Evaluation des modalités et techniques d'entrainement des patients dans le cadre de la chirurgie thoracique pulmonaire.

Francis Edouard Gravier

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THÈSE

Pour obtenir le diplôme de doctorat

Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE

Préparée au sein de l'Université de Rouen Normandie

Evaluation des modalités et techniques d'entrainement des patients dans le cadre de la chirurgie thoracique pulmonaire.

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Liste des sigles et abréviations

1-RM : répétition maximale, charge pouvant être mobilisée 1 seule fois

ADIR : Aide à Domicile aux Insuffisants Respiratoires (association)

ACC : « American College of Cardiology » (collège américain de cardiologie)

ACCP : American College of Chest Physicians (société savante Américaine des pneumologues)

ACSM : « American College of Sports Medicine » (collège américain de médecine du sport)

AHA : « American Heart Association »

BPCO : bronchopneumopathie chronique obstructive

CBNPC : cancer bronchique non à petites cellules

CBPC : cancer broncho-pulmonaire à petites cellules

CERDE : comité d'éthique pour la recherche sur données existantes

CNIL : Commission Nationale Informatique et Liberté

CPP : comité de protection des personnes

CVF : capacité vitale forcée

DLCO : diffusion pulmonaire du monoxyde de carbone

EFR : épreuve fonctionnelle respiratoire

EFX : exploration fonctionnelle à l'exercice

EMI : entrainement des muscles inspirateurs

EMR : entrainement des muscles respiratoires

ERS : European Respiratory Society (société savante Européenne de pneumologie)

ESTS : European Society of Thoracic Surgeons » (société savante Européenne des chirurgiens thoraciques)

FiO_2 : fraction en oxygène dans l'air inspirée

FMT : Fréquence cardiaque Maximale Théorique

GRADE : « The Grading of Recommendations Assessment, Development and Evaluation »

HIIT : « high intensity interval training », entrainement en intervalle à haute intensité

IMC : indice de masse corporelle

LPS : « lung perfusion scan » scintigraphie de perfusion pulmonaire

MICT : « moderate intensity continuous training » entrainement à intensité modérée continue

MR : méthodologie de référence (traitement des données selon la CNIL)

NRI : « Nutritional Risk Index »

OR : « odds ratio », risque relatif rapproché

P : puissance (en watts), se décline avec les suffixes « max » ou « pic »

PCA : antalgie contrôlée par le patient

Pimax : pressions maximales inspiratoires

POETTS : « Perioperative Exercise Testing and Training Society » (société savante anglosaxonne d'évaluation periopératoire)

PPO : valeurs prédictives postopératoires

RAAC : récupération accélérée après chirurgie

RATS : « robot-assisted thoracoscopic surgery » thoracoscopie par assistance robotique

RCP : réunion de concertation pluridisciplinaire

RCT : « randomized controlled trial » essais randomisés contrôlés

RER : « respiratory exchange ratio » quotient respiratoire (rapport $\dot{V}CO_2/\dot{V}O_2$)

RIPH : recherche impliquant la personne humaine

RR : risque relatif

SCT : « stair climbing test » test de montée d'escaliers

SEER : programme de surveillance, d'épidémiologie et de résultats finaux des Etats-Unis

SFAR : société française d'anesthésie réanimation

SI : spirométrie incitative

SFCTCV : société française de chirurgie thoracique et cardiovasculaire

SPECT-CT : « single-photon emission computed tomography – computed tomography » tomodensitométrie à émission monophotonique

STS : Society of Thoracic Surgeons » (société savante Américaine des chirurgiens thoraciques)

SV1 : premier seuil ventilatoire

SV2 : seuil de compensation ventilatoire (« Ventilatory Compensation Point » VCP)

SWT : « shuttel walk test » test navette

TDM6 : test de marche de 6 minutes

ThRCRI : « thoracic revised cardiac risk index »

TLC-1 : Test de levers de chaises d'une minute

TLC-3 : test de lever de chaise de 3 minutes

TNM : Tumor, Node, Metastasis, système de classification oncologique

TSA : « trial sequential analysis » analyse séquentielle des essais cliniques

VATS : « video-assisted thoracoscopic surgery » chirurgie thoracique assistée par vidéoscopie (thoracoscopie).

$\dot{V}CO_2$: débit de production de dioxyde de carbone

VEMS : volume maximal expiré en une seconde

$\dot{V}E$: ventilation à l'effort, se décline avec les suffixes « max » ou « pic »

VNI : Ventilation non-invasive

$\dot{V}O_2$: débit la consommation en oxygène, se décline avec les suffixes « max » ou « pic »

1. Introduction Générale

La chirurgie thoracique pulmonaire a connu ces vingt dernières années une modification profonde des techniques opératoires. La chirurgie mini-invasive vidéo et robot-assistée, l'imagerie en trois dimensions, combinées aux évolutions des techniques d'anesthésie et d'analgésie, ont permis d'améliorer à la fois la précision et la tolérance des interventions. Nous sommes entrés dans l'ère de la « chirurgie augmentée ».

Ces dix dernières années ont vu émerger et se diffuser des filières de soins dites de « récupération accélérée après chirurgie » (RAAC), combinant une évaluation multimodale, des techniques de chirurgie innovantes, et une mobilisation plus rapide du patient dans le temps postopératoire favoriser par une analgésie optimisée et personnalisée. Ces protocoles RAAC sont à présent considérés dans un vaste panel de chirurgie, dont la chirurgie thoracique pulmonaire.

La précision des techniques d'imagerie permet des diagnostics à la fois plus massifs et précoces, augmentant le nombre de cancers broncho-pulmonaires résécables. Malgré ce dépistage précoce, l'état général, les comorbidités, ou encore la capacité cardio-respiratoire des patients nouvellement diagnostiqués ne permettent pas toujours de concrétiser un projet chirurgical curatif. Après la chirurgie augmentée, la question du conditionnement des patients en vue d'une chirurgie majeure se pose, c'est l'émergence de la « préhabilitation ». Ce terme de « préhabilitation » inclut un ensemble d'interventions à la fois physique, nutritionnelle et éducative.

La préparation des patients à la chirurgie thoracique pulmonaire est une demande croissante en réhabilitation respiratoire. Le contexte, très majoritairement oncologique, incite l'ensemble de l'équipe thérapeutique à optimiser les parcours d'évaluation ainsi que de réentrainement pour proposer des programmes à la fois efficaces et condensés. Allons-nous entrer dans l'ère du « patient augmenté » ? Cette ambition requiert de poursuivre les recherches sur les critères d'évaluation ainsi que sur les modalités de préhabilitation proposées.

1.1. Objectifs de la thèse

Nos réflexions au cours de l'élaboration de ce projet de thèse se sont concentrées sur le parcours préopératoire des patients en attente de chirurgie thoracique. Bien que l'optimisation physique du patient soit un continuum débutant dès l'élaboration du projet chirurgical jusqu'à la période postopératoire chronique, nous avons pris le parti de nous concentrer sur la période préopératoire, temps crucial dans la prévention des complications postopératoire et l'anticipation d'un potentiel déficit fonctionnel résiduel. Nous nous sommes défini trois catégories d'objectifs :

Tout d'abord, évaluer la réponse à l'effort des patients adressés en évaluation fonctionnelle à l'exercice préopératoire, et identifier des outils d'évaluation complémentaires.

Deuxièmement, évaluer les effets des programmes de préhabilitation à la fois à l'échelle de la pratique locale et la concordance avec les études internationales.

Troisièmement, structurer le parcours de préhabilitation pour dégager les modalités les plus efficaces et réalisables en pratique clinique.

Après une introduction sur la chirurgie thoracique pulmonaire, cette thèse se présente en trois parties consacrées respectivement à l'évaluation, la préhabilitation, et enfin les axes d'optimisation de la préhabilitation.

1.2. La chirurgie thoracique pulmonaire

Le geste chirurgical le plus réalisé en chirurgie thoracique pulmonaire est très majoritairement la résection pulmonaire majeure. La technique de résection pulmonaire s'est développée à la fin du 19e siècle principalement en lien avec le traitement de la tuberculose. Ainsi, on note dans la littérature l'un des premiers rapports datant de 1906 d'une pneumonectomie, c'est-à-dire l'ablation d'un poumon complet, retraçant le cas clinique d'un patient atteint de tuberculose sévère ayant bénéficié d'une pneumonectomie en 1895 (1). La pneumonectomie pratiquée dans un cadre oncologique a ensuite été décrite en 1933 (2), suivie par le développement de la lobectomie encore considérée aujourd'hui comme le traitement de référence des lésions localisés (3).

Parallèlement à la résection pulmonaire, on retrouve dans les chirurgies thoraciques pulmonaires les interventions spécifiques de la trachée et des bronches (cure de sténose ou fistule), de la plèvre (pleurodèse, talcage, pleurectomie, décortication), ou encore la greffe pulmonaire. Ces aspects de la chirurgie pulmonaire ne seront pas développés dans le cadre de cette thèse.

1.2.1. Indications à la chirurgie thoracique pulmonaire

Au-delà de chirurgies traumatiques en urgence, la chirurgie pulmonaire programmée contribue aujourd'hui à la prise en charge de maladies malignes, mais aussi de certaines pathologies bénignes de type dégénératif ou infectieux. Elle garde également un rôle diagnostique, dans les cas où les méthodes moins invasives n'ont pas permis d'aboutir à un diagnostic avec certitude.

