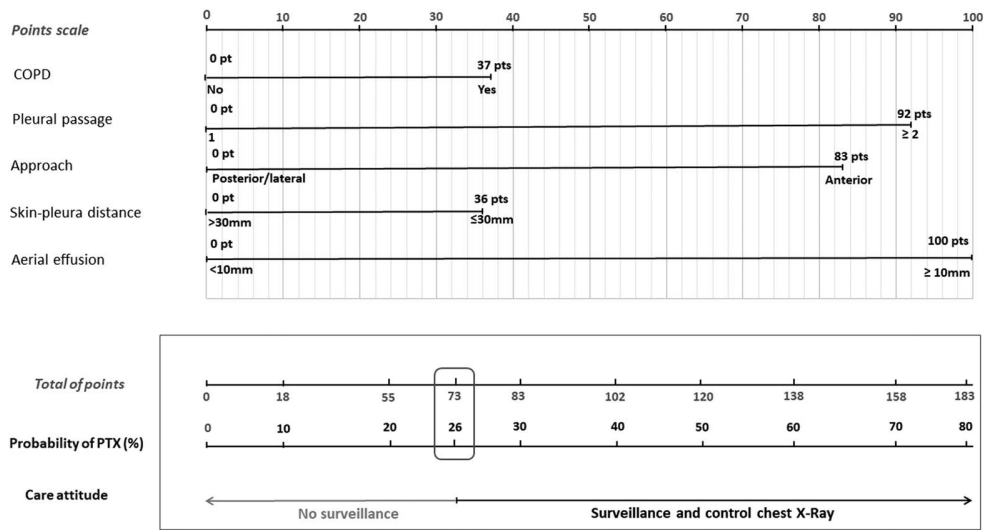
**DISCUSSION**

Our results showed a rate of pneumothorax of 24.9% in the retrospective cohort and 18.6% in the validation cohort. We determined and validated a score predicting the occurrence of post-PTLB pneumothorax based on COPD, anterior approach, several pleural passages, skin-pleura distance ≤ 30 mm, and aerial effusion ≥ 10 mm. The score had a



**FIGURE 2.** Predictive model C-index and statistical performance of the best cutoff values to predict the occurrence of pneumothorax after Percutaneous Transthoracic Lung Biopsy. Blue curves represent the retrospective study cohort and the green curve represents the prospective validation cohort. AUC indicates area under the curve, PTX, Pneumothorax, \*: the probability of pneumothorax occurrence.

Downloaded from http://journals.lww.com/thoracicimaging by BMDMSGPHKAV1ZFC00M1Q0N4A4KLLHEZQPSLH0AXM on 09/27/2023



**FIGURE 3.** Nomogram of the predictive pneumothorax score after percutaneous transthoracic lung biopsy: The upper part of the figure represents the score scale ranging from 0 to 100 points. Each of the 5 factors is assigned a different value, depending on whether it is present or absent. The total score is thus calculated and, the lower part of the figure is used to deduce the probability of pneumothorax occurrence. Up to 73 points (included), the risk of pneumothorax occurrence is considered mild, and the proposed management attitude is the absence of clinical and radiological surveillance, and discharge to home is proposed. Above 73 points, the risk is intermediate to high, and clinical and radiological surveillance is recommended. COPD indicates chronic obstructive pulmonary disease, PTX, Pneumothorax.

sensitivity of 81% and a specificity of 67%, and a high negative predictive value in both cohorts (92.6% and 91%, respectively).

The prediction score of PTLB complications is currently trending.<sup>14, 20</sup> Both the retrospective studies by Anzidei et al and Iezzi et al presented a score predicting the occurrence of several complications, including pneumothorax.<sup>14, 15</sup> Yang et al recently presented a predictive score for pneumothorax after a CT-guided co-axial core needle lung biopsy.<sup>16</sup> In a retrospective study of 489 patients, including a validation cohort of 158 patients, the pneumothorax rate was higher than ours, at 33%, and the area under the receiver operating characteristic curve used to determine the discrimination of the predictive model was lower (0.72) than in our study. Increased age, emphysema, absence of pleural thickening, upper lobe location, size < 3 cm, and lobulation sign were associated with an increased risk of pneumothorax. Wang et al developed a predictive model for pneumothorax following CT-guided PTLB for a solitary pulmonary nodule in 311 patients.<sup>17</sup> The

pneumothorax rate was 31% and the AUC was 0.80. Important risk factors like emphysema were not analyzed. Zhao et al, in an outpatient population, reported a pneumothorax rate of 31% in 864 patients.<sup>18</sup> The AUC was 0.73 and the sensitivity and specificity of the predictive score was 56.8% and 79.6%, respectively. Emphysema, absence of contact between lesion and pleura, and prone or lateral position were associated with an increased risk of pneumothorax. Again Zhao et al recently developed a predictive score similar to ours, which appears less efficient (AUC = 0.71) with an increased number of factors to assess (9).<sup>19</sup>

Among the variables included in our score, the biopsy approach is a debated risk factor for pneumothorax in the literature. We showed that an anterior approach was associated with a higher risk of pneumothorax. Mills et al found a higher risk of pneumothorax by multivariate analysis with the use of a lateral approach.<sup>21</sup> A posterior approach, with rapid reversion of patients, appears to protect from pneumothorax.<sup>22, 23</sup> Dorsal or even contralateral decubitus after posterior or lateral approach, with compression of the puncture point, may help to plug the

**TABLE 4.** Predictive Clinical Application of the Score Applied on the Prospective Validation Cohort

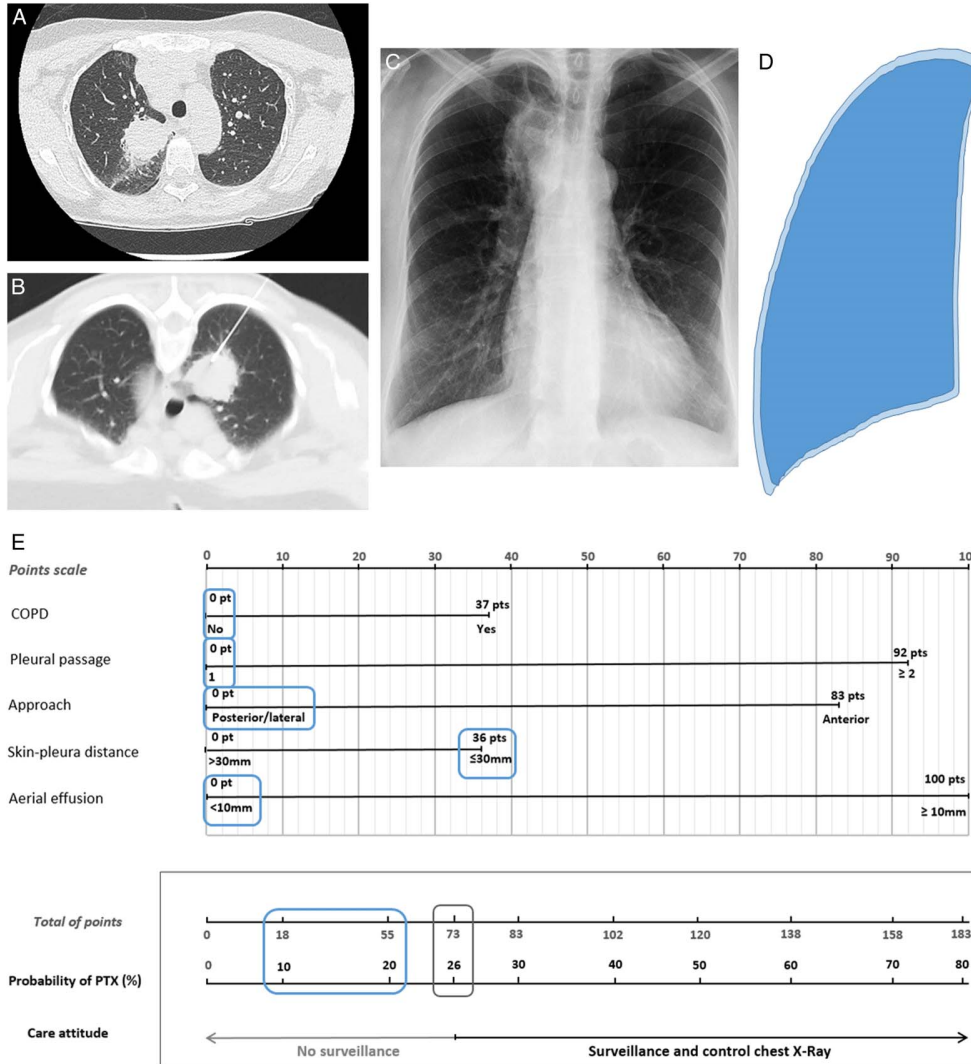
|   | Score <73 n = 122 | Score ≥ 73 n = 114 | OR [95% CI]      | P        |
|---|-------------------|--------------------|------------------|----------|
| Pneumothorax, n (%)                                   | 9 (7.4)           | 35 (30.7)          | 0.18 [0.08 0.39] | < 0.0001 |
| Chest tube insertion, n (%)                           | 3 (2.5)           | 16 (14)            | 0.15 [0.04 0.55] | 0.0037   |
| Duration (in days) of chest tube insertion, mean (SD) | 3.3 (1.5)         | 3.6 (1.6)          |                  | 0.863*   |
| Length (in days) of hospital stay, mean (SD)          | 1.1 (1.2)         | 1.6 (1.7)          |                  | 0.009    |

\*Wilcoxon rank test.

Student t-test.

CI indicates confidence interval; OR, odds ratio.

Downloaded from http://journals.lww.com/thoracicimaging by BMDMSegPhKa17EJum11Q1N4a4kL1hE2p5h1o4XXM10hCwCX1AVhVQp1lQH1D3D3D0DfY7ZTSF4G3VCA0A1pD48K8KX0V0mY+78= on 08/21/2023

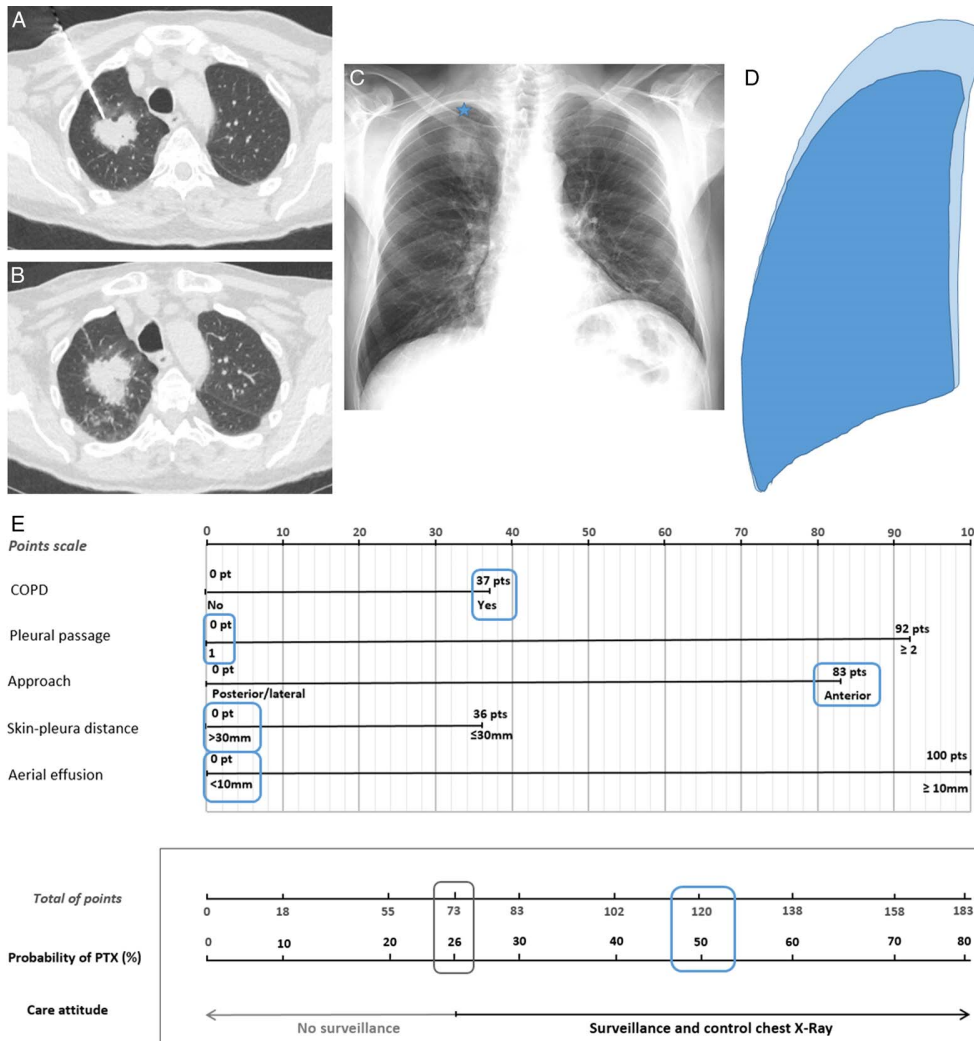


**FIGURE 4.** Example of score application: A 42-year-old old man with no history of chronic obstructive pulmonary disease, who benefited from a lung biopsy for the diagnosis of a right upper lobe mass using a posterior approach (A and B). In the absence of postprocedural aerial effusion, her score was calculated at 36 points, which represents a risk of 10% to 20% of postprocedural pneumothorax. She had a chest x-ray 2 hours following the biopsy, which showed no pneumothorax and was therefore discharged at H+4 (C). D, A schematic representation of her pleural space (deep blue visceral pleura, light blue parietal pleura) with no pneumothorax. E, Shows the score details.

freshly created breach, thus limiting the risk of air leakage and, therefore, pneumothorax. We showed that a skin-to-pleura distance <30 mm was predictive of pneumothorax, which has not been previously reported. In a series reported by Yeow et al, univariate analysis showed a significant relationship between chest wall thickness and the risk of pneumothorax after PTLB.<sup>7</sup> Keeping in mind that spontaneous pneumothorax occurs preferentially in tall and thin subjects, these variables suggest a

physiopathological mechanism protecting patients with a thick chest wall from the risk of pneumothorax. As anticipated, the presence of aerial effusion on final CT control was a significant risk factor for post-PTLB pneumothorax in the multivariate model. We could have considered this aerial effusion blade as a pneumothorax, rather than as a risk factor. Indeed, pneumothorax is defined as the presence of air in the pleural cavity. The ultimate aim of our study was to identify patients who would

Downloaded from http://journals.lww.com/thoracicimaging by BMDMSegPhKa17EJum1IQNA4kLLhE2pshl94XXM on 09/21/2023

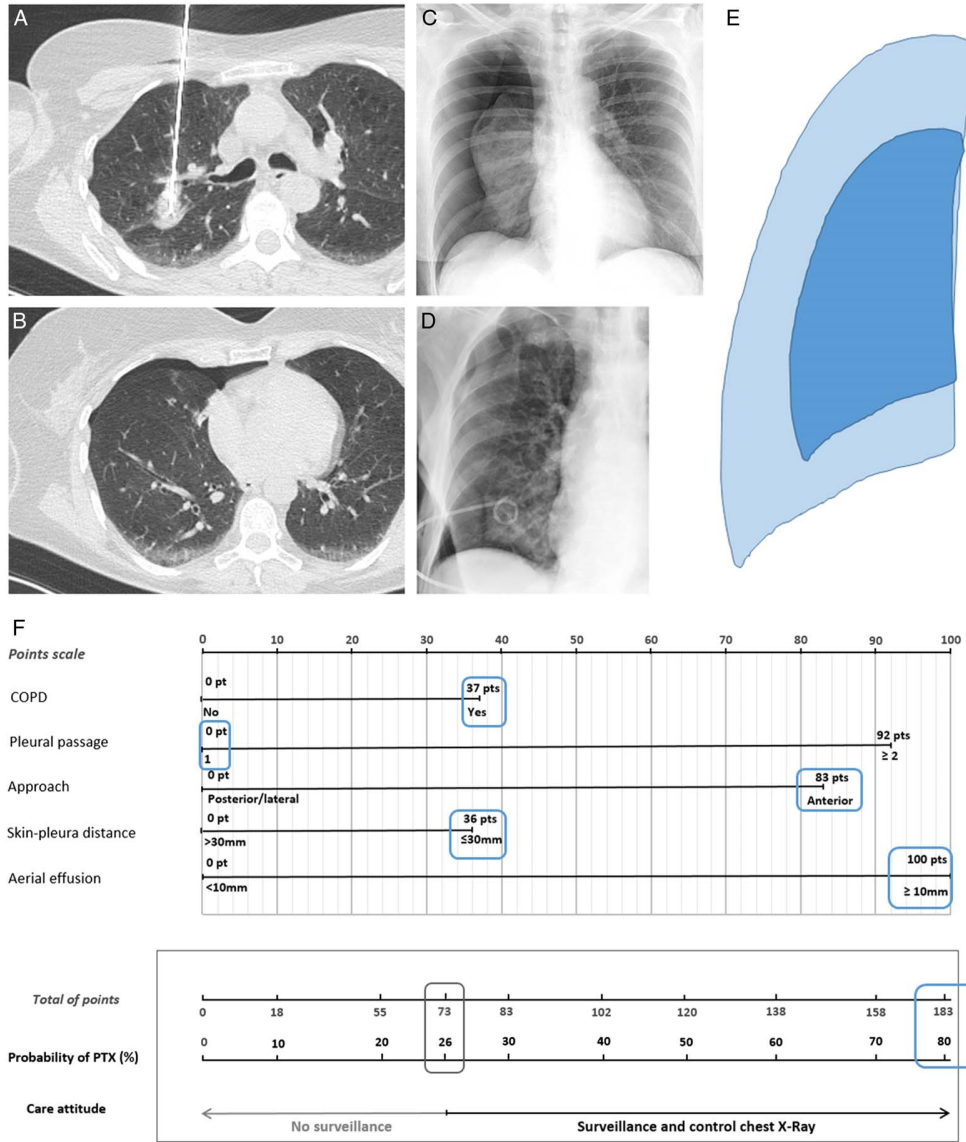


**FIGURE 5.** Example of score application: A 62-year-old old woman with a history of chronic obstructive pulmonary disease, who benefited from a lung biopsy for the diagnosis of a right upper lobe mass, using an anterior-posterior approach (A). In the absence of significant postprocedural aerial effusion (B), her score was calculated at 120 points, which represents a risk of 50% of postprocedural pneumothorax. She had a chest x-ray 2 hours following the biopsy, which showed an incomplete pneumothorax, asymptomatic, and was therefore hospitalized for surveillance (C). Pneumothorax resolved the day following the biopsy without specific care. D, A schematic representation of her pleural space (deep blue visceral pleura, light blue parietal pleura), showing incomplete pneumothorax. E, Shows the score details.

require clinical and radiologic monitoring because they were considered at risk of developing pneumothorax that might require possible evacuation. However, more than half of the patients had aerial effusion of all sizes at the end of PTLB, while the pneumothorax rate at the first chest x-ray was 24.9%. Thus, at least half of the patients with the presence of an aerial effusion would not have visible pneumothorax on chest x-rays and, therefore, could be eligible for outpatient care. The other risk

factors of pneumothorax identified in our study were consistent with those reported in the literature. COPD and particularly emphysema on the needle path are associated with a higher risk of pleural drainage.<sup>22,24-27</sup> The association between the number of pleural passages and the risk of pneumothorax is debated,<sup>22,25-27</sup> probably due to the difficulty of accurately evaluating this variable in the retrospective setting of most published studies. Pneumothorax occurrence with a score

Downloaded from http://journals.lww.com/thoracicimaging by BNDMfsgPHKaY1ZEmum1QON4a+kLLhEZpsHh0AXM  
IP: 095.095.170.203



**FIGURE 6.** Example of score application: A 69-year-old old woman with a history of chronic obstructive pulmonary disease and emphysema, who benefited from a lung biopsy for the diagnosis of a right upper lobe nodule using an anterior-posterior approach (A). In the presence of postprocedural aerial effusion but > 10 mm (B), her score was calculated at 183 points, which represents a risk of 80% of postprocedural pneumothorax (B). Indeed, the control chest biopsy-ray showed a complete pneumothorax associated with shortness of breath and right chest pain (C). Chest drainage was carried out under fluoroscopic guidance (control chest x-ray following drainage displayed (D)). E, A schematic representation of her pleural space (deep blue visceral pleura, light blue parietal pleura), with complete pneumothorax. F, Shows the score details.

<73 points was 7.4% and late evacuation of 2.5% by means of a high predictive negative value (92.6%) in our study. A score <73 points was strongly associated with a reduced risk of

pneumothorax and chest tube insertion. Length of hospital stay was also significantly lower in those with a score <73 (1.1 vs. 1.6 d). Patients for whom an anterior approach is chosen, when

more than 1 fissure is crossed during the biopsy, or who have a > 10 mm arial effusion on the CT control have automatically a score > 73 points, therefore requiring increased surveillance.

Our study has several limitations. Despite the large number of patients, the single-center design may have led to selection bias. However, patients were all managed by the same experienced team in a large university hospital, with reproducible operative techniques over time thanks to a local protocol. With the latter protocol, all patients were hospitalized for at least 1 day, and therefore all pneumothorax, in particular delayed pneumothorax, were diagnosed, either by symptoms or by systematic radiography (whereas most studies focus on immediate pneumothorax).<sup>11</sup> Due to the retrospective design of the study cohort, 60 patients had missing data for the variable BMI. The use of the skin-pleura distance, which might be a mediator of the relationship between BMI and the risk of pneumothorax, could carry part of the information included in the BMI. Hemorrhage-pleural contact has been previously reported as a risk factor for pneumothorax after PTLB,<sup>8</sup> accounting for the ability of blood to control the broncho-pleural fistula. It was not measurable in 51 patients because of the proximity between the lesion and the pleura. Our study and validation cohorts differ in terms of medical history (COPD, history of respiratory disease, homolateral chest surgery, and irradiation), probably because of missing data in the retrospective cohort. Although our study included one of the largest cohorts compared with published data, a larger sample size would nonetheless have conferred increased statistical power. We counterbalanced this difficulty by using the bootstrap technique.

In conclusion, we developed a practical predictive score for clinically relevant pneumothorax after PTLB. Patients with a score of less than 73, based on a history of COPD, anterior biopsy approach, number of pleural passes, skin-pleura distance, and presence of a significant arial effusion, had a 7.4% risk of developing a pneumothorax (and maximum 2.5% risk of requiring delayed evacuation), making them eligible for outpatient management. These results, and their economic impact, need to be confirmed in a multicenter trial.

#### ACKNOWLEDGMENT

Jean-Charles Dalphin (Deceased) contributed to the conceptualization and methodology of the study.

#### REFERENCES

- US Preventive Services Task Forces, Krist AH, Davidson KW, Mangione CM, et al. Screening for lung cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325:962-970.
- Priola AM, Priola SM, Cataldi A, et al. Accuracy of CT-guided transthoracic needle biopsy of lung lesions: factors affecting diagnostic yield. *Radiol Med (Torino)*. 2007;112:1142-1159.
- Lee H, Murphy C, Mortani Barbosa EJ Jr, et al. Prediction of complication risk in computed tomography-guided thoracic biopsy: a prescription for improving procedure safety. *J Thorac Imag*. 2023;38:88-96.
- Heerink WJ, de Bock GH, de Jonge GJ, et al. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol*. 2017;27:138-148.
- Vatrella A, Galderisi A, Nicoletta C, et al. Age as a risk factor in the occurrence of pneumothorax after transthoracic fine needle biopsy: our experience. *Int J Surg Lond Engl*. 2014;12(Suppl 2S):29-32.
- Rizzo S, Preda L, Raimondi S, et al. Risk factors for complications of CT-guided lung biopsies. *Radiol Med (Torino)*. 2011;116:548-563.
- Yeow K-M, Su I-H, Pan K-T, et al. Risk factors of pneumothorax and bleeding: multivariate analysis of 660 CT-guided coaxial cutting needle lung biopsies. *Chest*. 2004;126:748-754.
- De Filippo M, Saba L, Silva M, et al. CT-guided biopsy of pulmonary nodules: is pulmonary hemorrhage a complication or an advantage? *Diagn Interv Radiol Ank Turk*. 2014;20:421-425.
- Ohno Y, Hatabu H, Takenaka D, et al. CT-guided transthoracic needle aspiration biopsy of small (< or = 20 mm) solitary pulmonary nodules. *AJR Am J Roentgenol*. 2003;180:1665-1669.
- Huo YR, Chan MV, Habib A-R, et al. Pneumothorax rates in CT-Guided lung biopsies: a comprehensive systematic review and meta-analysis of risk factors. *Br J Radiol*. 2020;93:20190866.
- MacDuff A, Arnold A, Harvey J Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010:14.
- Lynch DA, Austin JH, Hogg JC, et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. *Radiology*. 2015;277:192-205.
- Cox JE, Chiles C, McManus CM, et al. Transthoracic needle aspiration biopsy: variables that affect risk of pneumothorax. *Radiology*. 1999;212:165-168.
- Anzidei M, Sacconi B, Fraioli F, et al. Development of a prediction model and risk score for procedure-related complications in patients undergoing percutaneous computed tomography-guided lung biopsy. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. 2015;48:e1-e6.
- Iezzi R, Larici A, Contegiacomo A, et al. A new score predicting intraprocedural risk in patients undergoing CT-guided percutaneous needle pulmonary biopsy (CATH-score). *Eur Rev Med Pharmacol Sci*. 2017;21:3554-3562.
- Yang L, Liang T, Du Y, et al. Nomogram model to predict pneumothorax after computed tomography-guided coaxial core needle lung biopsy. *Eur J Radiol*. 2021;140:109749.
- Wang S, Tu J, Chen W. Development and validation of a prediction pneumothorax model in CT-guided transthoracic needle biopsy for solitary pulmonary nodule. *Biomed Res Int*. 2019;2019:e7857310.
- Zhao Y, Wang X, Wang Y, et al. Logistic regression analysis and a risk prediction model of pneumothorax after CT-guided needle biopsy. *J Thorac Dis*. 2017;9:4750-4757.
- Zhao Y, Bao D, Wu W, et al. Development and validation of a prediction model of pneumothorax after CT-guided coaxial core needle lung biopsy. *Quant Imaging Med Surg*. 2022;12:5404-5419; PMID: 36465829; PMCID: PMC9703113.
- Weon J, Robson S, Chan R, et al. Development of a risk prediction model of pneumothorax in percutaneous computed tomography guided transthoracic needle lung biopsy. *J Med Imaging Radiat Oncol*. 2021;65:686-693.
- Mills M, Choi J, El-Haddad G, et al. Retrospective analysis of technical success rate and procedure-related complications of 867 percutaneous CT-guided needle biopsies of lung lesions. *Clin Radiol*. 2017;72:1038-1046.
- Kim JI, Park CM, Lee SM, et al. Rapid needle-out patient-rollover approach after cone beam CT-guided lung biopsy: effect on pneumothorax rate in 1,191 consecutive patients. *Eur Radiol*. 2015;25:1845-1853.
- O'Neill AC, McCarthy C, Ridge CA, et al. Rapid needle-out patient-rollover time after percutaneous CT-guided transthoracic biopsy of lung nodules: effect on pneumothorax rate. *Radiology*. 2012;262:314-319.
- Hiraki T, Mimura H, Gobara H, et al. Incidence of and risk factors for pneumothorax and chest tube placement after CT fluoroscopy guided percutaneous lung biopsy: retrospective analysis of the procedures conducted over a 9-year period. *Am J Roentgenol*. 2010;194:809-814.
- Kazerooni EA, Lim FT, Mikhail A, et al. Risk of pneumothorax in CT-guided transthoracic needle aspiration biopsy of the lung. *Radiology*. 1996;198:371-375.
- Chami HA, Faraj W, Yehia ZA, et al. Predictors of pneumothorax after CT-guided transthoracic needle lung biopsy: the role of quantitative CT. *Clin Radiol*. 2015;70:1382-1387.
- Poe RH, Kallay MC. Transthoracic needle biopsy of lung in nonhospitalized patients. *Chest*. 1987;92:676-678.

*Validation dans une cohorte externe du score prédictif de survenue du pneumothorax post-biopsie pulmonaire transthoracique*

**Résumé**

Contexte :

La complication la plus courante empêchant la prise en charge ambulatoire après une biopsie pulmonaire percutanée guidée par scanner (BPTC) est la présence d'un pneumothorax nécessitant la mise en place d'un drain thoracique. Récemment, notre équipe a établi un score pratique prédisant le risque de pneumothorax cliniquement pertinent après BPTC afin de guider le parcours du patient.

Objectifs :

Évaluer les performances de ce score pour prédire le pneumothorax dans une cohorte prospective externe indépendante de patients.

Méthode :

Les patients ayant réalisé une BPTC au CHU Bichat-Claude Bernard (Paris, France) entre le 1er janvier 2015 et le 31 décembre 2017 ont été évalués prospectivement sur les facteurs cliniques et radiologiques potentiellement liés à la survenue d'un pneumothorax. Le score utilisait 5 variables pour prédire la survenue d'un pneumothorax : BPCO, abord antérieur du PTLB, >1 passage plèvre, distance peau-pleure  $\leq 30$  mm et épanchement pleural aérique  $\geq 10$  mm au scanner réalisé en fin de procédure.

Résultats :

Le score a pu être évalué chez 313 patients. Un pneumothorax est survenu chez 95 patients (30,4 %). Dans cette cohorte externe, avec une valeur seuil de 73 points, le score avait un C-index de 0,77, une sensibilité de 75 % et une spécificité de 56 %. Les valeurs prédictives négatives et positives étaient respectivement de 84 % et 43 %. Un score  $< 73$  était significativement associé à un moindre recours au drainage thoracique (2,0 % chez les sujets avec un score  $< 73$  vs 12,0 % si  $\geq 73$ ,  $p = 0,002$ ), mais pas associé à une moindre durée d'hospitalisation ( $4,7 \pm 20,2$  jours chez les sujets avec un score  $< 73$ ,  $5,0 \pm 11,7$  jours chez les sujets avec un score  $\geq 73$ ,  $p = 0,86$ ).

Conclusion :

Ce score prédictif a confirmé des performances pronostiques intéressantes pour prédire le risque de pneumothorax après PTLB en pratique clinique courante.



**Original research**

**SCORE TO PREDICT THE OCCURRENCE OF PNEUMOTHORAX AFTER CT-GUIDED PERCUTANEOUS TRANSTHORACIC LUNG BIOPSY, EXTERNAL VALIDATION COHORT**

**Authors:**

Guillaume Eberst<sup>1, 2, 3, +</sup>, Waqaas Mohammad<sup>4</sup>, Alicia Guillien, PhD<sup>5</sup>, Antoine Khalil<sup>4</sup>, Joffrey Hamam<sup>1</sup>, Julien Behr<sup>6</sup>, Philippe Manzoni<sup>6</sup>, Paul Calame<sup>6</sup>, Franck Grillet<sup>6</sup>, Gérard Zalcman<sup>7</sup>, Valérie Gounant<sup>7</sup>, Virginie Westeel<sup>1,3</sup>

**Affiliations:**

<sup>1</sup> Chest Disease Department, University Hospital, Besançon, France

<sup>2</sup> Methodology and Quality of Life in Oncology Unit, University Hospital, Besançon, France

<sup>3</sup> Franche-Comté University, EFS, INSERM, UMR RIGHT, F-25000 Besançon, France

<sup>4</sup> Department of Radiology, Groupe Hospitalier Bichat–Claude-Bernard, Assistance publique–Hôpitaux de Paris, 75018 Paris, France

<sup>5</sup> University of Grenoble Alpes, French National Institute of Health and Medical Research, French National Center for Scientific Research, Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health, Institute for Advanced Biosciences, Grenoble, France;

<sup>6</sup> Department of Radiology, University Hospital of Besançon, Besançon, France

<sup>7</sup> Université Paris Cité, Department of Thoracic Oncology, CIC INSERM 1425, Groupe Hospitalier Bichat–Claude-Bernard, Assistance publique–Hôpitaux de Paris, 75018 Paris, France

\*  
**Correspondence to:**

Dr Guillaume EBERST, Chest Disease Department,  
University Hospital of Besançon, 3 Boulevard Fleming, Besançon cedex, 25030, France  
Tel: 03 70 63 22 06  
Email: [geberst@chu-besancon.fr](mailto:geberst@chu-besancon.fr)

**Key words**

Image-guided biopsy, lung cancer, pneumothorax, risk factors, outpatient procedure

**List of Abbreviations**

AOR: Adjusted Odds Ratio

AUC: Area Under the Curve

BMI: Body Mass Index

COPD: Chronic Obstructive Pulmonary Disease

CT: Computed Tomography

G: Gauge

HU: Hounsfield Units

OR: Odds-Ratio

SD: Standard Derivation

PTLB: Percutaneous Transthoracic Lung Biopsy

UIP: Usual Interstitial Pneumonia

## **ABSTRACT**

**Background:** The most common complication preventing outpatient management, after percutaneous CT-guided lung biopsy (PTLB) is the occurrence of a pneumothorax that requires chest tube placement. Recently, our team established a pragmatic score predicting the risk of clinically relevant pneumothorax after PTLB in order to guide the patient journey, called CAPAD score for this study.

**Objectives:** To evaluate the performance of this score for predicting pneumothorax using an independent, external prospective cohort of patients.

**Method:** Patients who underwent a PTLB performed at the University Hospital Bichat-Claude Bernard (Paris, France) between January 1<sup>st</sup> 2015 and December 31<sup>st</sup> 2017 were prospectively evaluated on clinical and radiological factors potentially related to pneumothorax occurrence. The CAPAD score uses 5 variables to predict the occurrence of a pneumothorax: COPD, Anterior PTLB approach, >1 crossing through the Pleura, Aerial effusion  $\geq 10$  mm on the CT-scan performed at the end of the procedure, and Distance skin-pleura  $\leq 30$ mm.

**Results:** The CAPAD score could be assessed in 313 patients. Pneumothorax occurred in 95 patients (30.4 %). In this external cohort, with a cut-off value of 73 points, the score had a c-index of 0.77, a sensitivity of 75% and a specificity of 56%. The predictive negative and positive values were 84% and 43%, respectively. A score < 73 was significantly associated with reduced chest tube insertion (2.0% in subjects with score < 73 vs 12.0% if  $\geq 73$ ,  $p = 0.002$ ).

**Conclusion:** Our pragmatic CAPAD score confirmed interesting prognostic performances in predicting the risk of clinically relevant pneumothorax after PTLB.

## INTRODUCTION

Increased use of chest computed tomography (CT) for lung cancer screening is associated with the discovery of a rising number of small lung lesions (1). Percutaneous CT-guided lung biopsy (PTLB) is recommended for obtaining a histological diagnosis of pulmonary nodules or masses when bronchial endoscopy is impracticable, especially in peripheral lesions (2, 3, 4). In all guidelines, evaluation of the risk of pneumothorax is crucial when deciding on a PTLB because pneumothorax is the most common complication that occurs during (or immediately after) a PTLB (5). Patients are typically monitored after CT-guided transthoracic procedures, given these potential complications. Keeping patients under nursing observation after procedure adds significant drain on nursing resources, severely limits the capacity of the radiology unit due to surveillance procedures and is more costly (6). As far as we know, there is no consensus in the literature on a specific post-operative follow-up protocol for these patients. A wide variation of protocols exists, between no surveillance imaging (7) and obtaining chest x-rays (CXRs) at 1 and 3 hours (8, 9), or 24 hours post procedure since pneumothorax late occurrence is possible (10). Alternatively, monitoring procedures increasingly recommend faster discharge from hospital and discharge only based on clinical observation without any follow-up imaging has even been proposed (7). However, the conclusion of this study was that obtaining a routine follow-up CXR in all patients after PTLB appears warranted, given the high rate of delayed pneumothorax and large percentage of patients who will eventually require a chest tube. Protocols are often based on institutional and operator preferences. In the guidelines proposed by the British Thoracic Society, a CXR should be performed one-hour post procedure (11), with no specific monitoring required following an uncomplicated biopsy procedure. To our knowledge, none of these guidelines, institutional protocol or operator preferences used adequate predictive scores to personalize post-PTLB monitoring.

Recently, our team established a pragmatic score predicting the risk of clinically relevant pneumothorax after PTLB (12). The aim of this score is to guide the patient journey, either towards

maximal monitoring with hospitalization or towards rapid discharge when the risk of pneumothorax requiring needle aspiration or tube drainage is low. It should also help to determine whether a patient requires "surveillance and control CXR " or "no surveillance". This score was first determined from a single-institution retrospective cohort of consecutive patients with diagnostic CT-guided PTLB for lung nodules or masses, and subsequently validated in a confirmatory validation cohort from the same institution. The CAPAD score is based on history of COPD, Anterior biopsy approach, number of Pleural crossings, skin-pleura Distance and presence of a significant Aerial effusion at CT-scan immediately after the procedure were the 5 variables to predict the occurrence of a pneumothorax with a cutoff score set at 73 points. Patients with a score less than 73 had a 7.4% risk of developing a pneumothorax (and a 2.5% risk of requiring pleural evacuation), making them eligible for outpatient management (12).

The objective of the current study was to assess the external validity of our CAPAD score to predict post-PTLB pneumothorax in an independent prospective cohort of patients from the University Hospital Bichat-Claude Bernard.

## **MATERIALS & METHODS**

### ***Study type, inclusion criteria and data collection***

This study is prospective cohort study conducted in the University Hospital Bichat-Claude Bernard (Paris, France) from January 2015 to December 2017.

Complications and associated risk factors from PTLB were secondary endpoints of this study. Data were collected retrospectively from patients' computer files for all consecutive patients who underwent PTLB: inpatient duration stay, demographic and lung function test data, CT scan analysis assessed emphysema (absence or presence) in the whole area of the lung and not specifically around the nodule, lesion characteristics including size, lobe location, distance from pleural puncture site and contact with a fissure, biopsy approach, skin-pleura distance and presence of a significant aerial effusion at CT-scan immediately after the procedure.

### ***Percutaneous Transthoracic lung biopsy procedure***

PTLB procedures at the University Hospital Bichat-Claude Bernard have been previously described (13). PTLB were conducted under CT guidance (Brilliance 40 Phillips or Aquilion PRIME Canon) with core biopsy sizes (18G or 20G semi-automated cutting needle: Temno, Cook, Bard, Argon) specified. All procedures were performed by one of six chest radiologists, including two seniors with >10 years' experience in CT-guided biopsies, and four juniors (13). Post-procedural whole-lung ultra-low-dose CT scans were systematically performed within 5 min after the last puncture to detect complications including post-procedure aerial effusion. Post-procedural immediate aerial effusion was defined as the maximum distance of detachment of the visceral pleura from the parietal pleura measured in mm on an axial post-procedure CT slice. If an aerial effusion was detected in an asymptomatic patient with a <3 cm distance between lung and chest wall, another whole-lung CT was performed 10 min later to check on any further expansion. If the patient was symptomatic or if the pneumothorax was even greater, a chest tube was inserted under CT-scan control and the patient is hospitalized. In all cases, CXR was performed between 4 and 6 hours post-PTLB procedure to check for late pneumothorax occurrence or worsening when a chest tube was not immediately inserted. In case of asymptomatic aerial effusion not requiring chest tube insertion, the patient was discharged with a planned outpatient visit and CXR 7 days later.

### ***Imaging analysis***

CT scan analysis assessed the occurrence of post-procedure aerial effusion, emphysema (absence or presence) in the whole area of the lung and not specifically around the nodule, and lesion characteristics including size (in mm), location, depth (distance from pleural puncture site to lesion), skin to pleura distance (in mm) and contact with a fissure. To use the same definition of pneumothorax than in the population used to develop the CAPAD score, the images were reviewed retrospectively by an investigator from University Hospital of Besançon (GE). with the following variables defined as in the cohort allowing the establishment of the score. In the event of disagreement, a discussion

between each team (University Hospital Bichat-Claude Bernard and University Hospital of Besançon) allowed a conclusion to be reached.

### ***Definition of outcome: pneumothorax***

The diagnosis of pneumothorax was made when on the post-procedure CT slice it was complete (>3 cm distance between lung and chest wall) as described by the British Thoracic Society (14) and required immediate drainage. On frontal CXR, pneumothorax was considered as complete if there was either a pulmonary detachment over the entire axillary height and more than 2 cm at the pulmonary hilum, or a detachment of more than 3 cm at the pulmonary apex (14). Indication of chest tube insertion followed BTS recommendations (14), essentially based on significant symptoms (breathlessness), underlying compromised respiratory function, and impossibility of ambulatory management (mainly for socio-cultural reasons).