Ainsi, le cancer broncho-pulmonaire, que nous décrirons plus spécifiquement ultérieurement, est l'indication largement majoritaire à la chirurgie de résection pulmonaire (Figure 1). Les autres motifs de résection sont principalement liés aux pathologies suivantes :

- **Tuberculose :** bien que le traitement soit en première intention médical par antibiothérapie appropriée, une indication à une résection en cas d'infections résistantes ou de séquelles localisées est parfois nécessaire ;
- **Dilatation des bronches (ou bronchiectasie) :** malgré un traitement médical et un drainage bronchique quotidien, certains cas de bronchiectasie peuvent nécessiter une résection en cas d'infections récidivantes localisées, ou d'hémoptysie ;
- **Aspergillose :** il s'agit d'une infection par un champignon présent dans l'environnement courant. Ce dernier peut coloniser des zones pulmonaires lésées par des pathologies antérieures, ou se développer chez des sujets immunodéprimés. La résection d'un aspergillome, zone nodulaire formée par l'aspergillose, est parfois envisagée pour contrôler l'infection et ses éventuelles conséquences (hémorragie intra-bronchique) ;
- **Abcès pulmonaire :** de même que pour les indications précédentes, le traitement d'un abcès pulmonaire, conséquence d'une infection bactérienne, est en première intention médical voire un drainage percutané. La résection pulmonaire n'est envisagée qu'en cas d'abcès chronique important ne répondant pas complètement au traitement de première intention.
- **Emphysème :** la destruction progressive et irréversible du parenchyme pulmonaire distal, qui caractérise l'emphysème, engendre une modification des propriétés élastiques du poumon et la création de zones inefficaces sur le plan respiratoire, piégeant l'air et impactant la mécanique pulmonaire dans son ensemble. La chirurgie de réduction de volume pulmonaire, grâce à la résection spécifique de territoires particulièrement touchés par la maladie emphysémateuse, a pour but de réduire le piégeage gazeux et ainsi permettre de restaurer une fonction diaphragmatique et de décomprimer le parenchyme sain avoisinant.

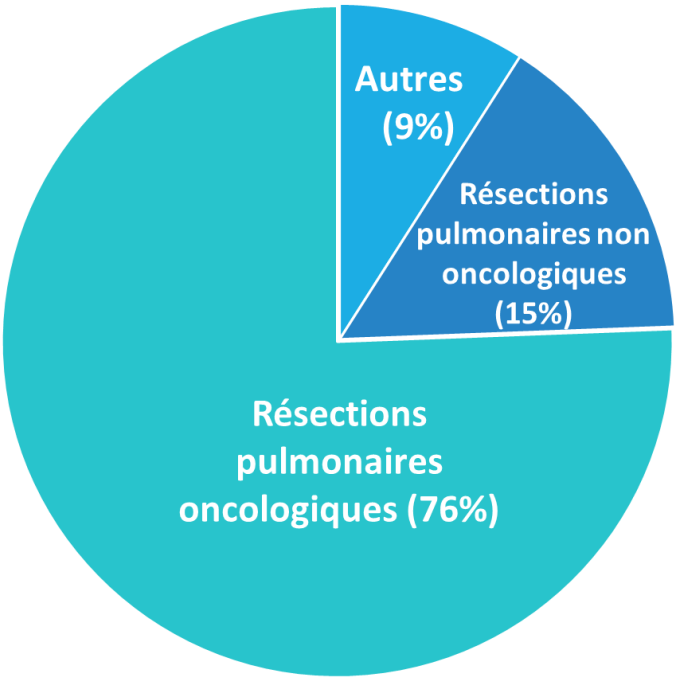


Figure 1 : répartition des indications à la chirurgie thoracique pulmonaire d'après Salati et al. 2017 (4) rapportant l'analyse de la base de données de la société européenne de chirurgie thoracique ; Autres : biopsie, chirurgie traumatique, transplantation.

Comme l'illustre la figure 1, on note une prépondérance forte des interventions pulmonaires liées à la résection de tumeurs cancéreuses. Bien que nous n'ayons pas de chiffres objectifs, cette proportion a certainement été d'autant plus notable ces deux dernières années dans le contexte la pandémie à SARS-CoV-2. En effet, de par leur nature urgente, les projets chirurgicaux oncologiques ont été majoritairement maintenus malgré le contexte sanitaire. Les travaux menés entre 2019 et 2021 regroupés au sein de cette thèse porteront donc exclusivement sur la thématique de la résection pulmonaire pour cancer broncho-pulmonaire.

1.2.2. Le Cancer broncho-pulmonaire

Epidémiologie

A travers le monde, le cancer est devenu la seconde voire même la première cause de décès prématuré dans 91 pays sur 172, d'après les dernières estimations GLOBOCAN de 2018 (5). Le poumon apparait comme un organe particulièrement exposé, puisque les cancers broncho-pulmonaires occupent la première place en termes d'incidence avec environ 2,1 millions de nouveaux cas à travers le monde chaque année, soit 11,6% de l'ensemble des nouveaux cancers diagnostiqués tous sites confondus. Le cancer du poumon occupe aussi la funeste première place des causes de mortalité liée au cancer avec environ 1,8 millions de décès imputables, soit 18,4% de l'ensemble des décès répertoriés (5).

En France, les projections les plus récentes de 2017 rapportent une incidence d'environ 32.500 nouveaux cas de cancer pulmonaire chez l'homme et 17.000 chez la femme, les portant respectivement au second et troisième rang des nouveaux cancers diagnostiqués chaque année. Alors que l'incidence se stabilise depuis plusieurs années chez l'homme, elle ne cesse de progresser chez la femme. Toujours selon ces mêmes rapports de 2017, le cancer pulmonaire est la première cause de mortalité liée aux cancers chez l'homme avec 21000 décès estimés, et de la seconde cause chez la femme avec 9.600 décès estimés (6).

Le facteur de risque principal du cancer est la consommation de tabac. En effet, 90% des cancers broncho-pulmonaires déclarés chez l'homme, et 75% chez la femme concernent des individus fumeurs ou ex-fumeurs (7).

Le programme de surveillance, d'épidémiologie et de résultats finaux (SEER) des Etats-Unis rapporte une incidence tous âge, sexe et ethnie confondus de 54 pour 100.000 individus. Il est important de noter que l'incidence passe de 16 versus 317 pour 100.000 individus chez les personnes de moins versus plus de 65 ans. Le cancer broncho-pulmonaire est donc également une maladie liée à l'âge, avec environ un tiers des patients ayant 75 ans et plus (8).

Notons que le tabagisme passif, l'exposition professionnelle ou environnementale, ainsi que les prédispositions génétiques, sont des facteurs de risques non négligeables (9).

Diagnostic et classification

Le cancer du poumon est suspecté en présence de signes respiratoires tels qu'une toux, une dyspnée, des douleurs thoraciques, ou encore une hémoptysie. Ces signes respiratoires n'étant pas spécifiques, c'est en général leur persistance ou leur récidive fréquente malgré les traitements qui guident le praticien vers les examens complémentaires à la recherche d'un cancer broncho-pulmonaire. D'autres signes thoraciques marquant une atteinte médiastinale peuvent conduire à sa mise en évidence tels qu'une dysphonie, une dysphagie, ou un syndrome cave supérieur. D'autres signes peuvent orienter le médecin, comme l'amaigrissement et l'anorexie, associés à l'altération de l'état général du patient. De plus, divers syndromes paranéoplasiques peuvent accompagner le développement du cancer broncho-pulmonaire. Enfin, des signes extra-thoraciques, en rapport avec le développement de métastases (le plus fréquemment localisées au niveau du cerveau, des os, du foie et des surrénales), peuvent ensuite être associés à une tumeur bronchique primitive (10).

En cas de signes cliniques, des examens complémentaires basés sur l'imagerie dans un premier temps, puis sur des prélèvements anatomopathologiques, permettent de qualifier puis de classer la tumeur. Les principales catégories anatomopathologiques sont les adénocarcinomes, les carcinomes épidermoïdes, les carcinomes à grandes cellules et les tumeurs neuroendocrines (parmi lesquelles on retrouve les cancers broncho-pulmonaires à petites cellules (CBPC)) (11).

Le pronostic du cancer broncho-pulmonaire est en général défavorable. En effet, le taux de survie est d'environ 43% à 1 an et 14% à 5 ans. Ceci est bien évidemment à mettre en perspective avec la précocité du diagnostic qui ne cesse de progresser grâces aux innovations médico-technologiques. Notons que les cancers bronchiques non à petites cellules (CBNPC) de stade I et II ont un taux de survie à 5 ans de l'ordre de 35 à 70% selon les études (12).

Les CBPC correspondent à environ 15% des cancers du poumon (13). De par leur caractère diffus et rapidement métastatique, leur prise en charge est exclusivement axée sur la radio-chimiothérapie complétée par les récents progrès de l'immunothérapie (13). Dans le

cadre de cette thèse, nous nous limiterons à l'étude des CBNPC qui représentent 85% des cancers du poumon et sont potentiellement éligibles à une chirurgie de résection. Des avancées sur l'analyse génétique de ces différentes classes anatomopathologiques élargissent aujourd'hui les sous-classifications et les thérapeutiques futures, éléments qui ne seront pas développés présentement.

Une fois le diagnostic de CBNPC fortement suspecté voire avéré par anatomopathologie, le patient bénéficie d'un bilan d'extension permettant de classer le stade du cancer. La classification internationale en vigueur est la « Tumor, Node, Metastasis » (TNM) dont la septième édition est utilisée depuis 2009 (12). Cette classification, exposée en annexes 1.1 et 1.2, permet de déterminer le stade en fonction du statut de la Tumeur dit « T », de l'envahissement métastatique des ganglions lymphatiques thoraciques dit statut « N » pour *Nodes*, et enfin de la mise en évidence ou non de métastases dit statut « M ». Une huitième version publiée fin 2016 a commencé à s'insérer dans les pratiques professionnelles à partir de 2017-2018 (14). Dans le cadre de cette thèse, une part des travaux (pour plusieurs rétrospectifs) se basent sur les stades décrits dans la 7^{e} édition de par le changement de pratique clinique en cours au moment de la mise en place des études qui sont exposées. Les travaux prospectifs entrepris au début de cette thèse se basent sur la 8ème édition. Le détail de la 8^{e} édition de la classification TNM est disponible en Annexe 1.

Indications spécifiques à la chirurgie de résection pulmonaire oncologique

Il est nécessaire de garder à l'esprit la différence entre les termes de « résécabilité » et d'« opérabilité ». Le premier fait référence à la possibilité d'une thérapie curative par la résection pulmonaire. Le second fait référence à la capacité du patient à supporter l'acte chirurgical au regard de l'étendue du geste opératoire, de son état général, ainsi que ses possibles comorbidités cardiovasculaires et respiratoires. L'équipe médicale détermine au cours de réunions de concertation pluridisciplinaire (RCP) regroupant notamment pneumologues, oncologues, chirurgiens, et anesthésistes, si le cancer est accessible à une stratégie curative ou palliative.

La chirurgie est le traitement de référence pour les CBNPC de stade I et II considérés en quasi-totalité comme résécables (3). Une large part des cancers de stade IIIA le sont aussi. En ce qui concerne les stades IIIB et IV, les indications à la chirurgie sont exceptionnelles car considérés comme non résécables de par la diffusion de la pathologie cancéreuse. Les recommandations intègrent cette approche chirurgicale pour les stades plus avancés dans le cadre de protocoles thérapeutiques multimodaux préalablement discutés en réunion multidisciplinaire (15). Ainsi, l'équipe de Bott et al. a mis en évidence une augmentation significative de la survie globale des patients atteints de stade IIIA, IIIB et IV, dont le protocole thérapeutique incluait une approche chirurgicale en complément des thérapies chimiques ou ionisantes (16). Plus récemment, la place de la chirurgie a été remise en avant pour obtenir un contrôle local du site primaire et synchrone (ou métachrone), chez une nouvelle catégorie de patients dite « oligométastatique » (17).

D'après les données de 2010 à 2016 du programme SEER des Etats-Unis, le stade des CBNPC nouvellement diagnostiqués était qualifié de « local » dans 20% des cas, « régional » dans 25% des cas et « métastatique » dans plus de 50% des cas (8). La découverte fréquemment tardive impacte l'option d'un traitement curatif radical par chirurgie. Bien que non établi à ce jour en France, il a été rapporté que le dépistage du cancer du poumon chez les personnes à haut risque au moyen d'examens annuels de tomodensitométrie à faible dose pourrait potentiellement réduire de 20% la mortalité liée au cancer du poumon et augmenterait parallèlement le volume de patients adressés en chirurgie thoracique (18).

1.2.3. Les différents types de chirurgie

L'intervention la plus courante proposée actuellement en première intention est la lobectomie, qui consiste en l'ablation complète du lobe pulmonaire dans lequel se situe la tumeur, plutôt que la pneumonectomie complète. La lobectomie représente environ les deux tiers de l'ensemble des résections réalisées pour cancer pulmonaire, dont 82% étaient réalisées en thoracotomie conventionnelle, selon l'analyse de la base de données de *l'European Society of Thoracic Surgeons* en 2017 (4). Le curage ganglionnaire médiastinal systématique associé à la résection pulmonaire du CBNPC est actuellement recommandé (19).

En cas d'envahissement plus large, une bilobectomie, voire une pneumonectomie, peuvent être nécessaires. Ces options plus radicales concernent 12.5% des résections pulmonaires oncologiques et sont réalisées de manière quasi systématique par thoracotomie (4).

Les progrès techniques chirurgicaux précédemment abordés, conjugués à ceux de l'imagerie et un diagnostic plus précoce, permettent des résections de plus petites tailles comme les segmentectomies, voire des résections atypiques très localisées comme les résections cunéiformes (« *wedge resection* »), dites sous-segmentaires. Ces résections plus ciblées représentent environ un quart des interventions pulmonaires oncologiques. Leur fréquence est en constante augmentation, parallèlement au recours à la chirurgie vidéo ou robot-assistée qui constitue leur voie d'abord principale (4).

L'objectif du chirurgien est de réséquer la tumeur en obtenant des marges dites « saines » ou une exérèse appelée « R0 » c'est à dire microscopiquement et macroscopiquement complète, tout en retirant le minimum de volume de l'organe atteint. La lobectomie est encore à ce jour la chirurgie de référence recommandée pour le traitement du cancer pulmonaire localisé (3). Une récente étude randomisée contrôlée sur 1106 patients ne rapporte aucune différence de résultats périopératoire chez les patients ayant bénéficié d'une segmentectomie ou d'une lobectomie, hormis davantage de fuites aériques prolongées dans le bras segmentectomie (20). Une seconde étude de phase III comparant ces types d'interventions est encore en cours (NCT00499330). La segmentectomie deviendra

probablement le traitement en première intention des stades les plus précoces si la supériorité attendue de la fonction pulmonaire postopératoire et la non-infériorité de la survie globale sont confirmées.

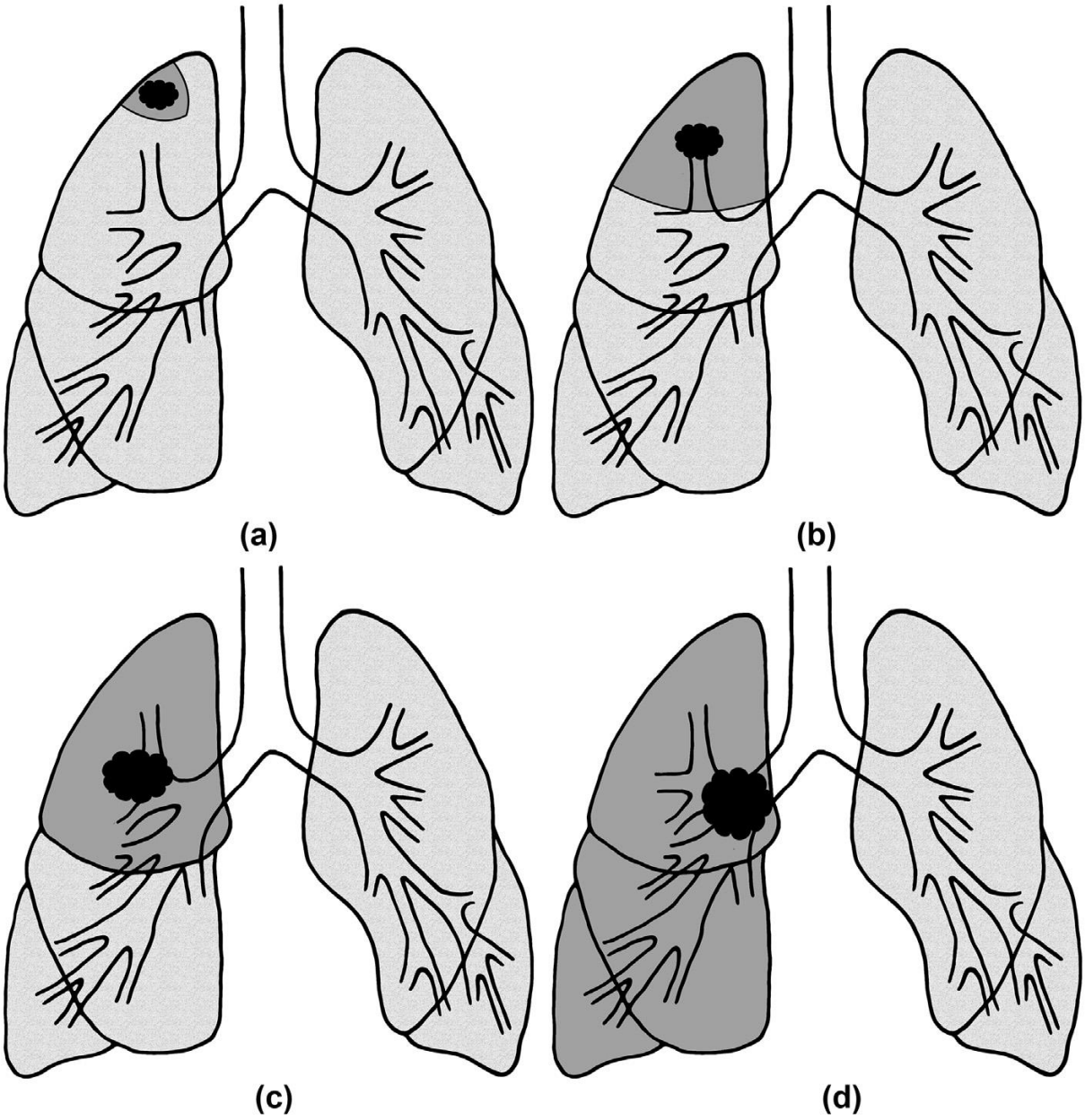


Figure 2 : Types de résection chirurgicales, a) wedge résection, (b) segmentectomie, (c) lobectomie, (d) pneumonectomie. D'après Thorpe et al. 2020 (21).