### ***Score definition***

The CAPAD score uses 5 variables to predict the occurrence of a pneumothorax: COPD (37 points if present), Anterior PTLB approach (83 points), >1 crossing through the Pleura (92 points), Distance skin-pleura  $\leq 30$ mm (36 points), and Aerial effusion  $\geq 10$  mm (100 points). The number of points of each variable was determined according to a weighting obtained in a multivariate logistic regression model in the initial Besançon cohort of patients (12). The score corresponds of the sum of the points and a cutoff of 73 points was established to classify the patients at high risk (score  $\geq 73$ ) or low risk (score  $< 73$ ) of pneumothorax occurrence (12). The COPD was defined using the recommendations of the Global Initiative on Obstructive Lung Disease (GOLD) with the use of a fixed ratio (FEV1/FVC  $< 0.7$ ), together with exposure to tobacco smoke or any noxious fumes or gases and respiratory symptoms (15).

### ***Ethical and legal considerations***



This study followed the ethical guidelines of the declaration of Helsinki and was approved by the Bichat-Claude Bernard Hospital institutional review board (CRM-1909-029). According to French observational study regulations, all patients received a printed information sheet explaining the procedure, complication risks and data collection, before providing their oral consent.

### *Statistical analysis*

Results are expressed as mean±standard deviation (SD) for quantitative variables, and as number and percentage for categorical variables. The chi<sup>2</sup> test was used to test the association between two categorical variables. For the comparison of means, the student test or the Wilcoxon test were used depending on the nature of the distribution. The performance of the model was evaluated using the c-index (equivalent to the area under the ROC curve) and its calibration by the Hosmer-Lemeshow test. We applied the multivariate logistic model in the external cohort, and assessed c-index, probability of pneumothorax, sensitivity, specificity, predictive negative and positive values using the cut-off of 73, determined in the initial cohort. All statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA) with a significant level < 0.05.

## **RESULTS**

### *Study cohort*

Among the 474 patients included in the initial cohort, constitutive data of the CAPAD score were available in 313 patients who therefore represented the final dataset of patients (**Figure 1**). The baseline characteristics and study outcomes (pneumothorax occurrence, chest tube insertion and length of hospitalization) did not differ between the excluded and included patients (**Supplementary Table 1**) except for gender with slightly more males in the included patients. The characteristics of patients and imaging analysis are summarized in table 1. The study population included 215 men (69%) with a median age of 65 years (interquartile range (IQR) 30–89 years), and 153 patients were considered as having a COPD (48.9%). The majority of PTLB indications were suspicion of malignancy for 293

patients (94%). The median (IQR) lesion diameter was 29 mm (3–148 mm) (**Table 1**). The only difference between the two cohorts (Besançon and Bichat) concerned the proportion of COPD, which was higher in the Bichat validation cohort (**Supplementary Table 2**).

### *Pneumothorax occurrence*

Pneumothorax occurred in 95 patients (30.4 %) but drainage was required in 23 patients (24% of all pneumothorax, 7.3% of the 313 patients). In bivariate analysis, among clinical and demographic characteristics, no variable was associated with a significantly higher risk of pneumothorax (**Table 1**). From the morphological analysis of CT scan, the risk of developing pneumothorax was significantly increased when the distance from the hilum to the lesion (in millimeters) was higher ( $p=0.0073$ ) and when the nodule size was smaller ( $p<0.0001$ ) (**Table 1**). Among the procedure-related factors, significantly increased risk of pneumothorax was observed with the following variables: biopsy needle size at 20G ( $p=0.0125$ ) and a higher duration from pleural puncture to end of PTLB (in minutes) ( $p=0.0117$ ) (**Table 2**).

### *Score validation in the external cohort*

The multivariate logistic regression using factors of the CAPAD score is presented in the **Table 3**. Only aerial effusion significantly correlated with the risk of pneumothorax occurrence (Adjusted OR: 52.49 [19.95 - 181.62];  $p<0.001$ ) (**Table 3**). Applying the predetermined score on this validation cohort, with a cut-off value of 73 points, 147 patients had a score  $<73$  and 166 had a score  $\geq 73$ . Regarding statistical performance of the score, c-index was 0.77, sensitivity and specificity were 75% and 56%, respectively. The predictive negative and positive values were 84% and 43%, respectively (**Figure 2**). A score  $< 73$  points was significantly associated with reduced pneumothorax occurrence (7.4% in patients with score  $< 73$  vs 30,7% in  $\geq 73$ ; OR : 0.15; 95% CI, 0.08-0.27;  $p<0.0001$ ), chest tube insertion (2.0% in patients with score  $< 73$  vs 12.0% in  $\geq 73$ ;  $p = 0.002$ ), but not the length of hospital

stay ( $4.7\pm 20.2$  days in patients with score  $< 73$ ,  $5.0\pm 11.7$  days in patients with score  $\geq 73$  ( $p=0.86$ )) (**Table 4**). As expected, patients with chest tube insertion had longer length of hospital stay (**Supplementary table 2**).

In multivariate analysis, aerial effusion  $\geq 10$ mm is associated with pneumothorax (adjusted OR= 52.49 [CI, 95%: 19.95-181.62]) (**Table 3**). Among the subjects without any aerial effusion ( $n=225$ ), 17 (7.6%) presented with a pneumothorax of whom only 4 (1.8%) required drainage according to BTS recommendations vs 78 (88.6%) and 19 (21.6%) in the 88 subjects with aerial effusion  $\geq 10$  mm, respectively ( $p<0.001$  for both). No correlation was found between each variable (**Table 3**).

## DISCUSSION

The current study aimed at validating a predictive score for the occurrence of pneumothorax after PTLB, the CAPAD score (based on COPD, anterior PTLB approach,  $>1$  passage through the pleura, distance skin-pleura  $\leq 30$ mm, and aerial effusion  $\geq 10$  mm) elaborated in a cohort of 498 patients from Besançon university hospital (from March 2018 to Oct. 2019). We now report in this independent validation using a series of 313 patients from Bichat university hospital (accrued from Jan. 2015 to Dec. 2017), a predictive negative value of 84%. Thus, the CAPAD score can reliably identify patients who have a low risk of pneumothorax, eligible for outpatient care management after PTLB. To our knowledge, this is the only study reporting scores to predict PLTB complications with an external cohort validation supporting the stability of the score. Accordingly, in both independent cohorts of patients a score  $< 73$  was associated to a low incidence of pneumothorax (7.4% in both cohorts), and a low frequency of chest tube insertion (respectively 2.5 and 2.0%).

Among all components of the CAPAD score, aerial effusion was, as in the initial cohort, the most significantly associated with the occurrence of pneumothorax in the multivariate analysis of the external cohort (adjusted OR= 52.49 [CI, 95%: 19.95-181.62]) (12). Aerial effusion is even the only variable associated with the risk of pneumothorax in the validation cohort. The comparison between the initial cohort and this external cohort showed that patient characteristics were similar, except for

the rate of COPD. This can be due to a difference in the collection of this variable: retrieved from the comorbidity list in the initial cohort, extracted from the results of lung function tests in the external cohort. In the literature, the link between post-PTLB pneumothorax occurrence and the severity of obstructive ventilatory disorder has not been established (16). When focusing on studies in which COPD is defined by extracting information from the medical record, then links are found (17). This suggests that they identify more advanced COPDs with possibly more frequently emphysema, which is a well-established risk factor for post-PTLB pneumothorax (18).

Procedures were the same in both series of patients with respect to experience of chest radiologists, indications, respect of contraindications, PTLB itself and immediate post-procedure early monitoring (12, 13). The main difference between the 2 centers concerns the late post-procedure monitoring. In the external cohort, CXR was performed 4 to 6 hours after PTLB to check for late pneumothorax occurrence or worsening when a chest tube had not been immediately inserted. In case of aerial effusion and/or asymptomatic pneumothorax with no indication of chest tube insertion, the patient was discharged with a planned outpatient visit and CXR 7 days later. In the initial cohort, a systematic CXR was performed 4 to 6 hours, and 24 hours after PTLB. All patients were hospitalized for at least one day, and therefore all pneumothorax, in particular delayed, were diagnosed. Pneumothorax frequencies were strikingly close in the two cohorts (24.9% in the initial cohort vs 30.4% in the external cohort and 28.3% when including patients with missing data impeding the calculation of the score), and in the range of rates of pneumothorax reported in the literature. Indeed, the pooled overall pneumothorax incidence was 25.9% (ranging from 4.3% to 52.4%), and the pooled incidence of pneumothorax requiring chest tube placement was only 6.9% (ranging from 0% to 15%) in a meta-analysis by Heerink WJ *and coll* (19).

According to current definitions (3), we did not consider aerial effusion observed at immediate post-PTLB chest CT-scan as a pneumothorax, but rather as a risk factor for subsequently developing one. Although debatable, since pneumothorax is defined as the presence of air in the pleural cavity,

our goal was to predict actual clinically relevant pneumothorax. More than half of the patients had an aerial effusion of all sizes at the end of a PTLB, while the pneumothorax rate at the first CXR was only 24.9%. Moreover, the term “delayed pneumothorax” is not clearly defined either. Both pneumothorax developing 3 or 4 hours after PTLB (20) and aerial effusions diagnosed at first post-PTLB CT-scan control have been reported as delayed pneumothorax in several papers (21). However, in patient without aerial effusion, only 17 (7.6%) made a PNO and 4 (1.8%) were drained while 78 (88.6%) and 19 (21.6%) in the 88 subjects with aerial effusion  $\geq 1$  mm (Supplementary figure 1). This highlights the weight of aerial infusion in the risk of post-PTLB pneumothorax and supports systematic CT-Scan at the end of the procedure, particularly when outpatient care is planned. This importance is in concert with the guidelines under motivating to obtain a CT-Scan of the chest, once the biopsy has been performed, to identify any immediate post-procedural complication such as pneumothorax (22). In addition, several teams have shown that if no aerial effusion was seen on the immediate post-PTLB chest CT-Scan, only mild, mostly asymptomatic pneumothorax was subsequently observed (23, 24). In the 17 patients without aerial effusion and presenting a pneumothorax, eight (47%) had a score  $>73$  and for the 4 of these 17 patients requiring chest drainage, two (50%) had a score  $>73$ . In this external cohort, in the absence of aerial effusion, the score made only missed 2 drained pneumothorax in the entire cohort. Modifying the aerial effusion variable within the score to a cutoff of 0 would have made possible to further increase the negative predictive value.

Our study has some limitations. Despite the large number of patients included, the score could be assessed only in 313 patients of the 474 constituting the external cohort. That can induce bias due to missing data. Omitting everyone without complete data is known as complete case (or available case) analysis and is probably the most common approach. The results may be biased unless the data are missing at random (25). The baseline characteristics and study outcomes (pneumothorax occurrence, chest tube insertion and length of hospitalization) did not significantly differ between the excluded and included patients except for gender, which is not known as a risk factor for post-PTLB complications

(19), supporting the hypothesis that most missing data were "missing at random". Another limitation could consist of the absence of evaluation at 24 hours as in the initial cohort from university Hospital of Besançon, which could have induced an attrition bias. We therefore cannot exclude that a minimal proportion of pneumothorax might have been missed, while being asymptomatic, still fully resolved on the control CXR a medical evaluation at 7 days. However, the probability that such infra-clinical, infra-radiological, late but transient pneumothorax might have distorted the weight of arial effusion remains low. Finally, the patients of the two study cohorts benefited from PTLB carried out by experienced teams, experts in interventional radiology. Intuitively, chest radiologists experience is thought to influence complication rate. In a large single-cohort study, Yeow *et al.* reported operator experience as the third major risk factor for pneumothorax (26) after lesion size and lesion depth. In our study, we did not take into account the experience of the chest radiologists. The accuracy of our predictive score was not found to be high in this external cohort, despite, the very high negative predictive value gives hope for significant routine utility.

In conclusion, our results support that such a pragmatic predictive score could be useful, by excluding with a 84% meaningful negative predictive value the occurrence of a symptomatic pneumothorax after PTLB. Patients with a score of less than 73, based on history of COPD, anterior biopsy approach, number of pleural passes, skin-pleura distance and presence of a significant arial effusion, only had a 7.4% risk of developing a pneumothorax (and a 2% risk of requiring delayed evacuation), making them eligible for ambulatory management.

## **ACKNOWLEDGEMENT**

## **STATEMENT OF ETHICS**

## **CONFLICT OF INTEREST STATEMENT**

The authors declare no conflicts of interest.

## **FUNDING SOURCES**

None

## **AUTHOR CONTRIBUTIONS**

The scientific guarantor of this publication is V.W.

A.G. and G.E. have significant statistical expertise.

The study protocol follows the ethical guidelines of the Helsinki Declaration and was approved by the institutional review board.

GE: Conceptualization, Methodology, Formal analysis, Investigation and Writing — Original Draft, Writing—Review & Editing W.M.: Investigation, Writing — A.K.: Investigation, Writing. — G.Z.: Investigation, Writing. — J.H.: Conceptualization, Methodology, and Investigation, Writing — A.G., and P.C.: Methodology, Formal analysis, Writing. J.B.: Methodology and Investigation. P.M.: Conceptualization. — F.G.: Conceptualization, Methodology, and Investigation, Writing — V.G.: Methodology, Investigation, Writing—Review & Editing. V.W.: Conceptualization, Validation, Writing—Original Draft, Writing—Review & Editing Supervision.

## **DATA AVAILABILITY STATEMENT**

## REFERENCES

1. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, & Field JK. Lung cancer LDCT screening and mortality reduction—evidence, pitfalls and future perspectives. *Nature reviews Clinical oncology*, 2021 18 (3): 135-151.
2. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? *Diagnosis and management of lung cancer*, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 2012; 143 (5): e93S-e120S.
3. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax*. 2015; 70 (Suppl 2): ii1–54
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer Version 2.2019. 2018. Nov 21, [Last accessed on 2023 Aug 07]. Available from: <https://www.nccn.org/>
5. Zeng L, Liao H, Ren F, Zhang Y, Wang Q, & Xie M. Pneumothorax induced by computed tomography guided transthoracic needle biopsy: a review for the clinician. *International Journal of General Medicine*, 2021; 1013-1022.
6. Chiu YW, Kao YH, Simoff MJ, Ost DE, Wagner O, *et al.* Costs of biopsy and complications in patients with lung cancer. *ClinicoEconomics and Outcomes Research*, 2021; 191-200.
7. Taleb S, Jalaieian H, Frank N, Golzarian J, D'Souza D. Is a routine chest x-ray necessary in every patient after percutaneous CT-guided lung biopsy? A retrospective review of 278 cases. *Cardiovasc Inter- vent Radiol* 2017;40:1415-20.
8. Wu CC, Maher MM, Shepard J-AO. CT-guided percutaneous needle biopsy of the chest: preprocedural evaluation and technique. *Am J Roentgenol* 2011;196:W511-4
9. Winokur RS, Pua BB, Sullivan BW, Madoff DC. Percutaneous lung biopsy: technique, efficacy, and complications. *Semin Interv Radiol* 2013;30:121-7.
10. Bae K, Ha JY, & Jeon KN. Pneumothorax after CT-guided transthoracic lung biopsy: A comparison between immediate and delayed occurrence. *PloS one*, 2020; 15 (8): e0238107.
11. Manhire A, Charig M, Clelland C, et al. Guidelines for radiologically guided lung biopsy. *Thorax* 2003;58:920-36.
12. Lamfichekh Y, Lafay V, Hamam J, et al. Score to Predict the Occurrence of Pneumothorax After Computed Tomography-guided Percutaneous Transthoracic Lung Biopsy. *Journal of Thoracic Imaging*, 2023 38 (5): 315-324.
13. Lissavalid E, Khalil A, Soussi G, et al. Transthoracic lung biopsy for pulmonary nodules  $\leq 20$ mm in routine clinical care. *ERJ Open Res* 2022; 8: 00562-2021
14. Roberts ME, Rahman NM, Maskell NA, Bibby AC, Blyth KG, Corcoran JP, ... & Walker S. British Thoracic Society Guideline for pleural disease. *Thorax*, 2023; 78 (Suppl 3), s1-s42.



15. From the global strategy for the diagnosis, management and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: <http://goldcopd.org>. (accessed 29 April 2017)
16. Zhou M, Wang T, Wei D, Zhu Y, Jiang Y, Zuo C, Yang L. Incidence, severity and tolerability of pneumothorax following low-dose CT-guided lung biopsy in different severities of COPD. *The Clinical Respiratory Journal*, 2021; 15 (1): 84-90.
17. Wiener RS, Schwartz LM, Woloshin S, & Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Annals of internal medicine*, 2011; 155 (3): 137-144.
18. Elshafee AS, Karch A, Ringe KI, Shin HO, Raatschen HJ, Soliman NY, *et al.* Complications of CT-guided lung biopsy with a non-coaxial semi-automated 18 gauge biopsy system: frequency, severity and risk factors. *PloS one*, 2019; 14 (3): e0213990.
19. Heerink WJ, de Bock GH, de Jonge GJ *et al.* Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol* , 2017; 27: 138–148.
20. Narula N, Siddiqui F, Siddiqui AH, Man WC, & Chalhoub M. Delayed pneumothorax: a potential complication of transbronchial lung biopsy. *Respiratory medicine case reports*, 2018; 23: 170-172.
21. Choi CM, Um SW, Yoo CG, *et al.* Incidence and risk factors of delayed pneumothorax after transthoracic needle biopsy of the lung. *Chest*. 2004;126(5):1516–1521. doi:10.1378/chest.126.5.1516
22. Dennie CJ, Matzinger FR, Marriner JR, & Maziak DE. Transthoracic needle biopsy of the lung: results of early discharge in 506 outpatients. *Radiology*, 2001; 219 (1): 247-251.
23. Anzidei M, Porfiri A, Andrani F, *et al.* Imaging-guided chest biopsies: techniques and clinical results. *Insights Imaging*. 2017; 8 (4): 419–428.
24. Khankan AA, & Al-Muaikeel M. Image-guided percutaneous transthoracic biopsy in lung cancer—emphasis on CT-guided technique. *Journal of infection and public health* 2012; 5: S22-S30.
25. Altman DG, & Bland JM. Missing data. *Bmj*, 2007; 334 (7590): 424-424.
26. Yeow KM, Su IH, Pan KT *et al.* Risk factors of pneumothorax and bleeding: multivariate analysis of 660 CT-guided coaxial cutting needle lung biopsies. *Chest*, 2004; 126: 748–54

**TABLES and FIGURE LEGENDS:**

**Table 1: Patients characteristics**

**Table 2: Procedure-related factors**

**Table 3. Pneumothorax risk factors after transthoracic lung biopsy: results of multivariate analysis in the study cohort.**

**Table 4. Predictive clinical application of the score applied on the external cohort.**

**Figure 1: Flowchart of external cohort**

**Figure 2. ROC curve of the score in external cohort**

**Supplementary Table 1: Patient characteristics and outcomes between excluded subjects and included subjects**

**Supplementary Table 2: Comparison between patients without/with chest tube insertion**

**Supplementary figure 1: Focus on aerial effusion**

**Table 1: Patients characteristics**

| Characteristic  | All<br>n = 313            | No pneumothorax<br>n = 218 | Pneumothorax<br>n = 95    | p-value              |
|---|---------------------------|----------------------------|---------------------------|----------------------|
| <b>Age</b>  | 65±11<br>[range: 30 - 89] | 65±11<br>[range: 30 - 89]  | 66±10<br>[range: 33 - 86] | 0.22 <sup>2</sup>    |
| <b>Gender</b>   |                           |                            |                           | 0.84 <sup>3</sup>    |
| Female  | 98 (31%)                  | 67 (31%)                   | 31 (33%)                  |                      |
| Male  | 215 (69%)                 | 151 (69%)                  | 64 (67%)                  |                      |
| <b>COPD</b>   |                           |                            |                           | 0.21                 |
| Yes   | 153 (49%)                 | 101 (47%)                  | 52 (55%)                  |                      |
| No  | 160 (51%)                 | 117 (53%)                  | 43 (45%)                  |                      |
| <b>PTLB indication</b>  |                           |                            |                           | 0.60 <sup>3</sup>    |
| Other   | 4 (1.3%)                  | 3 (1.4%)                   | 1 (1.1%)                  |                      |
| Rebiopsy  | 4 (1.3%)                  | 2 (0.9%)                   | 2 (2.1%)                  |                      |
| Suspicion of infection  | 12 (3.8%)                 | 10 (4.6%)                  | 2 (2.1%)                  |                      |
| Suspicion of malignancy   | 293 (94%)                 | 203 (93%)                  | 90 (95%)                  |                      |
| <b>Nodule size (in millimeters)</b>   | 29±21<br>[range: 3 - 148] | 32±22<br>[range: 5 - 148]  | 23±14<br>[range: 3 - 73]  | <0.0001 <sup>2</sup> |
| <b>Distance from the hilum to the lesion (in millimeters)</b>                 | 32±23<br>[range: 0 - 90]  | 30±23<br>[range: 0 - 90]   | 37±23<br>[range: 0 - 88]  | 0.007 <sup>2</sup>   |
| <b>Distance from the pleural puncture site to the lesion (in millimeters)</b> | 18±20[<br>range: 0 - 103] | 17±20<br>[range: 0 - 97]   | 20±19<br>[range: 0 - 103] | 0.19 <sup>2</sup>    |
| <b>Contact with a lung fissure</b>  | 49 (16%)                  | 36 (17%)                   | 13 (14%)                  | 0.64 <sup>3</sup>    |
| <b>Emphysema</b>  |                           |                            |                           | 0.31 <sup>3</sup>    |
| Absent  | 165 (53%)                 | 121 (56%)                  | 44 (46%)                  |                      |
| Moderate  | 111 (35%)                 | 72 (33%)                   | 39 (41%)                  |                      |
| Severe  | 37 (12%)                  | 25 (11%)                   | 12 (13%)                  |                      |