1.2.4. Modes interventionnels

Parallèlement au volume de la pièce anatomique réséquée, on retrouve deux grands modes interventionnels : l'approche par thoracotomie et la chirurgie vidéo-(/robot)-assistée (« *video/robot-assisted thoracoscopic surgery* » VATS/RATS).

La thoracotomie

La thoracotomie postérolatérale est jusque récemment la voie d'abord de référence recommandée par la société française de chirurgie thoracique et cardiovasculaire (SFCTCV) (22). Elle a l'avantage de conférer au chirurgien un large accès, notamment en cas de chirurgie volumineuse, avec cependant l'inconvénient d'une large section des muscles de la paroi thoracique. Les modalités latérale ou axillaire, et antérolatérale d'épargne musculaire sont aussi décrites dans la chirurgie d'exérèse pour cancer pulmonaire (22).

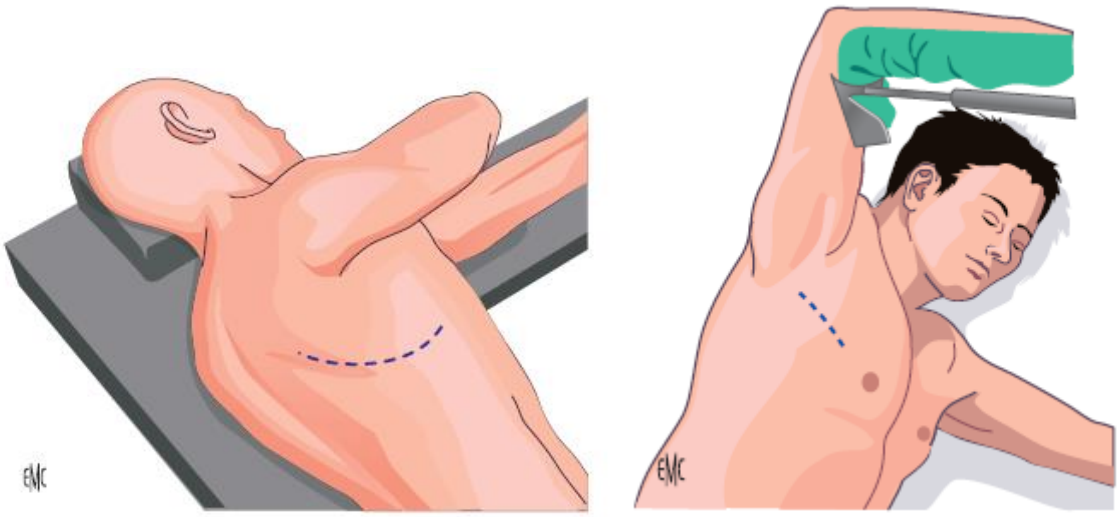


Figure 3 : intervention réalisée par thoracotomie, voie d'abord postéro-latérale (à gauche) ou axillaire (à droite), d'après Heyndrickx et al. 2016 (23)

La chirurgie par vidéo-thoracoscopie (VATS)

Les abords vidéo-thoracoscopiques comportant ou non une mini-thoracotomie avec ou sans écartement intercostal. Ils confèrent une alternative à la thoracotomie conventionnelle pour l'exérèse par lobectomie ou résection infra-lobaire. Bien que leur possible exiguïté ait pu être un frein lors de leur développement, les progrès techniques et la spécialisation de la pratique ont conduit à la diffusion de ce mode interventionnel qui accompagne les résections lobaires, segmentaires et atypiques. Cette technique combinée à des résections plus limitées a permis d'augmenter l'accès à la thérapeutique chirurgicale pour des patients fragiles (24).

Figure 4 : intervention réalisée par thoracoscopie vidéo-assistée (VATS), d'après Jaklitsch et al. 2003 (24).

La chirurgie robot-assistée (RATS)

Les avantages théoriques de la chirurgie robotique sont multiples : meilleure vision, plus grande dextérité intrathoracique et possibilité de sutures très précises. Les problèmes majeurs sont l'accès au système, son coût important et son apprentissage (25). La RATS s'est progressivement développée comme un outil d'extension de la VATS à la disposition des équipes chirurgicales.

A B

Figure 5 : intervention réalisée par thoracoscopie robot-assistées (RATS), exemple de positionnement des bras instrumentaux robotiques au niveau du thorax en (A) d'après Kang et al. 2019 (26), et positionnement de l'équipe dans la salle d'intervention (B) d'après Etienne et al. 2017 (19) ; 1. Chirurgien à la console opératoire ; 2. écran ; 3. anesthésiste ; 4. aide opératoire ; 5. panseuse ; 6. robot.

1.2.5. Complications postopératoires de résection pulmonaire

La chirurgie de résection pulmonaire expose le patient à un certain nombre de complications possibles tant sur le plan pulmonaire que cardio-vasculaire, neurologique ou infectieux. La majorité des complications possibles ont été listées et définies de manière précise par les sociétés américaine et européenne de chirurgie thoracique (« *Society of Thoracic Surgeons* » (STS) et « *European Society of Thoracic Surgeons* » (ESTS)) de manière à harmoniser le recueil de leur prévalence dans les études cliniques et les bases de données communes (27). Le tableau III résume les principales complications possibles.

Tableau I : Principales complications postopératoires en chirurgie thoracique pulmonaire définies par la STS et l'ESTS en 2015 (27).

Domaine	Liste des complications
Pulmonaire	• Fuite d'air nécessitant un drainage thoracique prolongé (>5 jours) • Atélectasie (+/- nécessité d'une bronchoscopie) • Pneumopathie • Syndrome de Détresse Respiratoire Aigue • Fistule broncho-pleurale • Embolie Pulmonaire • Ventilation mécanique prolongée (>48H) • Réintubation • Trachéotomisation
Cardio-vasculaire	• Fibrillation atriale • Fibrillation ventriculaire • Infarctus du myocarde
Neurologique	• Accident vasculaire cérébral • Paralysie diaphragmatique par lésion nerveuse • Délirium
Infectieux	• Pneumopathie infectieuse • Infection de paroi • Empyème
Autre	• Insuffisance rénale • Chylothorax

Concernant leur incidence, l'analyse de la base de données de l'ESTS publiée en 2017, rapporte un taux de complications postopératoires global à 18,5% et une mortalité à 2,6% dans les 30 jours postopératoires (4). Les complications pulmonaires représentent la majorité des complications postopératoires, suivies des complications cardiovasculaires. Ainsi, on retrouve selon les cohortes un taux de complications pulmonaires deux fois supérieur aux complications cardio-vasculaires, comme par exemple la cohorte de Stéphan et al. rapportant un taux de 25% de complications respiratoires et 11% de complications cardiaques dans une cohorte de 266 patients ayant bénéficié d'une résection pulmonaire oncologique (28).

L'explication physiopathologique de la genèse des complication respiratoires en chirurgie majeure repose principalement sur les éléments suivants.

Physiopathologie peropératoire

Dès la perte de conscience induite par l'anesthésie générale, la commande respiratoire du patient est altérée et sur le plan mécanique la position allongée (dorsale ou latérale) s'accompagne d'un déplacement céphalique du diaphragme dans les zones dépendantes, ceci étant accentué par la perte de tonus musculaire (29). Ceci se traduit par l'apparition rapide et extrêmement fréquente d'atélectasies, correspondant à des zones d'affaissement des voies respiratoires. Au-delà de la compression du poumon, ces zones d'affaissement sont aussi générées par une absorption rapide des gaz intra-pulmonaires au moment de l'induction, liée à l'utilisation d'une fraction en oxygène (FiO_2) importante représentant 80 à 100% de l'air insufflé (30). L'incidence de ces atélectasies peropératoires dépasserait 75% des patients au cours d'une chirurgie sous anesthésie générale (31).

A ces éléments il est pertinent d'ajouter la spécificité de la chirurgie pulmonaire qui nécessite une ventilation sélective, c'est-à-dire d'un seul des deux poumons, au cours de l'acte chirurgical. La ventilation d'un seul poumon s'accompagne d'un stress hypoxique et vasculaire important au moment de l'arrêt de la ventilation du poumon opéré. Ce stress physiologique est objectivé par la mesure de la libération importante de marqueurs inflammatoires et oxydatifs, tant au moment de la fermeture que de la ré-expansion du poumon opéré, ceci étant corrélé à la durée de la ventilation mono-pulmonaire (32).

Physiopathologie postopératoire

L'action résiduelle des substances anesthésiques, plusieurs heures après la reprise de conscience, contribue à perturber la régulation de la ventilation relative à l'hypercapnie et l'hypoxie. La vigilance et l'efficacité de la déglutition peuvent aussi être altérées avec des risques d'inhalation, pourvoyeuses de pneumopathies (29).

L'inflammation pulmonaire, conséquence du stress mécanique et physiologique peropératoire peut être à l'origine ou majorer une obstruction postopératoire des voies aériennes.

Enfin, le patient présente une modification de sa mécanique ventilatoire, liée à la fois à l'altération résiduelle de la commande ventilatoire et à une altération de la contraction du diaphragme. Enfin, bien que le recours à l'antalgie morphinique contrôlée par le patient (PCA), la péridurale thoracique ou les cathéters paravertébraux aient nettement amélioré le contrôle de la douleur (19), une inhibition de la respiration profonde et de la toux par réflexe antalgique peut se surajouter aux éléments précédemment décrits. L'ensemble de ces facteurs pouvant aboutir à un encombrement bronchique favorisant des complications potentiellement sévères (29).