<sup>1</sup> Mean±SD [range: Range]; n (%)<sup>2</sup> Welch Two Sample t-test<sup>3</sup> Pearson's Chi-squared test

**Table 2: Procedure-related factors**

| Characteristic  | All<br>n = 313  | No pneumothorax<br>n = 218 | Pneumothorax<br>n = 95 | p-value           |
|---|-----------------|----------------------------|------------------------|-------------------|
| <b>Biopsy needle brand</b>  |                 |                            |                        | 0.12 <sup>3</sup> |
| Argon   | 2 (0.7%)        | 2 (1.0%)                   | 0 (0%)                 |                   |
| Bard  | 135 (46%)       | 92 (45%)                   | 43 (49%)               |                   |
| Cook - Quickcore  | 55 (19%)        | 33 (16%)                   | 22 (25%)               |                   |
| Temno   | 99 (34%)        | 76 (37%)                   | 23 (26%)               |                   |
| Unknown   | 22              | 15                         | 7                      |                   |
| <b>Biopsy needle size</b>   |                 |                            |                        | 0.01 <sup>3</sup> |
| 18  | 77 (26%)        | 63 (31%)                   | 14 (16%)               |                   |
| 20  | 216 (74%)       | 142 (69%)                  | 74 (84%)               |                   |
| Unknown   | 20              | 13                         | 7                      |                   |
| <b>Needle repositioning count</b>                                 |                 |                            |                        | 0.40 <sup>3</sup> |
| 0   | 143 (46%)       | 107 (49%)                  | 36 (39%)               |                   |
| 1   | 73 (24%)        | 50 (23%)                   | 23 (25%)               |                   |
| 2   | 57 (18%)        | 38 (17%)                   | 19 (21%)               |                   |
| 3   | 29 (9.4%)       | 19 (8.7%)                  | 10 (11%)               |                   |
| 4   | 6 (1.9%)        | 3 (1.4%)                   | 3 (3.3%)               |                   |
| 5   | 1 (0.3%)        | 0 (0%)                     | 1 (1.1%)               |                   |
| 7   | 1 (0.3%)        | 1 (0.5%)                   | 0 (0%)                 |                   |
| Unknown   | 3               | 0                          | 3                      |                   |
| <b>Duration from pleural puncture to end of PTLB (in minutes)</b> | 11±7            | 10±7                       | 13±8                   | 0.01 <sup>2</sup> |
|   | [range: 2 - 39] | [range: 2 - 39]            | [range: 2 - 38]        |                   |
| Unknown   | 2               | 1                          | 1                      |                   |
| <b>Number of samples by PTLB</b>                                  |                 |                            |                        | 0.04 <sup>3</sup> |
| 1   | 35 (13%)        | 17 (9.3%)                  | 18 (22%)               |                   |
| 2   | 83 (31%)        | 56 (31%)                   | 27 (33%)               |                   |
| 3   | 107 (40%)       | 80 (44%)                   | 27 (33%)               |                   |
| 4   | 33 (12%)        | 25 (14%)                   | 8 (9.6%)               |                   |
| 5   | 7 (2.6%)        | 5 (2.7%)                   | 2 (2.4%)               |                   |
| 6   | 1 (0.4%)        | 0 (0%)                     | 1 (1.2%)               |                   |
| Unknown   | 47              | 35                         | 12                     |                   |

<sup>1</sup> Mean±SD [range: Range]; n (%) <sup>2</sup> Welch Two Sample t-test <sup>3</sup> Pearson's Chi-squared test

**Table 3. Pneumothorax risk factors after transthoracic lung biopsy: results of multivariate analysis in the study cohort.**

|                          | No pneumothorax<br>n = 218 | Pneumothorax<br>n = 95 | P value | Crude OR<br>[95% CI]   | Adjusted* OR<br>[95% CI] |
|--------------------------|----------------------------|------------------------|---------|------------------------|--------------------------|
| COPD                     |                            |                        | 0.21    |                        |                          |
| No                       | 117 (54%)                  | 43 (45%)               |         | 1.00                   | 1.00                     |
| Yes                      | 101 (46%)                  | 52 (55%)               |         | 1.40 [0.86 - 2.28]     | 1.20 [0.66 - 2.19]       |
| Approach                 |                            |                        | 0.86    |                        |                          |
| Posterior/lateral        | 75 (34%)                   | 31 (33%)               |         | 1.00                   | 1.00                     |
| Anterior                 | 143 (66%)                  | 64 (67%)               |         | 1.08 [0.65 - 1.82]     | 1.08 [0.65 - 1.82]       |
| Several pleural passages |                            |                        | 0.69    |                        |                          |
| No                       | 204 (94%)                  | 87 (92%)               |         | 1.00                   | 1.00                     |
| Yes                      | 14 (6%)                    | 8 (8%)                 |         | 1.34 [0.52 - 3.25]     | 2.14 [0.73 - 5.72]       |
| Skin-pleura distance     |                            |                        | 0.07    |                        |                          |
| >30mm                    | 189 (87%)                  | 74 (78%)               |         | 1.00                   | 1.00                     |
| ≤30mm                    | 29 (13%)                   | 21 (22%)               |         | 1.85 [0.98 - 3.44]     | 1.89 [0.85 - 4.02]       |
| Aerial effusion          |                            |                        | <0.001  |                        |                          |
| <10mm                    | 214 (98%)                  | 49 (52%)               |         | 1.00                   | 1.00                     |
| ≥10mm                    | 4 (2%)                     | 46 (48%)               |         | 50.22 [19.30 - 172.42] | 52.49 [19.95 - 181.62]   |

\*Multivariate model: PNO ~ COPD + approach + several pleural passages + skin-pleura distance + aerial effusion

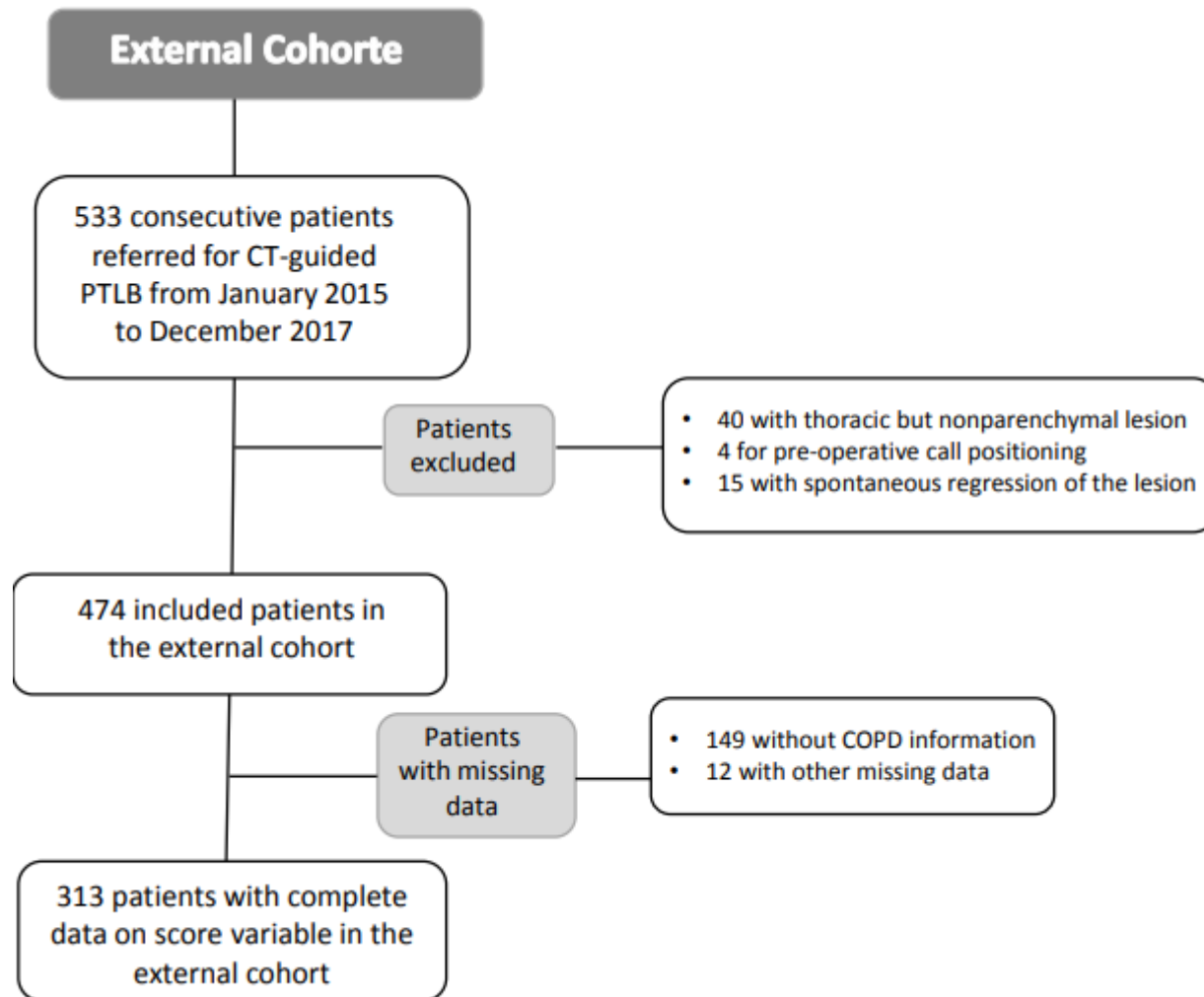
Score value in points for each risk factor as determined after logistic regression indexat.

COPD: Chronic obstructive pulmonary disease; BMI: Body Mass Index; AOR = Adjusted Odds-Ratio.

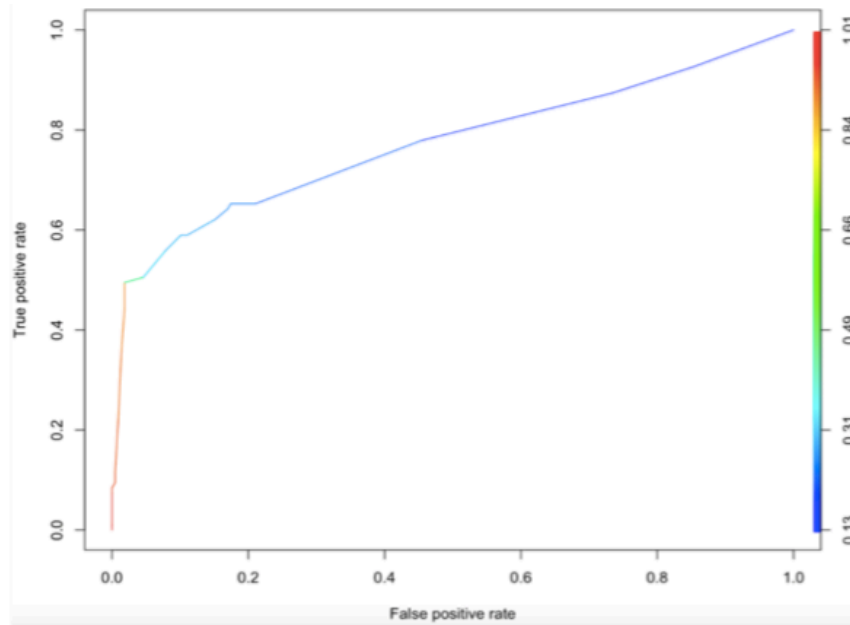
**Table 4. Predictive clinical application of the score applied on the external cohort.**

|  | <b>Score &lt;<br/>73<br/>n=147</b> | <b>Score ≥ 73<br/>n=166</b> | <b>p-value</b>    |
|--|------------------------------------|-----------------------------|-------------------|
| Pneumothorax, n (%)                            | 17 (7.4)                           | 78 (30.7)                   | <b>&lt;0.0001</b> |
| Chest tube insertion, n (%)                    | 3 (2.0)                            | 20 (12)                     | <b>0.002</b>      |
| Length (in days) of hospitalization, mean (SD) | 4.7 (20.2)                         | 5.0 (11.7)                  | 0.86              |

**Figure 1:** Flowchart of validation external cohort from Bichat Hospital



**Figure 2.** ROC curve of the score in external cohort



|                              | External Cohorte |
|------------------------------|------------------|
| Score (points)               | 73               |
| Sensibility, %               | 75               |
| Specificity, %               | 56               |
| Predictive positive value, % | 43               |
| Predictive negative value, % | 84               |
| C-Index                      | 0.77             |



**Supplementary Table 1: Patient characteristics and outcomes between excluded subjects and included subjects**

|  | <b>Excluded<br/>subjects<br/>n = 161</b> | <b>Included<br/>subjects<br/>n = 313</b> | <b>p</b>    |
|--|--|--|-------------|
| Age (years)  | 62.7 ± 15.9                              | 65.4 ± 10.7                              | 0.05        |
| Male, n(%)   | 94 (58%)                                 | 215 (69%)                                | <b>0.03</b> |
| Length (in days) of hospitalization                | 3.8 ± 9.2                                | 4.8 ± 16.2                               | 0.39        |
| Pneumothorax, n (%)                                | 39 (24%)                                 | 95 (30%)                                 | 0.2         |
| Pneumothorax requiring chest tube insertion, n (%) | 8 (5%)                                   | 23 (7%)                                  | 0.43        |

**Supplementary Table 2: Patient characteristics between validation cohort (Bichat) and initial cohort (Besançon)**

| Characteristic   | Validation Cohort<br>(Bichat)<br>n = 313 | Initial Cohort<br>(Besançon)<br>n = 236 | p-value             |
|------------------|--|---|---------------------|
| <b>Age</b>       | 65±11                                    | 68±11                                   | 0.008 <sup>2</sup>  |
| <b>Gender</b>    |  |   | 0.03 <sup>3</sup>   |
| Female           | 98 (31%)                                 | 96 (41%)                                |                     |
| Male             | 215 (69%)                                | 140 (59%)                               |                     |
| <b>COPD</b>      |  |   | <0.001 <sup>3</sup> |
| Yes              | 153 (49%)                                | 75 (32%)                                |                     |
| No               | 160 (51%)                                | 161 (68%)                               |                     |
| <b>Emphysema</b> |  |   |                     |
| Severe           | 37 (12%)                                 | 64 (27%)                                | 0.12 <sup>3</sup>   |

<sup>1</sup> Mean±SD [range: Range]; n (%)

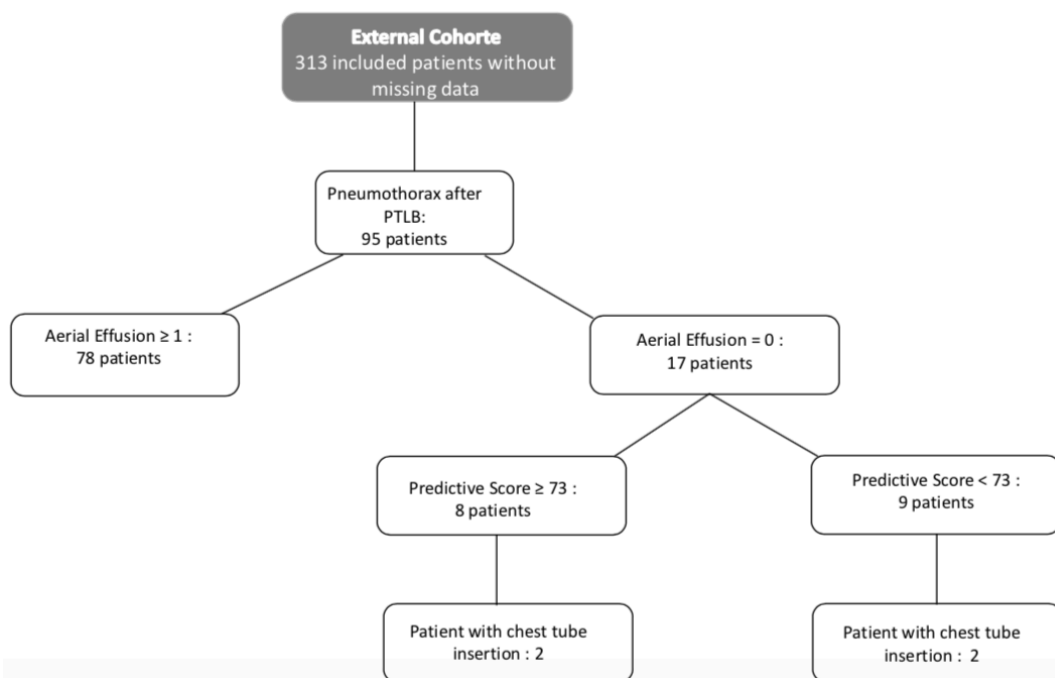
<sup>2</sup> Welch Two Sample t-test

<sup>3</sup> Pearson's Chi-squared test

**Supplementary Table 3: Comparison between patients without/with chest tube insertion**

|                                     | <b>Patients without chest tube insertion<br/>n = 290</b> | <b>Patients with chest tube insertion<br/>n = 23</b> | <b>p</b>          |
|-------------------------------------|--|--|-------------------|
| Age (years)                         | 66.5 [59.2 - 73.2]                                       | 60.2 [56.1 - 69.3]                                   | 0.10              |
| Male, n ( %)                        | 198 (68%)  | 17 (74%)   | 0.74              |
| Length (in days) of hospitalization | 1.0 [1.0 - 3.0]  | 8.0 [4.5 - 13.0]                                     | <b>&lt; 0.001</b> |
| Score $\geq$ 73, n (%)              | 146 (50%)  | 20 (87%)   | <b>0.002</b>      |

**Supplementary figure 1: Focus on aerial effusion**



## DISCUSSION 3ème AXE THEMATIQUE :

### Surveillance des patients opérés d'un CBNPC et stratégie d'obtention d'une preuve histologique de récurrence ou SCBP

---

#### **Surveillance**

La justification d'une surveillance après chirurgie d'un CBNPC est la détection précoce des complications des traitements chirurgicaux ou médicaux et le diagnostic des récurrences ou SCBP à un stade accessible à un traitement potentiellement curateur. Edelman *et al.* ont proposé des critères pour évaluer l'utilisation des tests dans le suivi d'un traitement anticancéreux à visée curative (96). Ceux-ci incluent les éléments suivants :

- l'intervalle de dépistage et la durée de suivi doivent être cohérents avec le risque maximal de récurrence et l'histoire naturelle de la tumeur ;
- le risque de second cancer doit également guider la surveillance ;
- les examens d'imagerie doivent être dirigés vers les sites de récurrence les plus probables avec des valeurs prédictives positives et négatives élevées ;
- un traitement doit être disponible permettant une guérison, ou au minimum une prolongation significative de la survie ou un meilleur contrôle des symptômes ;
- et l'initiation d'un traitement plus précoce devrait améliorer les résultats de ce traitement (que ce soit en survie, et/ou en qualité de vie).

L'analyse ancillaire de la qualité de vie dans l'essai IFCT-0302 a montré que l'ajout du scanner thoraco-abdominal injecté (plus de l'endoscopie bronchique chez les histologies non-adénocarcinomes) au suivi après une intervention chirurgicale pour un CPNPC n'a pas influencé la qualité de vie. La pénibilité était significativement plus élevée dans le groupe de suivi basé sur le scanner, influencé par la pénibilité associée à l'endoscopie bronchique. Cette étude est à notre connaissance, la seule s'intéressant à l'influence du suivi sur la qualité de vie.

La qualité de vie de la surveillance doit être interprétée dans le contexte de l'utilité de la stratégie. Pour les CBNPC résécables, la principale cause de décès reste la maladie cancéreuse, que ce soit par une récurrence du cancer du poumon index ou un SBPC. Comme montré précédemment, le risque de récurrence est le plus élevé au cours des deux premières années postopératoires (environ 10%) et diminue par la suite (44, 75, 76, 77). Younes RN *et al* ont démontré dans une cohorte rétrospective de 130 patients, le pronostic péjoratif de la récurrence, cela, quelle que soit la thérapie instituée après la détection de celle-ci. La grande majorité des patients (91,4%) présentant des récurrences étaient décédés de leur cancer dans les deux ans suivant la récurrence, quel que soit le

type de suivi. A l'inverse, l'incidence des SCBP reste stable, de l'ordre d'1 à 3 % par an, atteignant un risque cumulatif de 20 % à 10 ans, avec des diagnostics réalisés chez des patients en général asymptomatiques et à des stades précoces (97). L'étude IFCT-0302 n'a pas mis en évidence de gain de survie lorsque la surveillance comportait un scanner thoraco-abdominal et une endoscopie bronchique (en cas de cancer non épidermoïde), mais un diagnostic plus fréquent de récidives et SCBP précoces asymptomatiques accessibles à une nouvelle chirurgie (44). Les habitudes et la plupart des recommandations reposent sur la réalisation d'un scanner thoracique régulier de surveillance. L'absence d'impact sur la qualité de vie les conforte avec un suivi par examen clinique et scanner thoraco-abdominal, selon le schéma de l'étude IFCT-0302, semestriel pendant les deux premières années postopératoires puis annuel. La pénibilité de l'endoscopie bronchique, qui ne permet que très rarement (3,3% de manière isolée) le diagnostic d'une récidive ou d'un SCBP ne justifie pas son intégration à la surveillance des patients opérés d'un CBNPC.

Comme nous avons présenté par ailleurs, les traitements d'immunothérapie en situation péri-opératoire et les thérapies ciblées en situation adjuvante ont transformé le traitement des patients atteints d'un CBNPC résécable (stade I-III A/B). Les analyses de QdV de ces études n'ont pas montré de signal en faveur d'un changement de la QdV avec l'addition de ces thérapeutiques. Ces analyses ont pour limite un suivi limité dans le temps et un nombre restreint de temps de mesure. Il est montré que c'est le diagnostic d'une récidive qui génère une altération de la qualité de vie. En réduisant les récidives, on peut espérer une amélioration au long cours de la QdV par ces stratégies thérapeutiques non perçue dans les analyses présentées (98).

Il a par ailleurs été démontré que les évaluations de la qualité de vie chez les patients opérés d'un CBNPC peuvent contribuer à une amélioration de la prise en charge globale (diététique, psychologique...) et pourraient même avoir une valeur pronostique (99). Möller A *et al* ont montré chez 170 patients atteints d'un cancer du poumon réséqué, une association significative entre le score résumé de la composante physique du questionnaire SF-36 et la survie globale, avec un rapport de risque pour une augmentation d'un point sur l'échelle de 0 à 100 de 0,958 (95 % IC=0,932 à 0,985 ; p = 0,003) (100). Dans une étude de cohorte prospective basée sur la population de 249 patients chez qui était prévue une chirurgie thoracique pour un CBNPC, Al-Ameri M *et al*, ont montré qu'un score sur la composante physique inférieur à la valeur de référence était associé à une survie significativement plus mauvaise et cela indépendamment de l'histologie, du stade TNM, du type de chirurgie (lobectomie vs pneumectomie) et des comorbidités (HR 2.02, 95% CI: 1.34 to 3.06, p = 0.001) (101). Certains ont d'ailleurs recherché des interventions pour améliorer la qualité de vie des patients après la chirurgie. Il a été démontré, par exemple dans cette étude observationnelle publiée par Balduyck B *et al* chez 70 patients consécutifs traités par lobectomie ou pneumonectomie sur la cessation du tabagisme en situation péri-opératoire, que celle-ci améliorait la qualité de vie postopératoire (102). La qualité de vie est donc un outil sur lequel pourrait se reposer la surveillance, permettant d'implémenter une approche multi-modale plus personnalisée en fonction des symptômes et du vécu du patient, en associant à la clinique et au scanner thoraco-abdominal, toutes les composantes des soins de support avec une dimension socio-psychologique.

## **Score prédictif de pneumothorax post-ponction transthoracique scannoguidée**

Dans la cadre de la surveillance, à l'instar du dépistage, le scanner thoracique conduit à la découverte de nodules pulmonaires le plus souvent non accessibles en endoscopie bronchique simple. La biopsie pulmonaire percutanée guidée par scanner est recommandée pour obtenir un diagnostic histologique de nodules ou de masses pulmonaires lorsque l'endoscopie bronchique est non contributive, notamment pour les lésions périphériques. D'autres techniques sont possibles, comme l'utilisation de la mini-sonde d'échographie radiale et d'un cathéter guide avec ou sans repérage radioscopique, avec ou sans repérage spatial (au préalable ou en temps réel). De toutes ces techniques, la PTP sous scanner est la plus utilisée, plus pour des raisons d'accessibilité (disponibilité de la technique, pas d'anesthésie générale) que de performances. Le pneumothorax est la complication la plus courante survenant pendant ou après une ponction sous scanner, survenant dans 20 à 30 % des cas (103). Les patients sont généralement surveillés après le geste. Garder les patients en hospitalisation après l'intervention nécessite des ressources infirmières, limitant les capacités d'accueil tout en majorant le coût.

L'objectif d'établir un score prédictif de survenue de la principale complication (le pneumothorax) était d'orienter le parcours du patient, soit vers une surveillance maximale en hospitalisation, soit vers un retour à domicile rapide lorsque le risque de drainage d'un pneumothorax était faible. Dans une cohorte initiale, du CHU de Besançon, les composantes du score prédictif du pneumothorax dérivées par pondération d'une analyse multivariée étaient les 5 items suivants: la présence d'une BPCO, l'abord antérieur vs latéral ou postérieur, un nombre de passage de la plèvre supérieur à un, une distance peau-plèvre traversée par l'aiguille inférieure ou égale à 30 mm, et une lame d'épanchement aérique supérieure ou égale à 10 mm sur les coupes scannographiques de contrôle immédiat (104). Un score inférieur à 73 points (négatif) était prédictif d'une faible survenue de pneumothorax retardé. La validation du score sur la cohorte de Bichat Claude-Bernard démontrait que le score prédictif du pneumothorax était valide dans une cohorte externe, avec une valeur prédictive négative élevée de 84 %, suggérant une large applicabilité. Ce travail présentait plusieurs limites. Le score n'a pu être évalué que chez 313 patients sur les 474 constituant la cohorte externe, en raison de données manquantes. Toutefois, les caractéristiques des patients et scannographiques ainsi que les résultats de l'étude (apparition d'un pneumothorax, insertion d'un drain thoracique et durée de l'hospitalisation) ne différaient pas significativement entre les patients exclus et inclus, à l'exception du sexe, qui n'est pas connu comme un facteur de risque de complications post-PTP. Une autre limite pourrait être l'absence d'évaluation à 24 heures comme dans la cohorte initiale du CHU de Besançon, ce qui aurait pu induire un biais d'attrition. Nous ne pouvons donc pas exclure qu'une proportion minimale de pneumothorax asymptomatiques ait pu être manquée lors du contrôle radio et de l'évaluation médicale à 7 jours. Ceci reste néanmoins sans conséquences pratiques, puisque l'objectif de ce travail était de prédire les pneumothorax nécessitant une intervention médicale.

A notre connaissance, peu d'études portant sur l'établissement d'un tel score ont été publiées, sans pouvoir répondre précisément à cette question pragmatique de terrain de par leurs limites respectives (105, 106). Deux

études ont développé des scores prédictifs de survenue globale de complications post-PTP, sans se concentrer spécifiquement sur le pneumothorax (107, 108). Deux autres études, exclusivement focalisées sur le risque de pneumothorax mais sans cohorte de validation, ont établi pour outil prédictif des équations complexes difficiles à employer au chevet des patients. Seules les deux dernières études, plus récentes, proposent chacune un score sous forme de nomogramme facile d'utilisation, mais restent méthodologiquement imparfaites, reposant sur des séries rétrospectives sans validation externe (105, 109).

Dans les deux cohortes ayant permis l'élaboration du score, une très faible proportion des patients (2% dans la cohorte du CHU Besançon, non évalué dans la cohorte de Bichat-Claude Bernard) avait une ponction sous scanner pour une suspicion de récurrence ou de SCBP après chirurgie d'un CBNPC. Il est vraisemblable qu'en cas de PTP d'une image homolatérale à la chirurgie, le risque de pneumothorax soit très faible en raison de la symphyse pleurale. L'avènement espéré du dépistage dans les années à venir qui devrait faire découvrir des nodules dont la taille est inférieure à 2 cm, la réalisation de plus en plus fréquente de chirurgies infra-lobaires dont il a été montré que le risque de récurrence locale est plus important, va probablement faire accroître l'indication de PTP chez les patients opérés d'un CBNPC. La petite taille de ce sous-groupe dans nos études ne permet pas de conclusion quant à la pertinence du score prédictif de pneumothorax chez ces patients.

En conclusion, nos résultats soutiennent qu'un tel score prédictif pragmatique pourrait être utile, en prédisant avec une valeur prédictive négative significative de 84 % la survenue d'un pneumothorax symptomatique après PTP. Les patients avec un score inférieur à 73, basé sur les antécédents de BPCO, l'abord de biopsie antérieur, le nombre de passages pleuraux, la distance peau-plèvre et la présence d'un épanchement aérien important, n'avaient qu'un risque de 7,4 % de développer un pneumothorax (et un risque de 2 % de risque de nécessiter une évacuation retardée), les rendant éligibles à une prise en charge ambulatoire.

La surveillance des patients opérés d'un CBNPC pose encore de multiples questions, telles que l'influence du sevrage tabagique, du respect des critères qualité de la chirurgie initiale, du classement des récurrences /SCBP par un comité indépendant plutôt que par l'investigateur sur la survenue des récurrences et SCBP et l'intérêt du scanner thoracique. Ces analyses sont en cours sur les données de l'essai IFCT-0302. De nouvelles questions émergent avec les changements des stratégies périopératoires, telles que l'intérêt de l'ADN tumoral circulant et de l'éventuelle adaptation des modalités de surveillance en fonction de sa positivité ou de l'obtention d'une réponse pathologique complète après chimio-immunothérapie néoadjuvante. La surveillance se doit enfin d'être multimodale avec prise en charge des comorbidités et du sevrage tabagique, suivi diététique, psycho-social...et structurée. La mise en place de parcours de soins structurés et régulièrement évalués fait partie des objectifs à atteindre pour améliorer la prise en charge des patients opérés d'un CBNPC.

## CONCLUSION

---

En conclusion, ce présent travail de thèse a comporté la rédaction du premier protocole de type pronostique du groupe Cochrane Lung Cancer. Les premiers résultats de ce travail montrent que la définition classique, initialement publiée par Martini et Melamed en 1975, utilisée pour différencier les SCBP des récidives chez les patients opérés d'un CBNPC est cohérente avec l'histoire naturelle de ces événements en termes de délai de survenue et de survie. Les possibilités d'amélioration de cette définition reposent sur une analyse comparative histomoléculaire de la nouvelle tumeur pulmonaire avec le cancer du poumon index. Celle-ci n'étant pas systématiquement possible, donne toute sa valeur à la définition historique. Nous envisageons néanmoins de vérifier cette définition en la confrontant à une relecture des cas pour lesquels une preuve histologique de la nouvelle tumeur est disponible à l'échelle régionale.

Notre travail a ensuite porté sur les immunothérapies péri-opératoires des CBNPC résécables, avec la rédaction du premier protocole de revue systématique avec méta-analyse en réseau du groupe *Cochrane Lung Cancer*. Ce travail permettra de comparer indirectement les différentes stratégies péri-opératoires parmi lesquelles il est actuellement difficile de choisir celle qui allie la meilleure efficacité à la moindre toxicité, dans ce contexte particulier de patients considérés, jusqu'à preuve du contraire comme guéris. Cette revue sera une revue dite « vivante », c'est-à-dire actualisée à chaque fois que de nouveaux résultats seront connus, dans cette situation où la recherche clinique est particulièrement dynamique. Nous porterons un intérêt particulier lors de la diffusion des résultats à long terme, à l'incidence des seconds cancers primitifs et surtout des SCBP.

Enfin, alors que l'étude IFCT-0302 a montré que l'intégration du scanner thoraco-abdominal à la surveillance clinique dans le suivi des patients opérés d'un CBNPC permettait d'augmenter le nombre de récidives et SCBP asymptomatiques accessibles à une nouvelle chirurgie, sans toutefois allonger la survie globale, nous avons montré que le scanner n'impacte pas la qualité de vie. Ces résultats renforcent les habitudes et la plupart des recommandations selon lesquelles le scanner thoracique fait partie intégrante de la surveillance des patients opérés d'un CBNPC. Celle-ci se doit par ailleurs d'être multimodale afin d'optimiser la qualité de vie, qui a une valeur pronostique (gestion des comorbidités, nutrition, soutien psychologique, prise en charge sociale, aide au sevrage tabagique...). D'autres aspects de la surveillance des opérés sont en cours d'analyse dans l'étude IFCT-0302, comme l'impact du sevrage tabagique, de la qualité de la chirurgie ainsi que d'une analyse indépendante des événements (récidive/SCBP) sur l'intérêt de la surveillance par scanner thoracique. Dans le champ diagnostique, nous avons également travaillé sur le risque de pneumothorax après PTP sous scanner et élaboré un score reposant sur cinq items (présence d'une BPCO, l'abord antérieur vs latéral ou postérieur, un nombre de passage de la plèvre supérieur à un, une distance peau-plèvre traversée par l'aiguille inférieure ou égale à 30 mm, et une lame d'épanchement aérique supérieure ou égale à 10 mm sur les coupes scannographiques de



contrôle immédiat), validé sur une cohorte indépendante, permettant d'identifier les patients qui peuvent être pris en charge en ambulatoire, sans disposer de données spécifiques aux patients opérés d'un CBNPC.

## REFERENCES

---

1. Deo SVS, Sharma J, & Kumar S. GLOBOCAN 2020 report on global cancer burden: challenges and opportunities for surgical oncologists. *Annals of Surgical Oncology*, 2022; 1-4.
2. Lapôte-Ledoux B, Remontet L, Uhry Z, *et al.* Incidence des principaux cancers en France métropolitaine en 2023 et tendances depuis 1990. *Bulletin Épidémiologique Hebdomadaire* n°12-13, 2023; 189-204
3. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, *et al.* The 2021 WHO Classification of Lung Tumors: Impact of advances since 2015. *Journal of Thoracic Oncology*, 2021.
4. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology*, 2016; 11 (1): 39-51.
5. Huang J, Osarogiagbon RU, Giroux DJ, Nishimura KK, Bille A, Cardillo G, Detterbeck F, Kernstine K, Kim HK, Lievens Y, Lim E, Marom E, Prosch H, Putora PM, Rami-Porta R, Rice D, Rocco G, Rusch VW, Opitz I, Vasquez FS, Van Schil P, Jeffrey Yang C-F, Asamura H, Members of the Staging and Prognostic Factors Committee, Members of the Advisory Boards, and Participating Institutions of the Lung Cancer Domain, The IASLC Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 9th Edition of the TNM Classification for Lung Cancer, *Journal of Thoracic Oncology* (2023)
6. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of Stage I and II Non-small Cell Lung Cancer. *Chest*. mai 2013;143(5): e278S-e313S.
7. Remon J, Soria JC, & Peters S. Early and locally advanced non-small-cell lung cancer: An update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Annals of Oncology*, 2021; 32 (12): 1637-1642.
8. Forde PM, Spicer J, Lu S, *et al.* Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *New England Journal of Medicine*, 2022; 386 (21): 1973-1985.
9. [https://www.has-sante.fr/jcms/p\\_3460527/fr/decision-n2023-0309/dc/sem-du-7-septembre-2023-du-college-de-la-haute-autorite-de-sante-portant-autorisation-d-acces-precoce-de-la-specialite-opdivo](https://www.has-sante.fr/jcms/p_3460527/fr/decision-n2023-0309/dc/sem-du-7-septembre-2023-du-college-de-la-haute-autorite-de-sante-portant-autorisation-d-acces-precoce-de-la-specialite-opdivo)
10. Ferro A, Sepulcri M, Schiavon M, Scagliori E, Mancin E, *et al.* The Multidisciplinary Approach in Stage III Non-Small Cell Lung Cancer over Ten Years: From Radiation Therapy Optimisation to Innovative Systemic Treatments. *Cancers*, 2022; 14: 5700.
11. Houda I, Bahce I, Dickhoff C, *et al.* OA06. 03 An International EORTC Survey on Resectability of Stage III Non-small Cell Lung Cancer. *Journal of Thoracic Oncology*, 2023; 18 (11): S55-S56.
12. Xenophontos E, Levra NG, Durieux V, *et al.* P1. 28-08 Definition of Resectable Stage III Non-Small Cell Lung Cancer: A Systematic Review from EORTC Lung Cancer Group. *Journal of Thoracic Oncology*, 2023; 18 (11): S292.

13. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology*, 2017; 28: iv1-iv21.
14. Remon J, Soria JC, & Peters S. Early and locally advanced non-small-cell lung cancer: An update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Annals of Oncology*, 2021 32 (12): 1637-1642.
15. Scherpereel A, Martin E, Bouchet L, *et al.* Reaching multidisciplinary consensus on the management of non-bulky/non-infiltrative stage IIIA N2 non-small cell lung cancer. *Lung Cancer*, 2023; 177: 21-28.
16. Saji H, Okada M, Tsuboi M, Nakajima R, *et al.* Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *The Lancet*, 2022; 399 (10335): 1607-1617.
17. Altorki N, Wang X, Kozono D, Watt C, *et al.* Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer. *New England Journal of Medicine*, 2023; 388 (6): 489-498.
18. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer* 2005; 49: 25-33.
19. Osarogiagbon RU, Hilsenbeck HL, Sales EW, Berry A, Jarrett RW Jr, Giampapa CS, Finch-Cruz CN, Spencer D. Improving the pathologic evaluation of lung cancer resection specimens. *Transl Lung Cancer Res*, 2015; 4 (4): 432-7.
20. Heiden BT, Eaton DB, Chang SH, Yan Y, *et al.* Association Between Surgical Quality Metric Adherence and Overall Survival Among US Veterans With Early-Stage Non-Small Cell Lung Cancer. *JAMA surgery*, 2023; 158 (3): 293-301.
21. Kent MS, Mandrekar SJ, Landreneau R, Nichols F, Foster NR, DiPetrillo TA, et al. A nomogram to predict recurrence and survival of high-risk patients undergoing sublobar resection for lung cancer: an analysis of a multicenter prospective study (ACOSOG Z4032). *Ann Thorac Surg* 2016; 102: 239-46.
22. Smeltzer MP, Faris NR, Ray MA, Osarogiagbon RU. Association of pathologic nodal staging quality with survival among patients with non-small cell lung cancer after resection with curative intent. *JAMA Oncol* 2018; 4: 80-7.
23. Deng W, Xu T, Wang Y, Xu Y, Yang P, Gomez D, *et al.* Log odds of positive lymph nodes may predict survival benefit in patients with node-positive non-small cell lung cancer. *Lung Cancer* 2018; 122: 60-6.
24. Marinelli D, Gallina FT, Pannunzio S, *et al.* Surgical and survival outcomes with perioperative or neoadjuvant immune-checkpoint inhibitors combined with platinum-based chemotherapy in resectable NSCLC: a systematic review and meta-analysis of randomised clinical trials. *Critical Reviews in Oncology/Hematology*, 2023; 104190.
25. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *The Lancet*, 2014; 383 (9928): 1561-1571.