1.2.6. Facteurs de risques de complications postopératoires

Facteurs de risques non-modifiables

Plusieurs facteurs, malheureusement non modifiables, influencent à la fois la morbidité et la mortalité postopératoire.

Type de résection et approche chirurgicale

Le taux de complications postopératoires augmente proportionnellement à l'étendue de la résection réalisée. Ainsi, les taux de complications rapportés par la base de données de l'ESTS sont de 11,5% [IC 95% 10,5 à 12,6] pour une segmentectomie, 17,6% [IC 95% 17,3 à 18,0] en cas de lobectomie, et enfin relativement équivalents en cas de bilobectomie 26,5%

[IC 95% 24,7 à 28,2] et pneumonectomie 26.4% [IC 95% 25,2 à 27,6] (4). De même, ces taux de complications sont à terme associés avec une mortalité postopératoire graduelle allant de 1,6 % [IC 95% 1,2 à 2,2] pour une segmentectomie à 6,7% [IC 95% 6,0 à 7,3] pour une pneumonectomie (4).

Parallèlement, les approches chirurgicales mini-invasives présentent des suites opératoires significativement plus simples avec des taux de complications et de mortalité respectivement à 12,1% [IC 95% 11,4 à 12.8] et 1,1% [IC 95% 0,9 à 1,4] en cas d'approche par VATS, contre 19,9% [IC 95% 19,4 à 20,1] et 2,9% [IC 95% 2,7 à 3,0] en cas de thoracotomie conventionnelle (4). Bien que dans les chiffres précédents la VATS soit associée à des types de résections moins étendues, des analyses ajustées montrent que le recours à ces techniques de chirurgies mini-invasives et robotiques diminue le taux de complications et la durée de séjour postopératoire par rapport à la thoracotomie conventionnelle (33).

Age

Dans les bases de données, l'âge est associé à un taux de complications supérieur (4, 34). Ainsi on retrouve des taux de complications supérieurs chez les plus de 75 ans par rapport aux plus jeunes avec une morbidité respectivement à 23,9% [IC 95% 22,9 à 24,8] versus 17.6% [IC 95% 17,3 à 18,0] et une mortalité deux fois plus importante avec un taux de 4,6% [IC 95% 4,2 à 5,1] versus 2.3% [IC 95% 2,1 à 2,4] (4).

Malgré ces constatations, il n'en reste pas moins qu'il n'est pas factuellement possible de définir une limite d'âge pour la chirurgie pulmonaire oncologique, au risque de faire l'amalgame entre âge et fragilité. L''âge physiologique serait un meilleur prédicteur des résultats que l'âge chronologique. Parallèlement, les CBNPC sont plus fréquemment diagnostiqués à un stade plus précoce chez les sujets âgés que les patients plus jeunes (35). La restriction de l'accès à la chirurgie potentiellement curative sur la seule base de l'âge n'est plus envisagée. En effet, l'analyse complète des facteurs des comorbidités, de l'état fonctionnel, cognitif et l'accès potentiel à la chirurgie mini-invasive permettent d'envisager des chirurgies curatives avec des taux de complications faibles chez des patients de plus de 80 ans (24, 36).

Comorbidités

La prévalence de comorbidités cardio-vasculaires et pulmonaires est importante parmi les patients atteint de CBNPC, notamment de par le lien étroit entre l'intoxication tabagique et l'ensemble de ces comorbidités. Ainsi, les patients présentant un diagnostic de comorbidité cardio-vasculaire ont un taux de complications et de mortalité respectivement de 21,1% [IC % 20,5 à 21,7] et 3,2% [IC 95% 2,9 à 3,4] contre 17,2% [IC 95% 16,8 à 17,6] et 2,3% [IC 95% 2,2 à 2,5] chez les sujets n'en présentant pas (4). De même, les patients présentant une obstruction bronchique, mesurée par l'altération des débits expiratoires, ont un taux de complications supérieur avec 24,5% [IC 95% 23,9 à 25,1] versus 15,2% [IC 95% 14,7 à 15,6], et de mortalité à 3,5% [IC 95% 3,2 à 3,7] versus 1,8% [IC 95% 1,6 à 2,0] (4). L'évaluation des comorbidités cardio-vasculaires et pulmonaires sera spécifiquement développée dans la première partie de la thèse.

Parallèlement aux pathologies cardio-vasculaires et à l'altération de la fonction pulmonaire, le diabète est retrouvé dans les comorbidités significativement pourvoyeuses de complications postopératoires. Récemment, Kaseda et al. ont publié une étude rétrospective explorant les résultats post-résection pour CBNPC des patients atteints de diabète (37). Au sein d'une cohorte de 1231 patients, environ 11% présentaient un diabète avec une incidence significativement plus élevée de complications postopératoires que les sujets non-diabétiques (28,1 % versus 20,7 % ; p = 0,047), en particulier le taux d'infections de paroi (4,3 % contre 0,9 % ; p = 0,001) et de pneumopathies (5,0 % contre 0,8 % ; p = 0,004) (37).

Expérience du centre

L'expérience du centre en chirurgie thoracique a aussi été décrite comme un facteur influençant le risque de mortalité. Bhamidipati et al. ont comparé le taux de complications et de mortalité d'une cohorte d'environ 500.000 résections pulmonaires réalisées aux Etats-Unis dans des hôpitaux universitaires spécialisés en chirurgie thoracique, versus chirurgie générale et hôpitaux non universitaires généraux (38). Bien que ces résultats soient mesurés dans un système de santé différent, leurs résultats étayent une diminution significative des

complications et de la mortalité en lien avec un niveau de spécialisation croissant du centre chirurgical. Plus récemment, une étude française menée par Pagès et al. confirme un lien entre la spécialisation du centre chirurgical, modélisée cette fois-ci par le volume annuel de chirurgies pulmonaires oncologiques, et le taux de mortalité postopératoire (39).

Facteurs de risques modifiables

En complément des facteurs précédemment décrits, d'autres facteurs potentiellement « modifiables » influencent la survenue de complications postopératoires.

Tabagisme

Il a été rapporté qu'environ 25% à 50% des patients sont fumeurs actifs au moment du diagnostic de cancer pulmonaire, et on estime que 20% d'entre eux le sont toujours au moment de la chirurgie (40, 41).

Le statut tabagique est significativement impliqué dans la survenue des complications respiratoires. Selon les équipes et les modes de suivi de cohortes, on retrouve un risque de complications multiplié par trois à six chez les patients fumeurs actifs en comparaison aux non-fumeurs (42, 43).

Les récents travaux de Fukui et al. rapportent une diminution progressive du risque de complications pulmonaires à chaque tranche de délai de sevrage par rapport aux non-fumeurs : tabac actif Odds Ratio (OR) = 12,9 ; sevrage < 1 mois OR = 10,3 ; entre 1 et 3 mois OR = 8,5 ; entre 3 et 6 mois OR = 6,3 ; entre 6 et 12 mois OR = 6,0 ; > 12 mois OR = 5,0 (42). D'autre part, le maintien du tabagisme postopératoire est corrélé à une diminution de la qualité de vie (41). Dans ce contexte, la société française d'anesthésie réanimation (SFAR) recommande le sevrage tabagique avant toute chirurgie majeure, quel qu'en soit le délai (44).

Nutrition

Lors du diagnostic du CBNPC, un statut nutritionnel altéré est une variable pronostique négative indépendante de la qualité de vie et de la survie (45). Au-delà de la présence d'une

dénutrition déjà objectivée ou non, une chirurgie majeure expose elle-même le patient à un risque de dénutrition (60).

Concernant les patients bénéficiant d'une résection pour CBNPC, l'étude de Ramos et al. montre que l'insuffisance pondérale (indice de masse corporelle (IMC) < 18,5 kg/m^2) est un facteur péjoratif quant aux complications et la durée de séjour (46). De plus, sur le suivi à long terme, les patients présentant une insuffisance pondérale présentent un taux de survie sans récidive de la maladie oncologique à 3 ans significativement plus faible que les patients en surpoids (IMC ≥ 25,0 et < 30,0 kg/m^2) et obèses (IMC ≥ 30,0 kg/m^2) (40% versus 64,5% et 72,3% respectivement p < 0,001) (46). L'influence de l'IMC semble cependant protectrice jusqu'à un certain point. En effet, l'équipe de Xi et al. rapporte un effet bénéfique sur un principe de courbe en U chez des patients atteints de CBNPC de stade précoce (47). Ils décrivent la plus basse classe de risque de complications postopératoire et la survie globale plus favorable pour la catégorie de patients présentant un IMC compris entre 22,5 et 28,0 kg/m2 en comparaison des autres catégories adjacentes (47).

L'utilisation d'indices nutritionnels composites comme le *Nutritional Risk Index* (NRI), ou les indicateurs recommandés par la SFAR (perte de poids récente > 10 % ; IMC ≤ 18,5 (ou < 21 au-delà de 70 ans) ; albuminémie < 30 g/L) (48), permettent de dépister les patients malnutris. Comme souligné précédemment dans l'étude de Ramos et al., le taux de complications, en particulier le risque de pneumopathie, est notablement plus élevé en cas de malnutrition objectivée à l'aide du NRI qu'en situation d'insuffisance pondérale isolée (46). L'étude de Bagan et al. met elle aussi l'accent sur la malnutrition en tant que co-variable prédictive de complications et de mortalité après pneumonectomie (49).

Enfin, certains auteurs ont mis en avant l'intérêt d'évaluer la qualité de la répartition de la masse chez les sujets normo ou surpondérés pouvant cependant cacher une malnutrition. Outre la perte de poids, les troubles de la composition corporelle, en particulier l'état de sarcopénie, défini comme une perte de masse maigre associée à une perte de force musculaire (50), sont des caractéristiques récurrentes chez les patients atteints de CBNPC, malgré un IMC normal (51).

Niveau fonctionnel et capacité à l'exercice

Une étude réalisée par questionnaire sur les habitudes d'activité physique, rapporte que 42% des individus pratiquent une activité physique dans l'année précédant le diagnostic de cancer pulmonaire (Stade I à IIIA) (52). L'analyse rétrospective de cette cohorte de plus de 500 patients rapporte que la catégorie de patients pratiquant une activité physique régulière présente une survie globale supérieure (Hazard Ratio, 0.52 [IC 95% 0.39–0.69]) (52).

Le conditionnement physique du sujet a donc un impact important sur le déroulement du projet thérapeutique du patient, tant pour l'aider à supporter le stress physiologique de la maladie que celui des thérapies. Dans le cadre de l'évaluation préopératoire, la capacité à l'exercice, qui reflète le bon fonctionnement et la synergie des systèmes cardio-vasculaire, pulmonaire, et musculaire, tient aujourd'hui une part importante. Nous proposons d'approfondir cette thématique dans la première partie de cette thèse.

2. Première partie : Evaluation du patient adressé en chirurgie thoracique oncologique

L'évaluation du patient consiste à déterminer l'opérabilité, conditionnée par le niveau de risque du geste chirurgical nécessaire pour retirer la zone anatomique envahie. Comme dans toute décision thérapeutique, la balance bénéfice/risque guidera la stratégie thérapeutique conseillée au patient par l'équipe médicale.

Comme nous l'avons précédemment décrit, le cancer pulmonaire touche une population majoritairement âgée, avec potentiellement des comorbidités cardio-vasculaires et pulmonaires liées à un tabagisme important. Environ 25% des patients nouvellement diagnostiqués d'un CBNPC de stade I ne sont pas éligibles à la chirurgie de par leurs comorbidités (53). La fonction pulmonaire est l'une des causes majeures d'inopérabilité en lien avec une prévalence importante de bronchopneumopathie chronique obstructive (BPCO) sévère à très sévère chez des patients présentant un cancer pourtant résécable (54).

Au-delà de l'aspect cardio-respiratoire, le statut fonctionnel conditionne aussi l'état physique postopératoire, et la majoration d'un handicap fonctionnel suite à la chirurgie peut être redouté. Une équipe anglaise a analysé les causes d'inéligibilité à la chirurgie dans une cohorte rétrospective de 389 patients nouvellement diagnostiqués d'un CBNPC primitif de stades I et II (55). Leurs résultats sur les 90 patients récusés placent l'état général et fonctionnel à 28% en première cause, et combiné à la fonction pulmonaire et/ou cardiaque ou autre comorbidité dans 22% des cas. Il existe peu de données sur ce point précis, mais le statut physique du candidat à la chirurgie semble donc influer au moins en partie dans presque 50% des motifs d'inéligibilité.

Des algorithmes décisionnels permettant de planifier le processus d'évaluation préopératoire ont été définis par plusieurs sociétés savantes, dont les plus diffusés dans la pratique clinique sont ceux de *l'European Respiratory Society* (ERS) associée à *l'European*

Society of Thoracic Surgery (ESTS) (56) , celui de L' *American College of Chest Physicians* (ACCP) et la *Society of Thoracic Surgeons* (STS) (57), ou encore celui de la British Thoracic Society (BTS) (58).

2.1. Evaluation des patients avant résection pulmonaire pour CBNPC

2.1.1. Evaluation cardiologique

Plus d'un tiers des patients référencés dans l'analyse de la base de données de l'ESTS en 2017 présentaient une ou plusieurs comorbidités cardiovasculaires (4).

Le *thoracic revised cardiac risk index* (ThRCRI) est un questionnaire rapide en quatre questions portant sur les antécédents rénaux, cardiaques, cérébrovasculaires et l'étendue de la résection en particulier si une pneumonectomie est considérée. Cet index permet d'estimer la nécessité d'une consultation cardiologique en première intention avant d'entrer dans le processus thérapeutique (59). Cet outil permet de stratifier le risque cardiaque par le pneumologue et/ou l'oncologue lors du diagnostic initial, ou par le chirurgien thoracique lors de sa première consultation, afin d'accélérer la prise en charge. Au cours de la validation de ce questionnaire sur une cohorte de 2.631 patients bénéficiant d'une résection pulmonaire, 2,2% de complications cardiaques majeures ont été rapportées. L'augmentation de l'incidence de ces complications était liée au score du ThRCRI, permettant de déterminer quatre classes de risque A (0 point), B (1 à 1,5 points), C (2 à 2,5 points) et D (plus de 2,5 points) dont l'incidence des complications cardiaques majeure était respectivement de 0,9%, 4,2%, 8% et 18% ($p < 0,0001$) (60). Dans ce cadre, les sociétés européennes et américaines incluent l'utilisation du ThRCRI dans leurs recommandations de 2009 et 2013 (56, 57). Bien que les modalités chirurgicales évoluent rapidement, ces classes de risque ont de nouveau été validées en 2017 sur une nouvelle cohorte de 4.625 patients (61).

Sur la base du score ThRCRI, ainsi que l'évaluation clinique associée aux antécédents cardiovasculaires du patient, il peut être nécessaire d'approfondir les examens à la recherche

d'une insuffisance cardiaque, d'une coronaropathie, ou encore d'une hypertension artérielle pulmonaire (56, 57). L'évaluation cardiaque non invasive via électrocardiogramme, échographie, ou encore scintigraphie, peut être réalisée dans un premier temps au repos puis en condition de stress, grâce à une mesure au cours ou suite à un exercice ou administration d'une stimulation médicamenteuse comme la dobutamine. En cas d'examens positifs, c'est-à-dire anormaux, des examens diagnostiques invasifs par cathétérisme permettent d'aller vérifier la qualité des artères coronaires (coronarographie), ou de mesurer les pressions au niveau de l'artère pulmonaire (cathétérisme cardiaque droit).

L'éventuelle mise en évidence de comorbidités cardiaques pourra amener à entreprendre un traitement cardiologique médical ou interventionnel préalable et/ou, selon la balance entre le bénéfice et le risque de la chirurgie, orienter vers un autre projet thérapeutique. Quelque soit le processus d'évaluation évoqué parmi les trois algorithmes précédemment cités (56-58), ils se réfèrent chacun aux recommandations de *l'American College of Cardiology* (ACC) et de *l'American Heart Association* (AHA) de 2007 quant à l'évaluation cardiovasculaire préopératoire hors chirurgie cardiologique, dont une version actualisée détaillant chaque comorbidité cardiaque a été publiée en 2014 (62).

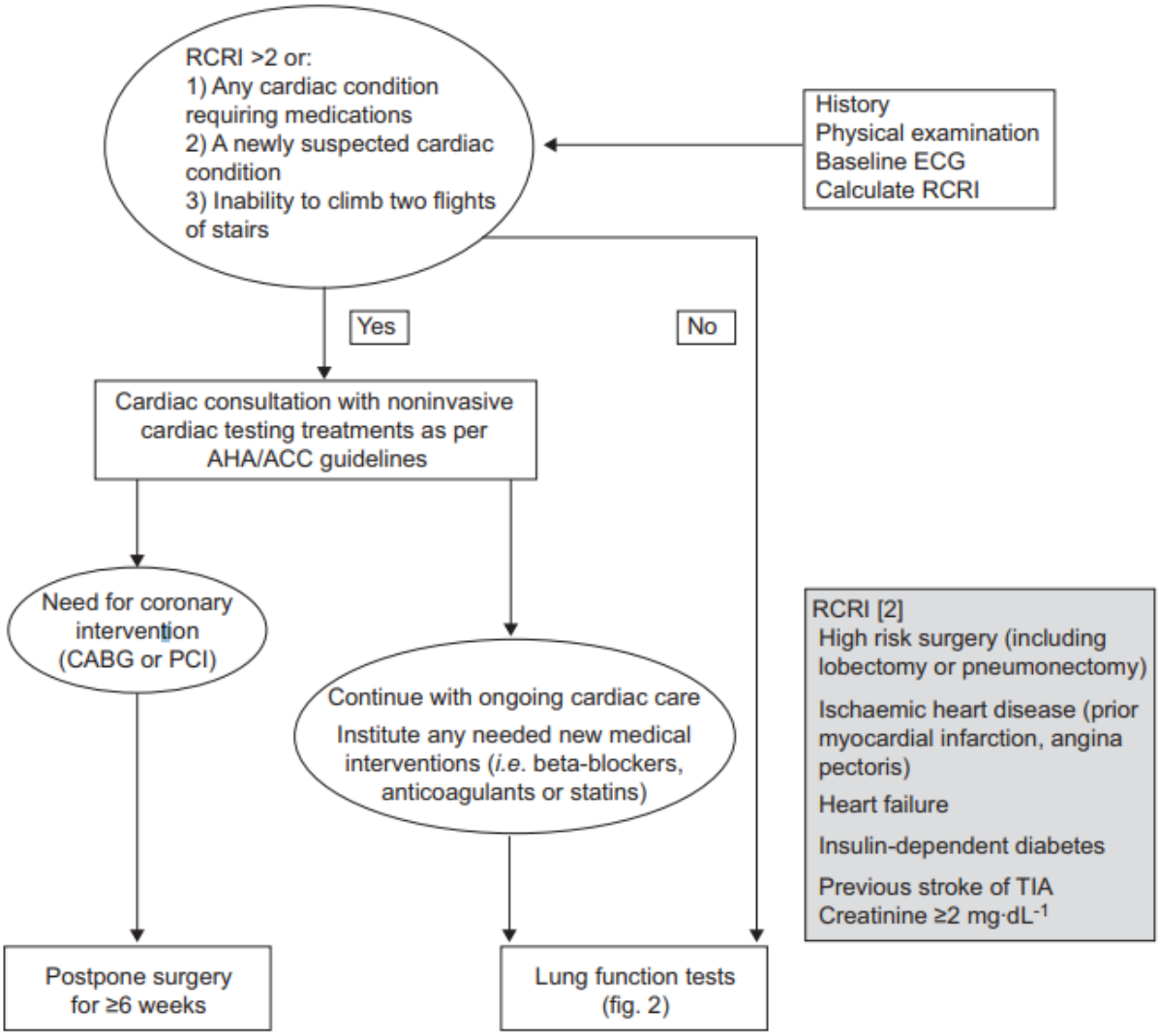


Figure 6 : Algorithme d'évaluation cardiaque avant résection pulmonaire oncologique, issu des recommandations de l'ERS/EST, Brunelli et al. 2009. RCRI : *revised cardiac risk index* ; CABG : pontage aorto-coronarien ; PCI : intervention coronarienne primaire ; TIA : accident ischémique transitoire.