26. Chaft JE *et al.* Evolution of systemic therapy for stages I-III non-metastatic non-small-cell lung cancer. *Nat. Rev. Clin. Oncol*, 2021; 18: 547–557.
27. Matzner P *et al.* Harnessing cancer immunotherapy during the unexploited immediate perioperative period. *Nat. Rev. Clin. Oncol*, 2020; 17: 313–326.
28. Felip E, Altorki N, Zhou C, *et al.* Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *The Lancet*, 2021; 398 (10308): 1344-1357.
29. O’Brien M, Paz-Ares L, Marreaud S, *et al.* Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *The Lancet Oncology*, 2022; 23 (10): 1274-1286.
30. Topalian SL, Taube JM & Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science*, 2020; 367: eaax0182.
31. Liu J. *et al.* Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov*, 2016; 6: 1382–1399.
32. Heymach JV, Harpole D, Mitsudomi T, *et al.* Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, 2023.
33. Wakelee H, Liberman M, Kato T, *et al.* Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, 2023.
34. Mountzios G, Remon J, Hendriks LE, García-Campelo R, *et al.* Immune-checkpoint inhibition for resectable non-small-cell lung cancer—opportunities and challenges. *Nature Reviews Clinical Oncology*, 2023; 20 (10): 664-677.
35. Herbst RS, Wu YL, John T, Grohe C. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIa non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. *Journal of Clinical Oncology*, 2023; 41 (10): 1830.
36. Solomon BJ, Ahn JS, Dziadziuszko R, Barlesi F, Nishio M, Lee DH, ... & Wu YL. LBA2 ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC). *Annals of Oncology*, 2023; 34: S1295-S1296.
37. Le Pechoux C, Pourel N, Barlesi F, Lerouge D, *et al.* Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART, IFCT 0503): an open-label, randomised, phase 3 trial. *The Lancet Oncology*, 2022 ; 23 (1) : 104-114.
38. Albain KS, Swann RS, Rusch VW, Turrisi AT, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR, *et al.* Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. *Lancet*, 2009; 374: 379–386.

39. Jeremic´ B, Casas F, Dubinsky P, Gomez-Caamano A, C´ihoric´ N, Videtic G, Igrutinovic I. Treatment-Related Predictive and Prognostic Factors in Trimodality Approach in Stage IIIA/N2 Non-Small Cell Lung Cancer. *Front. Oncol*, 2018; 8: 30
40. Mainguene J, Basse C, Girard P, Beaucaire-Danel S, Cao K, Brian E, & Girard N. Surgical or medical strategy for locally-advanced, stage IIIA/B-N2 non-small cell lung cancer: Reproducibility of decision-making at a multidisciplinary tumor board. *Lung Cancer*, 2022; 163: 51-58.
41. Colt HG, Murgu SD, Korst RJ, et al. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 2013; 143 (5): e437S-e454S.
42. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology*, 2017; 28: iv1-iv21.
43. Schneider BJ, Ismaila N, Aerts J, et al. Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. *Journal of Clinical Oncology*, 2020; 38 (7): 753-766.
44. Westeel V, Foucher P, Scherpereel A. Chest CT scan plus x-ray versus chest x-ray for the follow-up of completely resected non-small-cell lung cancer (IFCT-0302): a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*, 2022; 23 (9): 1180-1188.
45. Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg*. oct 1975; 70 (4): 606-12.
46. Rice D, Kim HW, Sabichi A, et al. The risk of second primary tumors after resection of stage I non-small-cell lung cancer. *Ann Thorac Surg* 2003; 76:1001-7.
47. Rostad H, Strand TE, Naalsund A, et al. Resected synchronous primary malignant lung tumors: a population-based study. *Ann Thorac Surg* 2008; 85:204-9.
48. Battafarano RJ, Force SD, Meyers BF, et al. Benefits of resection for metachronous lung cancer. *J Thorac Cardiovasc Surg* 2004; 127:836-42.
49. Voltolini L, Rapicetta C, Luzzi L, et al. Surgical treatment of synchronous multiple lung cancer located in a different lobe or lung: high survival in node-negative subgroup. *Eur J Cardiothorac Surg* 2010; 37:1198-204.
50. Antakli T, Schaefer RF, Rutherford JE, et al. Second primary lung cancer. *Ann Thorac Surg* 1995; 59:863-6.
51. Colice GL, Rubins J, Unger M, et al. Follow-up and surveillance of the lung cancer patient following curative-intent therapy. *Chest*, 2003; 123(suppl 1):272S-83S.
52. Girard N, Ostrovnya I, Lau C, Park B, et al. Genomic and mutational profiling to assess clonal relationships between multiple non-small cell lung cancers. *Clinical cancer research*, 2009; 15 (16): 5184-5190.

53. Shen KR, Meyers BF, Larnar JM, et al. Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*, 2007; 132: 290S-305S.
54. Lou F, Huang J, Sima CS, Dycoco J, Rusch V, Bach PB. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. *J Thorac Cardiovasc Surg.* janv 2013; 145 (1): 75-82.
55. Johnson BE. Second Lung Cancers in Patients After Treatment for an Initial Lung Cancer. *JNCI J Natl Cancer Inst.* 16 sept 1998; 90 (18): 1335-45.
56. Ripley RT, McMillan RR, Sima CS, Hasan SM, Ahmad U, Lou F, et al. Second Primary Lung Cancers: Smokers Versus Nonsmokers After Resection of Stage I Lung Adenocarcinoma. *Ann Thorac Surg.* sept 2014; 98 (3): 968-74.
57. Leroy T, Monnet E, Guertzider S, Jacoulet P, De Bari B, Falcoz P-E, et al. Let us not underestimate the long-term risk of SPLC after surgical resection of NSCLC. *Lung Cancer Amst Neth.* nov 2019; 137: 23-30.
58. Pairolero PC, Williams DE, Bergstralh EJ, Piehler JM, Bernatz PE, Payne WS. Postsurgical stage I bronchogenic carcinoma: morbid implications of recurrent disease. *Ann Thorac Surg.* oct 1984; 38 (4): 331-8.
59. Deschamps C, Pairolero PC, Trastek VF, Payne WS. Multiple primary lung cancers. Results of surgical treatment. *J Thorac Cardiovasc Surg.* mai 1990; 99 (5): 769-77; discussion 777-778.
60. Hamaji M, Allen MS, Cassivi SD, Deschamps C, Nichols FC, Wigle DA, et al. Surgical treatment of metachronous second primary lung cancer after complete resection of non-small cell lung cancer. *J Thorac Cardiovasc Surg.* mars 2013; 145 (3): 683-90; discussion 690-691.
61. van Bodegom PC, Wagenaar SS, Corrin B, Baak JP, Berkel J, Vanderschueren RG. Second primary lung cancer: importance of long term follow up. *Thorax.* oct 1989;44(10):788-93.
62. Cho S, Yum S, Kim K, Jheon S. Prognostic factors for post-recurrence survival in patients with completely resected Stage III (N2) non-small-cell lung cancer. *Eur J Cardiothorac Surg.* 1 sept 2018; 54 (3): 554-9.
63. Wang C, Wu Y, Shao J, Liu D, Li W. Clinicopathological variables influencing overall survival, recurrence and post-recurrence survival in resected stage I non-small-cell lung cancer. *BMC Cancer.* 24 févr 2020; 20: 150.
64. Wu Y, Han C, Chong Y, Liu J, Gong L, Wang Z, et al. Prognostic study for survival outcome following the treatment of second primary lung cancer in patients with previously resected non-small cell lung cancer. *Thorac Cancer.* 2020; 11 (10): 2840-51.
65. Rice D, Kim H-W, Sabichi A, Lippman S, Lee JJ, Williams B, et al. The risk of second primary tumors after resection of stage I nonsmall cell lung cancer. *Ann Thorac Surg.* oct 2003; 76 (4):1001-8.
66. Anzidei M, Porfiri A, Andrani F, Di Martino M, Saba L, Catalano C, & Bezzi M. Imaging-guided chest biopsies: techniques and clinical results. *Insights into imaging*, 2017; 8: 419-428.
67. DiBardino DM, Yarmus LB, Semaan RW. Transthoracic needle biopsy of the lung. *J Thorac Dis*, 2015; 7 (Suppl 4): S304–S316

68. Wang Y, Jiang F, Tan X, Tian P. CT-guided percutaneous transthoracic needle biopsy for paramediastinal and nonparamediastinal lung lesions: diagnostic yield and complications in 1484 patients. *Medicine*, 2016; 95 (31): e4460
69. Chiu YW, Kao YH, Simoff MJ, Ost DE, *et al.* Costs of biopsy and complications in patients with lung cancer. *ClinicoEconomics and Outcomes Research*, 2021; 191-200.
70. Kodama F, Ogawa T, Hashimoto M, Tanabe Y, Suto Y, Kato T. Fatal air embolism as a complication of CT-guided needle biopsy of the lung. *J Comput Assist Tomogr. déc 1999; 23 (6): 949-51.*
71. Heerink WJ, de Bock GH, de Jonge GJ *et al.* Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol*, 2017; 27: 138–148.
72. Choi CM, Um SW, Yoo CG, *et al.* Incidence and risk factors of delayed pneumothorax after transthoracic needle biopsy of the lung. *Chest*. 2004; 126 (5): 1516–1521.
73. Huo YR, Chan MV, Habib AR, Lui I, & Ridley L. Pneumothorax rates in CT-guided lung biopsies: a comprehensive systematic review and meta-analysis of risk factors. *The British Journal of Radiology*, 2020; 93 (1108): 20190866.
74. Manhire A, Charig M, Clelland C, *et al.* Guidelines for radiologically guided lung biopsy. *Thorax* 2003; 58: 920-36.
75. Fink-Neuboeck, Lindenmann J, Porubsky C, Fediuk M, Anegg U, Maier A *et al.* Hazards of recurrence, second primary, or other tumor at ten years after surgery for non–small-cell lung cancer. *Clinical lung cancer*, 2020; 21 (4): 333-340.
76. Endo C, Sakurada A, Notsuda H, Noda M, *et al.* Results of long-term follow-up of patients with completely resected non-small cell lung cancer. *The Annals of thoracic surgery*, 2012; 93 (4): 1061-1068.
77. Mayne NR, Mallipeddi MK, Darling AJ, Yang CFJ, *et al.* Impact of surveillance after lobectomy for lung cancer on disease detection and survival. *Clinical Lung Cancer*, 2020; 21 (5): 407-414.
78. Rosenbaum PR, & Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*, 1983; 70 (1): 41-55.
79. Cepeda MS, Boston R, Farrar JT, & Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *American journal of epidemiology*, 2003; 158 (3): 280-287.
80. Lonjon G, Porcher R, Ergina P, Fouet M, & Boutron I. Potential Pitfalls of Reporting and Bias in Observational Studies With Propensity Score Analysis Assessing a Surgical Procedure: A Methodological Systematic Review. *Annals of Surgery*, 2017; 265 (5) 901-909.
81. Beyer T, Townsend DW, Brun T, Kinahan PE, Charron M, Roddy R, & Nutt R. A combined PET/CT scanner for clinical oncology. *Journal of nuclear medicine*, 2000; 41 (8) 1369-1379.

82. Vansteenkiste JF, & Stroobants SS. PET scan in lung cancer: current recommendations and innovation. *Journal of Thoracic Oncology*, 2006; 1 (1): 71-73.
83. Martucci F, Pascale M, Valli MC, Pesce GA, Froesch P, Giovannella L, & Treglia G. Impact of 18F-FDG PET/CT in staging patients with small cell lung cancer: a systematic review and meta-analysis. *Frontiers in medicine*, 2020; 6: 336.
84. Song IH, Yeom SW, Heo S, Choi WS, Yang HC, Jheon S, & Cho S. Prognostic factors for post-recurrence survival in patients with completely resected Stage I non-small-cell lung cancer. *European journal of cardiothoracic surgery*, 2014; 45 (2): 262-267.
85. Kim HS, Hoseok I, Choi YS, Kim K, Shim YM, & Kim J. Surgical resection of recurrent lung cancer in patients following curative resection. *Journal of Korean medical science*, 2006 ; 21 (2), 224-228.
86. Debieuvre D, Molinier O, Falchero L, *et al.* Lung cancer trends and tumor characteristic changes over 20 years (2000–2020): Results of three French consecutive nationwide prospective cohorts’ studies. *The Lancet Regional Health–Europe*, 2022; 22.
87. Subotic D, Molins L, Soldatovic I, Moskovljevic D, Collado L, & Hernández J. Completion pneumonectomy: a valuable option for lung cancer recurrence or new primaries. *World Journal of Surgical Oncology*, 2018; 16: 1-9.
88. Barlesi F, Mazières J, Merlio JP, Debieuvre D, *et al.* Routine molecular profiling of cancer: results of a one-year nationwide program of the French Cooperative Thoracic Intergroup (IFCT) for advanced non-small cell lung cancer (NSCLC) patients. *The Lancet*, 2016; 387: 1415-1426.
89. Chaimani A, Caldwell DM, Li T, Higgins JP, & Salanti G. Undertaking network meta-analyses. *Cochrane handbook for systematic reviews of interventions*, 2019; 285-320.
90. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*, 1997; 50: 683–91.
91. Blanchard P, Hill C, Guihenneuc-Jouyaux C, Baey C, Bourhis J, & Pignon JP. Mixed treatment comparison meta-analysis of altered fractionated radiotherapy and chemotherapy in head and neck cancer. *Journal of clinical epidemiology*, 2011; 64 (9): 985-992.
92. Provencio M, Calvo V, Romero A, Spicer JD, & Cruz-Bermudez A. Treatment sequencing in resectable lung cancer: the good and the bad of adjuvant versus neoadjuvant therapy. *Am Soc Clin Oncol Educ Book*, 2022: 1–18.
93. Cascone T, Awad MM, *et al.* LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. *Annals of Oncology*, 2023; 34 : S1295.
94. Bott MJ *et al.* Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg*, 2019; 158: 269–276



95. Wislez M *et al.* Neoadjuvant durvalumab for resectable non- small-cell lung cancer (NSCLC): results from a multicenter study (IFCT-1601 IONESCO). *J Immunother Cancer*, 2022; 10: e005636 (2022).
96. Edelman MJ, Meyers FJ, & Siegel D. The utility of follow-up testing after curative cancer therapy: a critical review and economic analysis. *Journal of general internal medicine*, 1997; 12 (5): 318-331.
97. Younes RN, Gross JL, & Deheinzelin D. Follow-up in lung cancer: how often and for what purpose?. *Chest*, 1999; 115 (6): 1494-1499.
98. Majem M, Goldman J, John T, Grohe C *et al.* OA06. 03 patient-reported outcomes from ADAURA: osimertinib as adjuvant therapy in patients with resected EGFR mutated (EGFRm) NSCLC. *Journal of Thoracic Oncology*, 2021; 16 (3): S112-S113.
99. Montazeri A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health and quality of life outcomes*, 2009; 7: 1-21.
100. Möller A, & Sartipy U. Associations between changes in quality of life and survival after lung cancer surgery. *Journal of Thoracic Oncology*, 2012; 7 (1): 183-187.
101. Al-Ameri M, Bergman P, Franco-Cereceda A, & Sartipy U. Self-reported physical quality of life before thoracic operations is associated with long-term survival. *The Annals of Thoracic Surgery*, 2017; 103 (2): 484-490.
102. Balduyck B, Sardari Nia P, Cogen A, Dockx Y, Lauwers P, Hendriks J, et al. The effect of smoking cessation on quality of life after lung cancer surgery. *Eur J Cardiothorac Surg*, 2011; 40 (6): 1432–8.
103. Heerink WJ, de Bock GH, de Jonge GJ et al. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol* , 2017; 27: 138–148.
104. Lamfichekh Y, Lafay V, Hamam J, et al. Score to Predict the Occurrence of Pneumothorax After Computed Tomography-guided Percutaneous Transthoracic Lung Biopsy. *Journal of Thoracic Imaging*, 2023 38 (5): 315-324.
105. Yang L, Liang T, Du Y, Guo C, Shang J, Pokharel S, et al. Nomogram model to predict pneumothorax after computed tomography-guided coaxial core needle lung biopsy. *Eur J Radiol*, 2021; 140: 109749.
106. Wang S, Tu J, Chen W. Development and Validation of a Prediction Pneumothorax Model in CT-Guided Transthoracic Needle Biopsy for Solitary Pulmonary Nodule. *BioMed Res Int*, 2019: e7857310.
107. Anzidei M, Sacconi B, Fraioli F, Saba L, Lucatelli P, Napoli A, et al. Development of a prediction model and risk score for procedure-related complications in patients undergoing percutaneous computed tomography-guided lung biopsy. *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg*. juill 2015; 48 (1): e1-6.
108. Iezzi R, Larici A, Contegiacomo A, Congedo MT, Siciliani A, Infante A, et al. A new score predicting intraprocedural risk in patients undergoing CT-guided percutaneous needle pulmonary biopsy (CATH-score). *Eur Rev Med Pharmacol Sci*, 2017; 21 (16): 3554-62.

109. Zhao Y, Wang X, Wang Y, Zhu Z. Logistic regression analysis and a risk prediction model of pneumothorax after CT-guided needle biopsy. *J Thorac Dis*, 2017; 9 (11).

## ANNEXE :

---

### *Valeur pronostique de la lymphopénie T CD4+ dans le cancer du poumon non à petites cellules*

#### **Résumé**

##### Introduction :

La cohorte TELOCAP a permis d'évaluer l'influence de divers paramètres immunologiques dans le cancer bronchique non à petites cellules (CBNPC). Nous présentons ici l'influence de la lymphopénie T CD4+sanguine dans cette cohorte.

##### Méthodes :

Ont été inclus les patients diagnostiqués d'un CBNPC, de stade clinique I à IV, traités au CHU de Besançon et à l'hôpital européen Georges-Pompidou. La lymphopénie T CD4+ la lymphopénie T CD8+dans le sang circulant, étaient respectivement définies comme un nombre absolu de lymphocytes (ALC) $<500/\mu\text{L}$  et  $<224/\mu\text{L}$  au diagnostic. Le critère principal de jugement était la survie globale.

##### Résultats :

Au total, 186 patients ont été inclus de 2010 à 2014. Les analyses univariées ont montré que la lymphopénie T CD4+était corrélée à une plus faible survie globale (HR 1,616 [IC95 %=1,107 ; 2,358]  $p=0,0127$ ). En revanche, aucune association n'a été trouvée avec la lymphopénie T CD8+. En analyse multivariée, le statut de performance  $\geq 2$  (HR : 2,191 [IC95 %=1,413 ; 3,396]  $p=0,0005$ ), le stade métastatique (HR : 2,558 [IC95 %=1,722 ; 3,802]  $p<0,0001$ ) ont été significativement corrélés avec une faible survie. On retrouve, par la même analyse, une valeur pronostique défavorable de la lymphopénie T CD4+dans la population de cancer au stade localisé (SG médiane à 21,8 versus 72 mois,  $p=0,035$ ). Dans l'ensemble de la cohorte CBNPC, l'interpolation de fonction spline cubique a montré que les patients avec un nombre de lymphocyte T CD4+ $\leq 500/\mu\text{L}$  étaient les plus à risque de décès. L'analyse a montré une relation linéaire entre le nombre de lymphocytes T CD4+et la survie globale. En revanche, aucune relation linéaire n'a été trouvée entre le risque de décès et le nombre de lymphocytes T CD8+.

##### Conclusion

Dans la présente étude, nous avons identifié la lymphopénie T CD4+comme un facteur pronostique indépendant, péjoratif, pour la survie globale dans le CPNPC chez les patients atteints de CBNPC localisé.

RESEARCH

Open Access

# Prognostic value of CD4+ T lymphopenia in non-small cell lung Cancer



Guillaume Eberst<sup>1,2,3\*</sup>, Dewi Vernerey<sup>2,3</sup>, Caroline Laheurte<sup>3,4</sup>, Aurélia Meurisse<sup>2</sup>, Vincent Kaulek<sup>1</sup>, Laurie Cuhe<sup>1</sup>, Pascale Jacoulet<sup>1</sup>, Hamadi Almotlak<sup>5</sup>, Jean Lahourcade<sup>1</sup>, Marie Gainet-Brun<sup>1</sup>, Elizabeth Fabre<sup>6</sup>, Françoise Le Pimpec-Barthes<sup>7</sup>, Olivier Adotevi<sup>3,4,5†</sup> and Virginie Westeel<sup>1,2,3†</sup>

## Abstract

**Background:** There is a paucity of data regarding the prognostic influence of peripheral blood CD4+ T lymphopenia in non-small cell lung cancer (NSCLC). Therefore, we investigated the prognostic value of T lymphopenia in NSCLC.

**Materials:** Treatment-naïve patients with a pathological diagnosis of NSCLC, at clinical stage I to IV were included in the prospective TELOCAP1 study. Lymphocytes count was evaluated in peripheral blood by flow cytometry. CD4+ and CD8+ T lymphopenia were defined as an absolute count of < 500/μL and < 224/μL respectively. The prognostic value of T lymphopenia was analyzed in the whole population, in local/loco-regional (stage I-IIIb) and in advanced (stage IV) NSCLC disease, using the Kaplan-Meier method and Cox regression models for survival curves and multivariate analysis, respectively.