2.1.2. Evaluation respiratoire

Environ 40% des patients nouvellement diagnostiqués d'un cancer pulmonaire présentent une BPCO (63). Comme nous l'avons précédemment abordé, la fonction pulmonaire est l'une des causes majeures d'inopérabilité (54). Au cours de l'évaluation

préopératoire, le patient bénéficie d'une épreuve fonctionnelle respiratoire (EFR) incluant une mesure de la mécanique respiratoire par spirométrie et pléthysmographie ainsi que la mesure du transfert alvéolo-capillaire. Les indicateurs de risque sélectionnés pour l'établissement des valeurs seuils dans les algorithmes sont développés ci-dessous.

Le volume maximal expiré en une seconde (VEMS).

La mesure des débits expiratoires est réalisée avec un embout buccal connecté à un spiromètre selon une méthode standardisée (64). Suite à une inspiration complète, le patient réalise, sous encouragement vigoureux, une expiration elle aussi complète, le volume expiré sur la première seconde correspondant au VEMS. Afin d'en vérifier la reproductibilité, objectivée avec une différence inférieure à 5%, au moins trois mesures sont généralement réalisées (64). Le ratio entre le VEMS et la capacité vitale forcée (CVF), correspondant au volume total expiré permet de caractériser la présence d'un syndrome dit obstructif. Bien que la définition rigoureuse du syndrome obstructif corresponde à une valeur du rapport VEMS/CVF inférieure au 5^{e} percentile de la valeur prédite (65), la valeur fixe de 0,7 est couramment utilisée en pratique clinique en lien avec la définition GOLD (66). Le VEMS sert ensuite à classer la sévérité du trouble obstructif (65, 66). Bien qu'il s'agisse d'une mesure de repos, le VEMS se rapproche du volume d'air que le patient peut expirer à chaque cycle à fréquence respiratoire élevée y compris en l'absence de trouble obstructif, il est donc logiquement corrélé à la ventilation maximale volontaire (67).

Ainsi, le VEMS a été décrit comme un puissant facteur de risque des complications respiratoires postopératoires. Licker et al. ont rapporté qu'un VEMS préopératoire inférieur à 60 % de la théorique était un prédicteur puissant de complications respiratoires avec un OR de 2,7 [IC 95% 1,3 à 6,6] et de mortalité à 30 jours avec un OR de 1,9 [IC 95% 1,2 à 3,9], comparativement à une valeur supérieure à 60% (68). De même, Powell et al. rapportent une augmentation progressive du risque de décès dans les 30 et les 90 jours postopératoires chez les patients présentant une diminution du VEMS, exprimé en % de la théorique, comparativement aux sujets ayant un VEMS conservé (>80% de la théorique) (34).

La diffusion (ou transfert) pulmonaire du monoxyde de carbone (DLCO ou TLCO).

La capacité de diffusion alvéolo-capillaire peut être estimée selon une méthode standardisée, grâce à la mesure de la diffusion du monoxyde de carbone (CO) contenu dans un mélange de gaz préalablement inspiré par le patient et maintenu en apnée environ 10 secondes (69). Cette mesure permet d'apprécier la qualité des échanges gazeux qui peuvent être altérés malgré des débits ventilatoires préservés sur la spirométrie.

Il s'agit d'un puissant marqueur prédictif de la morbidité postopératoire. Au sein d'une cohorte de 1008 patients analysée par Fergusson et al., la DLCO était significativement plus basse parmi les patients ayant développé une complication postopératoire, qu'il s'agisse de patients diagnostiqués BPCO (DLCO = 81,6 ± 1,2% versus 73,0 ± 2,3% ; p=0,001), ou non-BPCO (DLCO = 90,1 ± 1,0% versus 78,9 ± 3,3 ; p=0.002) (70).

Associer la DLCO à la mesure du VEMS permet d'apprécier la fonction respiratoire de manière globale et d'affiner la stratification du risque péri-opératoire. En effet, ainsi que rapporté par Brunelli et al. dans une cohorte de 508 patients ayant bénéficié d'une résection pulmonaire, le coefficient de corrélation entre le VEMS et la DLCO est limité ($r < 0,5$), et ce quel que soit le modèle statistique d'ajustement (stratification par âge, sexe, sévérité de l'obstruction). On note aussi que 43% des patients avec un VEMS conservé (> 80% prédit) avaient une DLCO altérée (< 80%) (71).

Estimation des valeurs postopératoires

Le VEMS et la DLCO peuvent être considérés dans leurs valeurs théoriques préopératoires, ou bien sous leurs valeurs résiduelles postopératoires attendues : on parle alors de « valeurs prédictives postopératoires » (PPO). Les VEMSppo et DLCOppo peuvent être estimés grâce au calcul suivant : ***(Valeur préopératoire mesurée/S) x R*** ; où « S » est défini par le nombre total de segments fonctionnels en préopératoire, et « R » par le nombre résiduel de segments fonctionnels en postopératoire.

La fonctionnalité des lobes et segments pulmonaires peut être évaluée pour optimiser le calcul des valeurs PPO (56). La mesure des zones pulmonaires fonctionnelles peut être évaluée par scintigraphie de perfusion pulmonaire (*lung perfusion scan* : LPS), ou

tomodensitométrie à émission monophotonique (*single-photon emission computed tomography - computed tomography* : SPECT-CT) développée plus récemment. Ces deux techniques ayant démontré une fiabilité équivalente dans la prédiction de la fonction pulmonaire résiduelle (72).

Ces techniques d'imageries avancées sont potentiellement nécessaires chez certains sujets dont la fonction pulmonaire PPO serait à la limite de l'opérabilité oncologique, voire indispensables dans le cadre spécifique de la chirurgie de réduction de volume pulmonaire pour emphysème. Cependant, dans le cadre de la chirurgie de résection pour CBNPC, la technique de mesure anatomique conventionnelle rapporte des valeurs PPO équivalentes chez une large part des patients que ce soit en comparaison à la LPS (73), comme au SPECT-CT (74).

Bien que le VEMSppo et la DLCOppo soient considérés comme des variables indépendantes de prédiction de morbi-mortalité postopératoire (75), leurs capacités prédictives des VEMS et DLCO réels mesurées au cours des EFR postopératoires est limitée (76). Ces valeurs sont donc plus à considérer comme des indicateurs de risques périopératoires que comme des prédicteurs réels de la fonction résiduelle postopératoire du patient.

Valeurs seuils retenues dans les algorithmes décisionnels actuels

Selon les recommandations européennes de 2009, des valeurs préopératoires conjointes du VEMS et de la DLCO ≥ 80% de la théorique, considérées dans les limites de la normale, permettent de considérer le risque opératoire comme faible (56). Si le patient ne présente pas de risque cardiaque, ce dernier peut être adressé directement vers la chirurgie. Des valeurs de VEMS et de DLCO plus basses conditionnent des examens complémentaires, notamment la mesure de la capacité à l'exercice, et le calcul de la fonction résiduelle postopératoire que nous avons décrit (56).

Les recommandations américaines de 2013 incitent pour leur part à une mesure d'emblée de la fonction résiduelle dans leur arbre décisionnel (57). Si le risque cardiaque est écarté, des valeurs conjointes du VEMSppo et de la DLCOppo > 60% de la théorique

permettent de considérer le risque opératoire comme faible. Une valeur de ces indicateurs comprise entre 30 et 60 % conditionne à minima le recours à un test physique simplifié, voire à une évaluation approfondie de la capacité à l'exercice (57).

Les recommandations britanniques se basent aussi directement sur les mesures PPO, cependant elles ne définissent pas directement un risque opératoire, mais un risque de séquelle postopératoire associée à une dyspnée invalidante (58). Une valeur conjointe du VEMSppo et de la DLCOppo ≥ 40% de la théorique est associé à un faible risque de dyspnée invalidante postopératoire. Si une des deux valeurs est inférieure à 40%, alors une évaluation à l'exercice doit être pratiquée pour affiner les capacités fonctionnelles résiduelles du patient et l'informer des risques éventuels de handicap ventilatoire séquellaire dont la dyspnée et l'oxygénodépendance (58).