**Results:** Between July 2010 and January 2014, 169 evaluable patients with clinical stage I to IV NSCLC were prospectively enrolled. The prevalence of CD4+ and CD8+ T lymphopenia was similar in the study population (around 29%). Patients with CD4+ T lymphopenia showed lower overall survival than those with CD4+ T lymphocytes count > 500/μL (median overall survival (OS) 16.1 versus 21.7 months, hazard ratio (HR): 1.616 [95% CI: 1.1–2.36],  $p = 0.012$ ). This association with OS was especially marked in local/loco-regional NSCLC stages (median OS, 21.8 versus 72 months, respectively, HR: 1.88 [95% CI: 0.9–3.8],  $p = 0.035$ ). Multivariate analysis confirmed the worse prognosis associated with CD4+ T lymphopenia in local/loco-regional NSCLC, but not in metastatic patients (HR 2.028 [95% CI = 1.065–3.817]  $p = 0.02$ ). Restricted cubic spline analysis showed that patients with CD4+ T lymphocytes count  $\leq 500/\mu\text{L}$  displayed a high risk of death regardless of NSCLC clinical stage. There was no obvious relationship between CD8+ T lymphopenia and clinical outcome.

**Conclusion:** We identified CD4+ T lymphopenia as an independent prognostic factor in local/loco-regional stages of NSCLC and CD4+ T lymphopenia is also associated with a high risk of death, regardless of NSCLC clinical stage.

**Trial registration:** EUDRACT: 2009-A00642–55.

<sup>†</sup>Olivier Adotevi and Virginie Westeel contributed equally to this work.

\*Correspondence: geberst@chu-besancon.fr

<sup>3</sup> Université de Bourgogne Franche-Comté, EFS BFC, INSERM, UMR1098, RIGHT, Besançon, France  
Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

### Highlights

This study investigates the unknown prognostic influence of peripheral blood CD4+ T lymphopenia in non-small cell lung cancer (NSCLC) with long-term follow-up

CD4+ but not CD8+ T lymphopenia was associated with poor survival in patients with localized NSCLC

The CD4+ T lymphopenia appears to be an independent prognostic factor for poor overall survival in local/loco-regional NSCLC.

CD4+ T lymphocyte count  $\leq 500/\mu\text{L}$  in peripheral blood is associated with a high risk of death in NSCLC

**Keywords:** CD4+ T lymphopenia, Non small cell lung cancer, Prognosis, CD8+ T lymphopenia - local/loco-regional NSCLC

### Introduction

Recent progress in the treatment of non-small cell lung cancer (NSCLC) includes the introduction of immunotherapy, especially immune checkpoint inhibitors [1]. Although the use of immunotherapy in NSCLC has shown promising results, there remains a lack of predictive biomarkers indicating treatment benefit from immunotherapy [2]. Therefore, a better understanding of patient immune response is needed.

Evidence supports the role of the immune system in lung cancer development [3]. Indeed, high levels of tumor-infiltrating lymphocytes (TILs) have been shown to be associated with longer survival, and a significant reduction in the risk of death in patients with NSCLC [4–7]. More recently, a report by Mascaux et al. suggested that lung carcinogenesis involves a dynamic co-evolution of tumor bronchial cells and a decrease in local immune response [8]. Because evaluation of TILs requires large lung cancer specimens, there are few data on TILs in patients with advanced NSCLC. A retrospective cohort of 159 stage III and IV NSCLC patients did not show any association between TILs and prognosis [9].

The anti-tumor immune response is provided by both adaptive and innate immunity, in which T lymphocytes play a central role. Although, CD8+ T lymphocytes (CD8 TL) have been considered to be the main protagonists, due to their cytotoxic activity on tumor cells, it is now clear that CD4+ T lymphocytes (CD4 TL) also play a critical role in orchestrating the antitumor immune response [10–12]. Tumor-reactive CD4 TL have been found to ensure recruitment of cytotoxic CD8 TL at the tumor site [13]. In cancer patients, a high density of tumor-infiltrating CD4 Th1 cells has been identified as a good prognostic marker in several human cancers, including lung cancer [14]. CD4 TL can also exert a direct antitumor activity that is independent of CD8 TL, by recruiting and activating innate immune cells, such as natural killer lymphocytes and macrophages [15].

The critical role of CD4 T cell in antitumor immunity is supported by the poor prognosis associated with

CD4 T lymphopenia in several cancers [16, 17]. CD4+ T lymphopenia has been found to be an independent risk factor for early death and for febrile neutropenia in lymphoma, myeloma, sarcoma, breast carcinoma, digestive tract carcinoma and germ cell tumor [16]. Furthermore, CD4+ lymphopenia was associated with non-response to chemotherapy, suggesting the important role of CD4+ T cells in controlling tumor progression [17]. There is a paucity of data regarding the prognostic influence of peripheral blood CD4+ T lymphopenia in NSCLC. Therefore, in the present study, we analyzed the prognostic value on overall survival of CD4+ T lymphopenia in patients with stage I to IV NSCLC.

### Patients and methods

#### Study population

Patients with a pathological diagnosis of NSCLC, clinical stage I to IV, were included between July 2010 and January 2014, at the University Hospital Jean Minjot, in Besançon and the European Hospital Georges Pompidou (EHGP), Paris, France, in the prospective TELOCAP01 study (EUDRACT: 2009-A00642–55) [18, 19]. The TeloCap01 study is a prospective, multicenter, immune-monitoring study conducted in patients with stage I–IV NSCLC, whose primary objective was to evaluate the landscape of telomerase-specific CD4+ T-cell responses in patients with NSCLC. The prognostic value of CD4+ T lymphopenia was a secondary endpoint of the TELOCAP01 trial. Before any therapy, including surgery, we collected and isolated blood lymphocytes, serum and plasma, which were frozen until later analysis. Survival data were collected at 1 and 2 years after inclusion.

Patients who were HIV positive, those receiving corticosteroids treatment, those with immunosuppression or another cancer diagnosis (except for basal cell carcinoma of the skin and in situ carcinoma of the uterine cervix) were excluded from the TELOCAP01 study. Stage I, II,

and III NSCLC were considered as local/loco-regional NSCLC (7th edition of the TNM [20]).

All patients provided written informed consent and the protocol was approved by the ethics committee CPP (Comité de Protection des Personnes) Ile de France IV on 07/09/2009. The Telocap01 study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

#### Assessment of blood lymphocyte count

Fresh, peripheral blood samples were collected before any treatment. Phenotypic analysis of peripheral blood lymphocyte subsets and absolute numbers of T cells, CD4+ and CD8+, were determined by single platform flow cytometry using the TetraCXP<sup>®</sup> method, Flow-Count fluorospheres, and FC500<sup>®</sup> cytometer (Beckman Coulter, Villepinte, France) according to the manufacturer's recommendations [21].

CD4+ T and CD8+ T lymphopenia were defined as absolute lymphocyte counts (ALC) < 500/ $\mu$ L and < 224/ $\mu$ L respectively, according to a previous study by D'Hautcourt JL et al. [22]. These thresholds correspond to the lower limit of normal at the laboratory of the French Blood Transfusion Centre (Etablissement Français du Sang) where the lymphocyte counts were performed by flow cytometry, as justified by the study of D'Hautcourt et al. [22].

#### Statistics

Overall survival (OS) was defined as the time from the date of inclusion to the date of death from any cause, or the date of last follow-up, for patients who were alive at last contact. Patients last known to be alive were censored at the time of their last follow-up assessment. The endpoint date was July 2020. Continuous variables are presented as median (interquartile range) and categorical variables as number (percentage). The relationship between main patient characteristics and T cell counts was studied. Medians and percentages were compared using the Wilcoxon rank test and Chi-square test (or Fisher's exact test, if appropriate), respectively. OS was estimated using the Kaplan-Meier method and described using median or rate at specific time points with 95% confidence intervals (95% CI). Follow-up was calculated using a reverse Kaplan-Meier estimation when feasible [18]. Cox proportional hazards regression was performed to estimate hazard ratios (HR) and 95% CIs for factors associated with OS. The association of baseline parameters with OS was first assessed using univariate Cox analyses and variables with a *p*-value  $\leq 0.05$  were entered into a final multivariate Cox regression model. When used continuously, the association

between biological parameters and OS was investigated using the restricted cubic splines method with graphical evaluation. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and R software version 2.15.2 (R Development Core Team; <http://www.r-project.org>). A *p*-value  $\leq 0.05$  was considered statistically significant and all tests were two-sided.

## Results

### Influence of clinical parameters on peripheral T cell count in NSCLC

Between July 2010 and January 2014, 170 NSCLC patients with a clinical stage I to IV were enrolled for the prospective study TELOCAP1. Among them, T lymphocyte count could not be measured in one patient.

The characteristics of the 169 evaluable patients are detailed in Tables 1 and 2. Median age was 64.5 years (95% CI = 57.5–70.5 years). 1 hundred and ten patients (65%) were males. A total of 147 patients (87%) were current or former smokers. A majority of patients had an ECOG performance status of 0 or 1 (80%). The histological type was adenocarcinoma in 87 patients (62%). Molecular analyses were available in 79 patients and EGFR mutations were observed in 11 patients and KRAS mutations in 19 patients. The proportion of patients with local/loco-regional NSCLC was 51%. No patient received immunotherapy (Tables 1 and 2).

The T lymphocyte subset counts are summarized in Table 1. In the overall cohort, the mean lymphocyte count was 778/ $\mu$ L and 410/ $\mu$ L for CD4 and CD8 subsets respectively. We observed that both CD4 and CD8 T cell counts declined with increasing age and NSCLC stage. As expected, the level of CD4 T lymphocytes was significantly lower in advanced stages compared to localized stages (710 versus 840 CD4/ $\mu$ L, *p* = 0.05). No obvious association was observed for the other main clinical parameters (Table 1).

Next, to assess the prognostic value of T lymphocyte count (CD4 or CD8) in the whole cohort, we used thresholds to define CD4+ and CD8+ T lymphopenia (< 500/ $\mu$ L and < 224/ $\mu$ L) respectively [22]. In whole cohort, CD4+ T lymphopenia (< 500/ $\mu$ L) and CD8+ T lymphopenia (< 224/ $\mu$ L) were observed in 28.4 and 29.6% of patients respectively. CD4+ T lymphopenia was significantly more frequently observed in elderly patients (*p* = 0.053), and in patients with performance status  $\geq 2$  (*p* = 0.041). There was a trend towards an increased frequency of CD4+ T lymphopenia (56%) in metastatic patients versus 44% in patients with localized NSCLC (*p* = 0.24). No association was found between CD4+ or CD8+ count T cell counts and other variables such as gender, smoking, and histology (Table 2).

**Table 1** Absolute CD4 and CD8 lymphocyte counts according to patients' characteristics. †: large cell carcinoma, adenosquamous carcinoma and sarcomatoid carcinoma

|                           |                          | N (%)     | Absolute CD4 Lymphocyte counts |              | Absolute CD8 Lymphocyte counts |              |
|---------------------------|--------------------------|-----------|--------------------------------|--------------|--------------------------------|--------------|
|                           |                          |           | Mean                           | P            | Mean                           | P            |
| <b>Overall population</b> |                          | 169       | 778                            |              | 410                            |              |
| <b>Age - Years</b>        | <65                      | 90 (53%)  | 841                            | <b>0.029</b> | 460                            | <b>0.033</b> |
|                           | ≥65                      | 79 (47%)  | 706                            |              | 354                            |              |
| <b>Sex</b>                | Men                      | 110 (65%) | 739                            | 0.088        | 417                            | 0.705        |
|                           | Women                    | 59 (35%)  | 851                            |              | 398                            |              |
| <b>Smoking status</b>     | Current or former smoker | 147 (87%) | 790                            | 0.259        | 416                            | 0.411        |
|                           | Never smoker             | 22 (13%)  | 701                            |              | 375                            |              |
| <b>Performance status</b> | 0-1                      | 134 (80%) | 796                            | 0.522        | 419                            | 0.661        |
|                           | 2                        | 33 (20%)  | 715                            |              | 390                            |              |
| <b>Histologic subtype</b> | Adenocarcinoma           | 87 (62%)  | 725                            | 0.118        | 368                            | 0.394        |
|                           | Squamous cell carcinoma  | 37 (26%)  | 617                            |              | 439                            |              |
|                           | Other                    | 17 (12%)  | 961                            |              | 428                            |              |
| <b>KRAS Mutation</b>      | Yes                      | 19 (26%)  | 739                            | 0.546        | 344                            | 0.510        |
|                           | No                       | 55 (74%)  | 685                            |              | 323                            |              |
| <b>EGFR Mutation</b>      | Yes                      | 11 (14%)  | 698                            | 0.956        | 315                            | 0.887        |
|                           | No                       | 68 (86%)  | 697                            |              | 329                            |              |
| <b>Stage</b>              | Local/loco-regional      | 86 (51%)  | 840                            | <b>0.050</b> | 448                            | 0.129        |
|                           | Advanced                 | 83 (49%)  | 714                            |              | 371                            |              |

#### CD4+ but not CD8 + T lymphopenia was associated with poor survival in NSCLC patients

The estimated median OS was 20.4 months for the overall cohort, 44.8 months in local/loco-regional NSCLC and 13.4 months in metastatic patients. In the whole cohort, median OS was better for patients with CD4 TL counts >500/μL compared with those who had CD4 + T lymphopenia (21.7 versus 16.1 months, respectively, HR: 1.616 [95% CI: 1.1–2.36],  $p=0.012$ ) (Fig. 1A). The favorable prognostic value of CD4 TL count >500/μL was observed in patients with local/loco-regional disease (stage I to IIIB), but not in metastatic patients (median OS, 72 versus 21.8 months, respectively, HR: 1.88 [95% CI: 0.9–3.8],  $p=0.0286$ ) (Figs. 1B and C).

In contrast, no obvious association was visible between CD8 + T lymphopenia and survival (median OS 21.3 versus 18.8 months, HR: 1.0 [95% CI: 0.70–1.5]  $p=0.991$ ) (Fig. 1D). A trend towards a favorable prognostic value of CD8 + TL count >224/μL was observed in patients with local/loco-regional disease but not in metastatic

patients (median OS 55.6 versus 31.1 months,  $p=0.339$ ) (Figs. 1E–F).

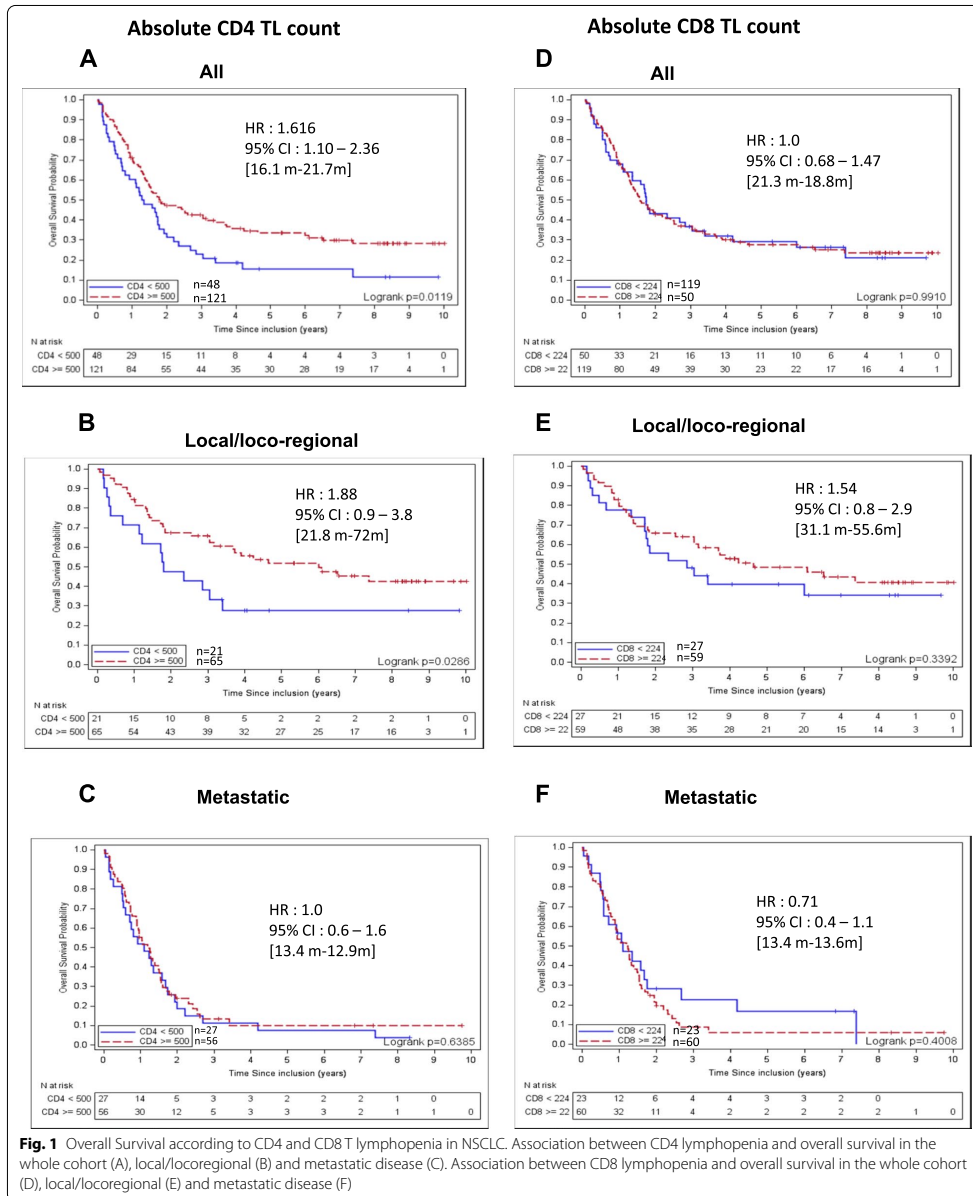
Univariate analyses showed that among the main patient characteristics, CD4 + T lymphopenia, total lymphocyte count, performance status  $\geq 2$  and advanced NSCLC were associated with worse OS (Table 3); CD4 + T lymphopenia (HR 1.61 [95% CI=1.107; 2.358]  $p=0.012$ ); performance status  $\geq 2$  (HR 2.88 [95% CI=1.88; 4.405]  $p<0.0001$ ); advanced stage (HR 3.03 [95% CI=2.08; 4.43]  $p<0.0001$ ); total lymphocyte count <1000/μL (HR 1.65 [IC 95%=1.06; 2.56]  $p=0.0262$ ). In contrast, no association was found between the absolute CD8 T cell count and OS (Table 3). Colinearity was observed between immunological parameters. Only CD4 + T lymphopenia was included in the multivariate analysis because among the immunological parameters, this variable was most strongly associated with survival in univariate analysis.

The multivariate analyses performed in whole cohort showed that performance status  $\geq 2$  (HR 2.191 [95%

**Table 2** Patients characteristics according to CD4+ and CD8+ T lymphopenia

|                                     | Overall population (N = 169) |     | Absolute TL CD4 count ≤ 500 (N = 48) |    | Absolute TL CD4 count > 500 (N = 121) |     | Absolute TL CD8 count ≤ 224 (N = 50) |    | Absolute TL CD8 count > 224 (N = 119) |     | P      |
|-------------------------------------|------------------------------|-----|--------------------------------------|----|---------------------------------------|-----|--------------------------------------|----|---------------------------------------|-----|--------|
|                                     | N                            |     | N                                    |    | N                                     |     | N                                    |    | N                                     |     |        |
| <b>Clinical characteristics</b>     |                              |     |                                      |    |                                       |     |                                      |    |                                       |     |        |
| <b>Age (years)</b>                  | 64.5 (57.5 - + 70.5)         | 169 | 65.5 (60.5E76.6)                     | 48 | 63.7 (56.9E69.7)                      | 121 | 65.7 (61.9E72.1)                     | 50 | 63.3 (56.8E70.5)                      | 119 | 0.0925 |
| <b>Patient male sex</b>             | 110 (65%)                    | 169 | 33 (69%)                             | 48 | 77 (64%)                              | 121 | 35 (70%)                             | 50 | 75 (63%)                              | 119 | 0.3853 |
| <b>Smoking status</b>               |                              | 169 |                                      | 48 |                                       | 121 |                                      | 50 |                                       | 119 |        |
| Current or former smoker            | 147 (87%)                    |     | 42 (87%)                             |    | 105 (87%)                             |     | 45 (90%)                             |    | 102 (85.7%)                           |     |        |
| Never smoker                        | 22 (13%)                     |     | 6 (13%)                              |    | 16 (13%)                              |     | 5 (10%)                              |    | 17 (14.3%)                            |     | 0.4498 |
| <b>Performance status OMS</b>       |                              | 167 |                                      | 47 |                                       | 120 |                                      | 48 |                                       | 119 |        |
| 0/1                                 | 134 (80%)                    |     | 33 (70%)                             |    | 101 (84%)                             |     | 39 (81.3%)                           |    | 95 (79.3%)                            |     |        |
| 2                                   | 33 (20%)                     |     | 14 (30%)                             |    | 19 (16%)                              |     | 9 (18.2%)                            |    | 24 (20.2%)                            |     | 0.8350 |
| <b>Pathological characteristics</b> |                              |     |                                      |    |                                       |     |                                      |    |                                       |     |        |
| <b>Histologic subtype</b>           |                              | 141 |                                      | 46 |                                       | 95  |                                      | 44 |                                       | 97  |        |
| Adenocarcinoma                      | 87 (62%)                     |     | 26 (57%)                             |    | 61 (64%)                              |     | 29 (65.9%)                           |    | 58 (59.8%)                            |     |        |
| Squamous cell carcinoma             | 37 (26%)                     |     | 17 (37%)                             |    | 20 (21%)                              |     | 11 (25%)                             |    | 26 (26.8%)                            |     |        |
| other                               | 17 (12%)                     |     | 3 (6%)                               |    | 14 (15%)                              |     | 4 (9.1%)                             |    | 13 (13.4%)                            |     | 0.7091 |
| <b>KRAS mutation</b>                | 19 (26%)                     | 74  | 5 (20%)                              | 25 | 14 (29%)                              | 49  | 4 (15.4%)                            | 26 | 15 (31.3%)                            | 48  | 0.1358 |
| <b>EGFR mutation</b>                | 11 (14%)                     | 79  | 4 (15%)                              | 26 | 7 (13%)                               | 53  | 4 (14.3%)                            | 28 | 7 (13.7%)                             | 51  | 1.000  |
| <b>Stage</b>                        |                              | 169 |                                      | 48 |                                       | 121 |                                      | 50 |                                       | 119 |        |
| Local/loco-regional                 | 86 (51%)                     |     | 21 (44%)                             |    | 65 (54%)                              |     | 27 (54%)                             |    | 59 (49.6%)                            |     | 0.5998 |
| Advanced                            | 83 (49%)                     |     | 27 (56%)                             |    | 56 (46%)                              |     | 23 (46%)                             |    | 60 (50.4%)                            |     |        |





**Table 3** Univariate analysis for overall survival

|                                       | No. of patients | Nr of deaths | HR    | 95% CI         | P      |
|---------------------------------------|-----------------|--------------|-------|----------------|--------|
| <b>Age <math>\bar{N}</math> years</b> | 169             |              |       |                |        |
| < 70                                  | 123             | 90           | 1     |                |        |
| $\geq$ 70                             | 46              | 32           | 1.074 | 0.717 to 1.608 | 0.7301 |
| <b>Patient sex</b>                    | 169             |              |       |                |        |
| Male                                  | 110             | 83           | 1     |                |        |
| Female                                | 59              | 39           | 0.805 | 0.550 to 1.179 | 0.2651 |
| <b>Smoking status</b>                 | 169             |              |       |                |        |
| Current or former smoker              | 147             | 108          | 1     |                |        |
| Never smoker                          | 22              | 14           | 0.813 | 0.465 to 1.419 | 0.4659 |
| <b>Performance status OMS</b>         | 167             |              |       |                |        |
| 0/1                                   | 134             | 91           | 1     |                |        |
| $\geq$ 2                              | 33              | 30           | 2.881 | 1.885 to 4.405 | <.0001 |
| <b>Histologic subtype</b>             | 141             |              |       |                |        |
| Adenocarcinoma                        | 87              | 67           | 1     |                |        |
| Squamous cell carcinoma               | 37              | 31           | 1.221 | 0.797 to 1.871 |        |
| other                                 | 17              | 15           | 1.711 | 0.974 to 3.003 | 0.1549 |
| <b>Stage</b>                          | 169             |              |       |                |        |
| Local/Loco-regional (I-III)           | 86              | 49           | 1     |                |        |
| Advanced (IV)                         | 83              | 73           | 3.039 | 2.083 to 4.433 | <.0001 |
| <b>CD8+ T Lymphocytes</b>             | 169             |              |       |                |        |
| $\geq$ 224 / $\mu$ l                  | 119             | 86           | 1     |                |        |
| < 224 / $\mu$ l                       | 50              | 36           | 0.998 | 0.676 to 1.472 | 0.9903 |
| <b>CD4+ T lymphocytes</b>             | 169             |              |       |                |        |
| $\geq$ 500 / $\mu$ l                  | 121             | 81           | 1     |                |        |
| < 500 / $\mu$ l                       | 48              | 41           | 1.616 | 1.107 to 2.358 | 0.0127 |
| <b>Total lymphocytes count</b>        | 169             |              |       |                |        |
| $\geq$ 1000 / $\mu$ l                 | 129             | 73           | 1     |                |        |
| < 1000 / $\mu$ l                      | 40              | 28           | 1.65  | 1.06 to 2.56   | 0.0262 |

CI=1.413; 3.396]  $p=0.0005$ ) and advanced stage (HR 2.558 [95% CI=1.722; 3.802]  $p<0.0001$ ) were significantly correlated with poor survival, whereas a trend towards worse prognosis with CD4+ T lymphopenia was observed (HR 1.422 [95% CI=0.971; 2.083]  $p=0.0704$ ) (Table 4). However, the multivariate analyses carried out in the subgroups of patients showed CD4+ T lymphopenia was significantly correlated with poor survival in local/loco-regional but not in metastatic patients (HR 2.028 [95% CI=1.065; 3.817]  $p=0.02$ ) (Table 4).

Next, the risk of death was analyzed using the restricted cubic spline (RCS) model, which characterizes a non-linear dose-response association between a continuous variable and an outcome. In the whole NSCLC cohort, the RCS model showed that patients with CD4 TL count  $\leq$ 500/ $\mu$ L displayed a higher risk of death. Notably, the gradual risk observed in the whole cohort, local/loco-regional NSCLC and in metastatic

stage suggested a linear relation between CD4 TL count and patient OS (Fig. 2A, B, C). In contrast, the RCS approach showed no linear relation between risk of death and CD8+ T cell count (Fig. 2D, E, F). Thus, low level of CD4 TL count in peripheral blood appears to be an independent risk factor for death in NSCLC.

### Discussion

In the present study, we identified the CD4+ T lymphopenia (count <500/ $\mu$ L) as a poor prognostic factor associated with a high risk of death in NSCLC. However, no association between CD8+ TL lymphopenia and patients' clinical outcome was found in this cohort. This suggests that in contrast to CD8 T cells, high levels of peripheral CD4 T cells play a protective role in NSCLC patients. This is the first prospective study addressing the prognostic value of CD4+ T lymphopenia in NSCLC with long-term follow-up.

**Table 4** Multivariate analysis for overall survival

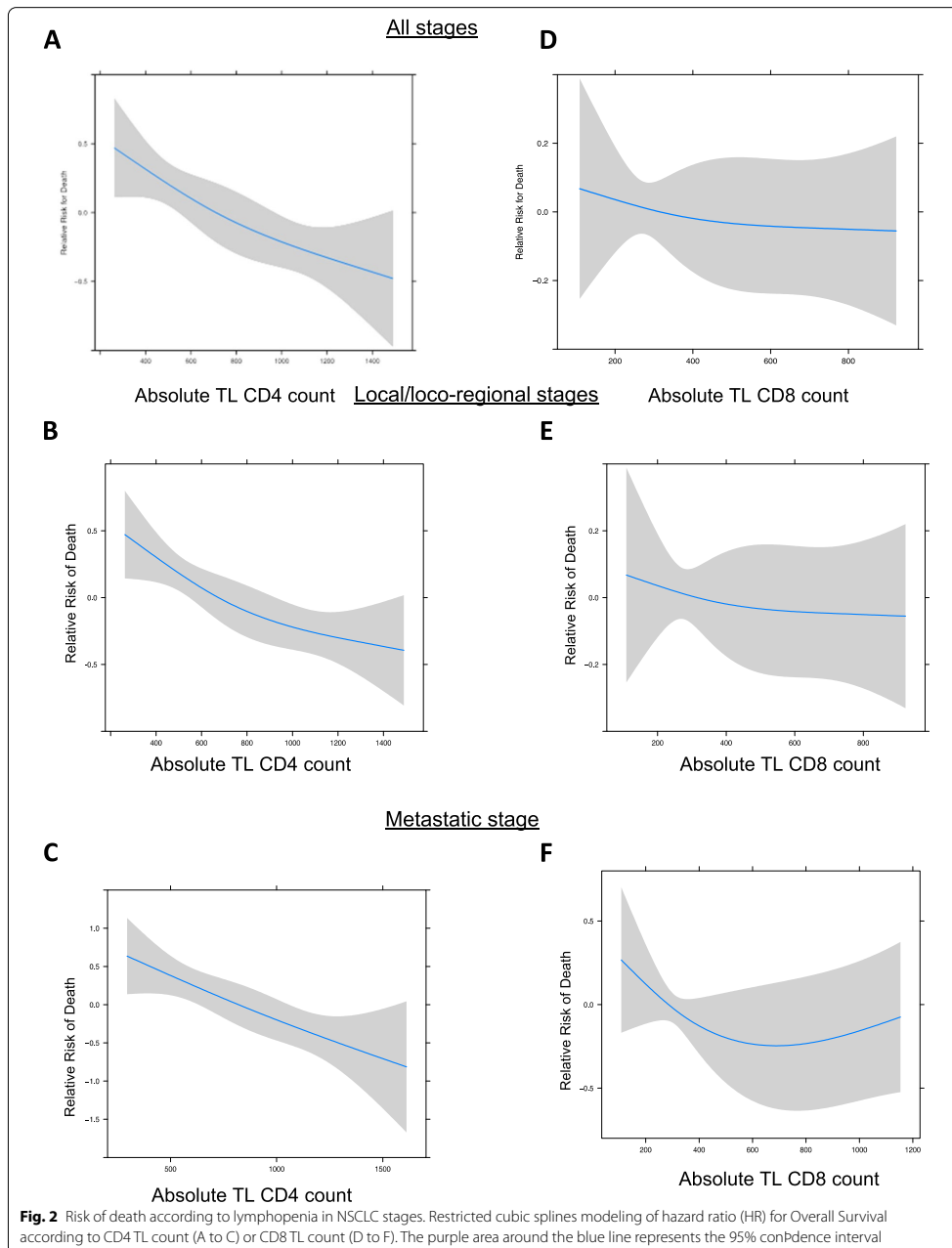
| In All Patients                            |                 |               |       |                |                  |
|--|-----------------|---------------|-------|----------------|------------------|
|  | No. of patients | No. of deaths | HR    | 95% CI         | P                |
| <b>Performance status OMS</b>              |                 |               |       |                |                  |
| 0/1  | 134             | 91            | 1     |                |                  |
| ≥ 2  | 33              | 30            | 2.191 | 1.413 to 3.396 | <b>0.0005</b>    |
| <b>Stage</b>                               |                 |               |       |                |                  |
| Local/Loco-regional                        | 84              | 48            | 1     |                |                  |
| Advanced                                   | 83              | 73            | 2.558 | 1.722 to 3.802 | <b>&lt;.0001</b> |
| <b>CD4+ T lymphocytes</b>                  |                 |               |       |                |                  |
| ≥ 500 /μl                                  | 120             | 80            | 1     |                |                  |
| < 500 /μl                                  | 47              | 41            | 1.422 | 0.971 to 2.083 | <b>0.0704</b>    |
| In patients with local/loco-regional NSCLC |                 |               |       |                |                  |
|  | No. of patients | No. of deaths | HR    | 95% CI         | P                |
| <b>Performance status OMS</b>              |                 |               |       |                |                  |
| 0/1  | 78              | 43            | 1     |                |                  |
| ≥ 2  | 6               | 5             | 1.788 | 0.687 to 4.649 | 0.2335           |
| <b>CD4+ T lymphocytes</b>                  |                 |               |       |                |                  |
| ≥ 500 /μl                                  | 64              | 33            | 1     |                |                  |
| < 500 /μl                                  | 20              | 15            | 2.028 | 1.065 to 3.817 | <b>0.0288</b>    |
| In Advanced NSCLC                          |                 |               |       |                |                  |
|  | No. of patients | No. of deaths | HR    | 95% CI         | P                |
| <b>Performance status OMS</b>              |                 |               |       |                |                  |
| 0/1  | 56              | 48            | 1     |                |                  |
| ≥ 2  | 27              | 25            | 2.270 | 1.354 to 3.806 | <b>0.0019</b>    |
| <b>CD4+ T lymphocytes</b>                  |                 |               |       |                |                  |
| ≥ 500 /μl                                  | 56              | 47            | 1     |                |                  |
| < 500 /μl                                  | 27              | 26            | 1.198 | 0.737 to 1.946 | <b>0.4668</b>    |

Previous studies have reported that CD4 lymphopenia was associated with poor prognosis in cancer patients [16, 17, 23], but these studies did not include patients with lung cancer. Here, we found that metastatic patients were more frequently affected by CD4 lymphopenia than patients with localized disease. However, the results showed that CD4+ T lymphopenia was significantly associated with poor survival in local/loco-regional disease, but not in metastatic patients. An explanation may be related to functional impairment of CD4 T cells, regardless of their circulating levels. Indeed, chronic inflammation and the accumulation of immunosuppressive factors at the metastatic stage can lead to functional alterations in CD4 T lymphocytes, which play a crucial role in the immune surveillance of cancers [24–26].

The metastatic status is the result of an accumulation of co-founding clinical parameters (PS, site of metastasis ...), as well as a chronic inflammatory, and immune-suppressive environment [8]. Interestingly, a CD4 TL count < 500/μL increases the risk of death in this cohort of both in localized and metastatic NSCLC. This is particularly relevant for the management of localized patients, to identify

patients with poor outcomes after surgery and adapt the treatment, with adjuvant therapy or intensified follow-up. In line with our data, a high preoperative total lymphocyte count was shown to reduce 5-year OS and 5-year relapse-free survival rates in resected colorectal cancer [27]. Moreover, CD4 T lymphopenia was found to have prognostic value only in patients with localized disease in our study, so it would be interesting to explore factors involved in CD4 lymphopenia in this setting, such as immune senescence. Indeed, CD4 T lymphopenia was found significantly more frequently in older patients including in patients with localized disease (mean age around 70 years).

We found that only peripheral CD4 lymphopenia influences the prognosis of NSCLC patients. This finding could be related to the central role of CD4 T cell in antitumor immunity [10, 28]. Indeed, CD4 T cells, particularly the Th1 subset, control cell-mediated immunity against tumors and have a “helper” role towards antitumor CD8 T cells [12]. Consequently, tumor-infiltrating Th1 cells have been identified as a good prognostic marker in many human cancers [29, 30]. Furthermore, we recently reported that the presence of circulating



tumor-specific CD4<sup>+</sup> Th1 was associated with better prognosis in lung cancer patients, notably in patients with localized disease [19]. Unlike peripheral CD4<sup>+</sup> TL, peripheral CD8<sup>+</sup> T lymphopenia did not appear to be related to patients' survival. One possible explanation may be the fact that CD8<sup>+</sup> T cells predominantly act as effectors in the tumor microenvironment. Accordingly, evidence supports the prognostic value of CD8<sup>+</sup> TILs reported in many cancers, including lung cancer [7, 14].

Although we found a statistical association with meaningful clinical implications for patient care, the low number of patients included in our study reduces the robustness of these results. Another limit of this study is the absence of information on treatments received by patients so that their link between CD4<sup>+</sup> T lymphopenia could not be addressed. Thus, the use of CD4 lymphopenia in NSCLC as predictive biomarker deserves future confirmation even more during immunotherapy. Indeed, a large multicenter prospective immune monitoring study in NSCLC called TELOCAP2 (NCT02846103) is under way, and will make it possible to address these limitations. These data also support the value of peripheral blood immune monitoring in NSCLC. Liquid biopsy (ctDNA), neutrophil to lymphocyte ratio (NLR), LDH, absolute lymphocyte count, MDSC, represent interesting potential blood biomarkers in lung cancer [31]. The poor prognosis associated with CD4 lymphopenia is widely documented in many cancers. Like other circulating biomarkers, such as the NLR, the assay is routinely done everywhere, with results being available quickly with standardized thresholds worldwide. For example, CD4 count is a good indicator of immune status, and is routinely used for the management of patients with HIV infection and other immunodeficiency disorders [32]. The deleterious effect of CD4 lymphopenia observed in patients with localized disease suggests an important role of these cells in cancer progression, as recently described in the study by Mascaux et al. [8]. In this regard, the role of peripheral CD4 TL has gained considerable interest for cancer immunotherapy in the last few years [33–36]. Hence, the critical role of peripheral CD4 T-cell populations but not CD8 TL for real-time blood-based monitoring has recently been highlighted in NSCLC patients treated with immune checkpoint inhibitors [37]. Finally, this study may suggest that CD4 TL count can guide the use of possible adjuvant therapy, according to the personalized risk for each patient.

## Conclusion

In the present study, we showed that CD4 TL count in the peripheral blood represents a promising prognostic factor for early stages of NSCLC. This is the first prospective study to address the prognostic value of CD4<sup>+</sup> T lymphopenia in NSCLC with long-term follow-up of over 10 years.

## Abbreviations

NSCLC: Non-Small Cell Lung Cancer; EGFR: Endothelial growth factor receptor; ALK: Anaplastic lymphoma kinase; PS: Performance status; TL: T lymphocyte; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed cell death 1; PD-L1: Programmed cell death-ligand 1; TIL: Tumor-infiltrating lymphocyte; OS: Overall Survival; PFS: Progression Free Survival; HR: Hazard Ratio.

## Acknowledgements

We thank all patients who contributed to this study. We thank all of the medical doctors, and nurses, from oncology department of University Hospital of Besançon and European Georges Pompidou hospital in Paris, for their contribution. The authors also thank the Biomonitoring platform of CIC-1431 for their technical support.

## Authors' contributions

GE, VW and OA conceived the study. GE, DW, AM, CL, EF, FLPB, VW and OA contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors performed the measurements. GE, DW, AM, CL, LC, VK, EF, FLPB, VW and OA were involved in planning and supervision of the work. All authors processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. All authors discussed the results and commented on the manuscript.

## Funding

This work was supported by grants from Assistance Publique Hopitaux de Paris, La Ligue Contre le Cancer, the Conseil Regional de Franche-Comte, Canceropole Grand Est.

## Availability of data and materials

The data from this study are available from the corresponding author on reasonable written request. The data are not publicly available because they containing information that could compromise research participant privacy.

## Declarations

### Ethics approval and consent to participate

All patients provided written informed consent and the protocol was approved by the ethics committee ComiZ de Protection des Personnes (CPP) Ile de France IV on 07/09/2009. The Telocap01 study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

### Consent for publication

Not applicable.

### Competing interests

I declare that the authors have no competing interests as defined by BMC, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

### Author details

<sup>1</sup>Chest Disease Department, University Hospital, 3 Boulevard Fleming, 25030 Besançon, France. <sup>2</sup>Methodology and Quality of Life in Oncology Unit, University Hospital, Besançon, France. <sup>3</sup>Université de Bourgogne Franche-Comté, EFS BFC, INSERM, UMR1098, RIGHT, Besançon, France. <sup>4</sup>INSERM CIC-1431, Clinical Investigation Center in Biotherapy, Biomonitoring Platform, F-25000 Besançon, France. <sup>5</sup>Department of Medical Oncology, University Hospital, Besançon, France. <sup>6</sup>Department of Medical Oncology, Assistance Publique-Hopitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France. <sup>7</sup>Department of Thoracic surgery, Assistance Publique-Hopitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France.

Received: 28 September 2021 Accepted: 26 April 2022

Published online: 11 May 2022

## References

- Jardim DL, de Melo GD, Giles FJ, Kurzrock R. Analysis of drug development paradigms for immune checkpoint inhibitors. *Clin Cancer Res*. 2018;24(8):1785E94.