2.1.3. Evaluation de la capacité à l'exercice

La mesure de la réponse cardio-respiratoire à l'exercice en tant que facteur prédictif postopératoire est décrite depuis un peu plus de vingt ans dans la littérature scientifique (77). Soumettre le patient à l'exercice permet de mesurer l'efficacité et la synergie des systèmes cardiovasculaire et pulmonaire, communément évalués indépendamment et au repos. En effet, une comorbidité cardiaque ou pulmonaire isolée peut être en partie compensée ou aggravée selon le niveau de conditionnement physique du patient. Ces mesures apportent donc en complément un reflet de la réserve physiologique disponible pour répondre au stress de la chirurgie et à la période de convalescence qui conditionne la récupération postopératoire.

L'exploration fonctionnelle à l'exercice (EFX)

L'EFX évalue la réponse physiologique liée à un niveau d'exercice calibré, et fournit une mesure objective de la capacité à l'exercice (capacité fonctionnelle ou forme physique). Elle permet également d'identifier l'étiologie de l'intolérance à l'effort lorsque la capacité

d'exercice est amoindrie. L'optimisation de la consommation en oxygène d'un individu dépend de l'ensemble des systèmes pulmonaire, cardiaque, vasculaire, et musculaire. Les fonctions de transport (convection) à l'intérieur de ces systèmes, ainsi que d'échange (diffusion ou transfert) à chaque interface entre ces derniers, va influencer la capacité de l'individu à consommer une quantité de molécules de dioxygène (O_2) nécessaire à la réalisation de l'effort engagé. Ceci reflète sa capacité à l'effort dite aérobie, principale filière énergétique mise en jeu dans les activités physiques prolongées, et qui est donc intrinsèquement liée au niveau fonctionnel de l'individu (78).

Le débit maximal (ou pic) de la consommation en oxygène ($\dot{V}O_2$max/pic) est donc devenu une donnée clé de l'évaluation préopératoire pour aider à affiner le pronostic du patient atteint de CBNPC. Brunelli et al. ont rapporté en 2014 que les patients ayant une $\dot{V}O_2$max préopératoire à moins de 60% de leur théorique attendue (testé comme valeur charnière) présentaient une survie moindre, avec un taux de survie à 5 ans de 40% vs 73% ($p<0.001$), en faveur de ceux présentant une $\dot{V}O_2$max supérieure à 60% de la théorique (79). Concernant les résultats postopératoires à court terme, Benzo et al. ont estimé dans leur méta-analyse de 2007 que les patients qui développent une complication dans les 30 jours postopératoires présentaient une valeur préopératoire de $\dot{V}O_2$max significativement plus faible, avec une différence moyenne estimée de 3,0 ml/kg/min [IC 95% 1,9 à 4,0], où 8,1 % de la théorique [IC 95% 3,3 à 12,8] (80).

Valeurs seuils retenues dans les algorithmes décisionnels actuels

Malgré quelques différences, les trois principaux arbres décisionnels s'accordent sur la recommandation d'une EFX pour les patients présentant une altération notable de leur fonction respiratoire (56-58) (Figures 7, 8 et 9). Les sociétés savantes américaines et européennes s'accordent sur les valeurs seuils de $\dot{V}O_2$max ou pic développées par les patients au cours de l'EFX pour déterminer trois niveaux de risques (56, 57). En dessous de 10 ml/kg/min de $\dot{V}O_2$pic, le risque opératoire est considéré comme élevé, il est recommandé actuellement d'envisager des stratégies chirurgicales spécifiques (intervention infra-lobaires par voie mini-invasive), ou des options thérapeutiques alternatives à la chirurgie. Au-delà de

20 ml/kg/min de $\dot{V}O_2$pic, le risque opératoire est considéré comme faible et le patient est directement éligible à une chirurgie pouvant aller jusqu'à la pneumonectomie. Entre ces deux valeurs, le risque opératoire est considéré comme modéré et le patient nécessite une surveillance rapprochée postopératoire avec potentiellement une hospitalisation en unité de soins intensifs préprogrammée (56, 57). Dans le cadre des recommandations britanniques, orientées vers l'évaluation des séquelles postopératoires, la valeur seuil ≥ 15 ml/kg/min a été retenue pour discriminer une capacité à l'exercice favorable définissant un risque modéré chez les patients avec une fonction pulmonaire altérée, au-dessous de laquelle le risque de séquelle est élevé (58).

Solution préalable ou alternative : les tests fonctionnels de terrain

Les recommandations anglosaxonnes plus récentes (57, 58), intègrent la réalisation de tests fonctionnels pour pallier à la difficulté d'accès à l'EFX, ou le réserver aux patients les plus à risque. Ainsi les deux algorithmes préconisent le test navette incrémental (« *incremental shuttel walk test* » ISWT) avec une valeur seuil de 400 mètres au-delà de laquelle la $\dot{V}O_2$pic est d'emblée rassurante sur le niveau de risque (57, 58). Le test de montée d'escaliers (« *stair climbing test* » SCT) est un second test fonctionnel simple recommandé par les sociétés américaines avec une performance favorable ≥ 22 mètres d'ascension (57). Cependant, les recommandations britanniques estiment la fiabilité des seuils insuffisante pour intégrer ce test (58). Devant le peu de centres évaluateurs, la recommandation de ces test intermédiaire a pour but de trier les patients dont la capacité à l'effort peut être considérée d'emblée comme acceptable afin de réserver l'accès à l'EFX aux patients les plus fragiles. En l'absence d'accès à l'EFX, l'ERS recommande la réalisation d'un test de monté d'escalier en retenant, tout comme les sociétés américaines, une performance ≥ 22 mètres d'ascension étant retenue comme un seuil de risque de complication postopératoire faible (56).

Les synthèses des trois recommandations auxquelles nous nous sommes référés sont disponibles en figure 7, 8 et 9.

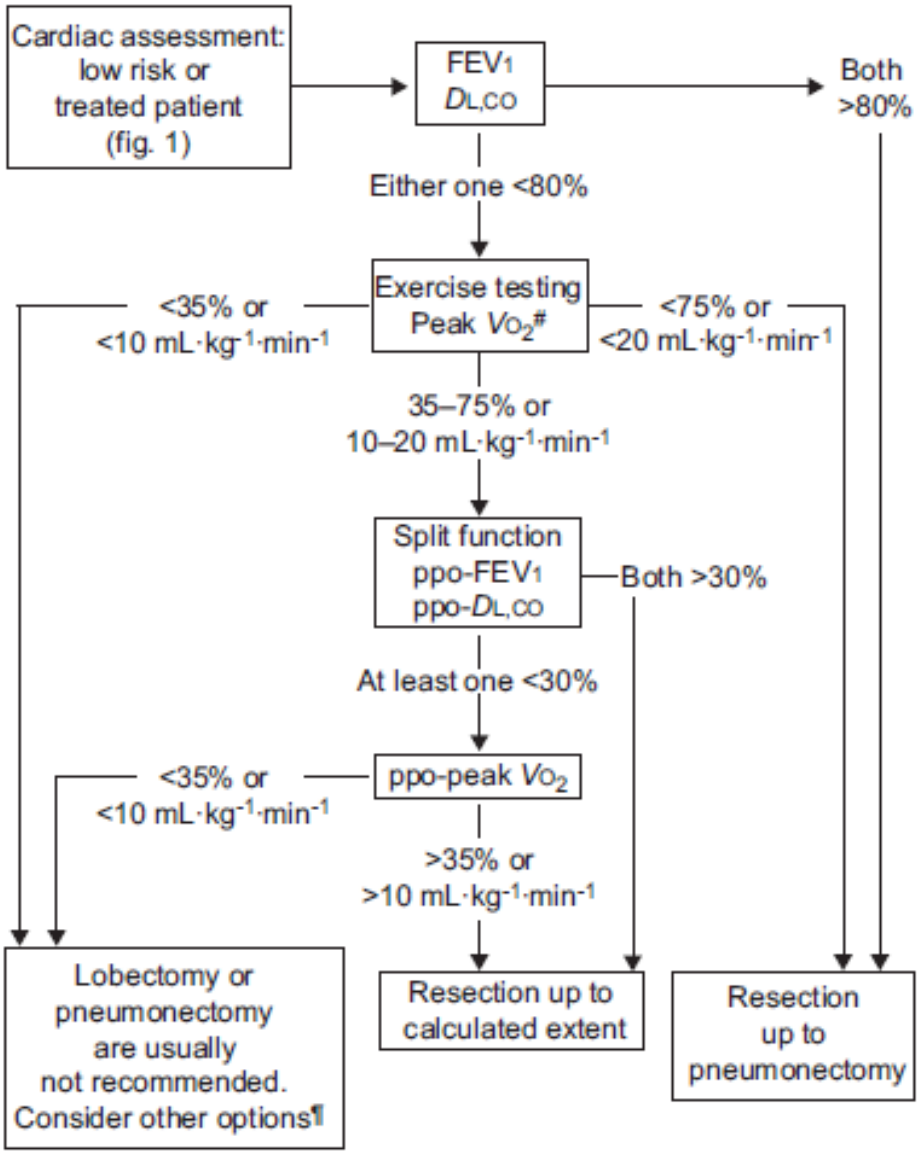


Figure 7 : processus d'évaluation préopératoire avant résection pulmonaire oncologique proposé par l'ERS/EST, d'après Brunelli et al. 2009 (56). FEV1 : volume expiratoire maximal en 1 seconde ; DLCO : capacité de diffusion du poumon pour le monoxyde de carbone ; peak $\dot{V}O_2$: valeur pique de la consommation d'oxygène ; ppo : prédictive postopératoire.

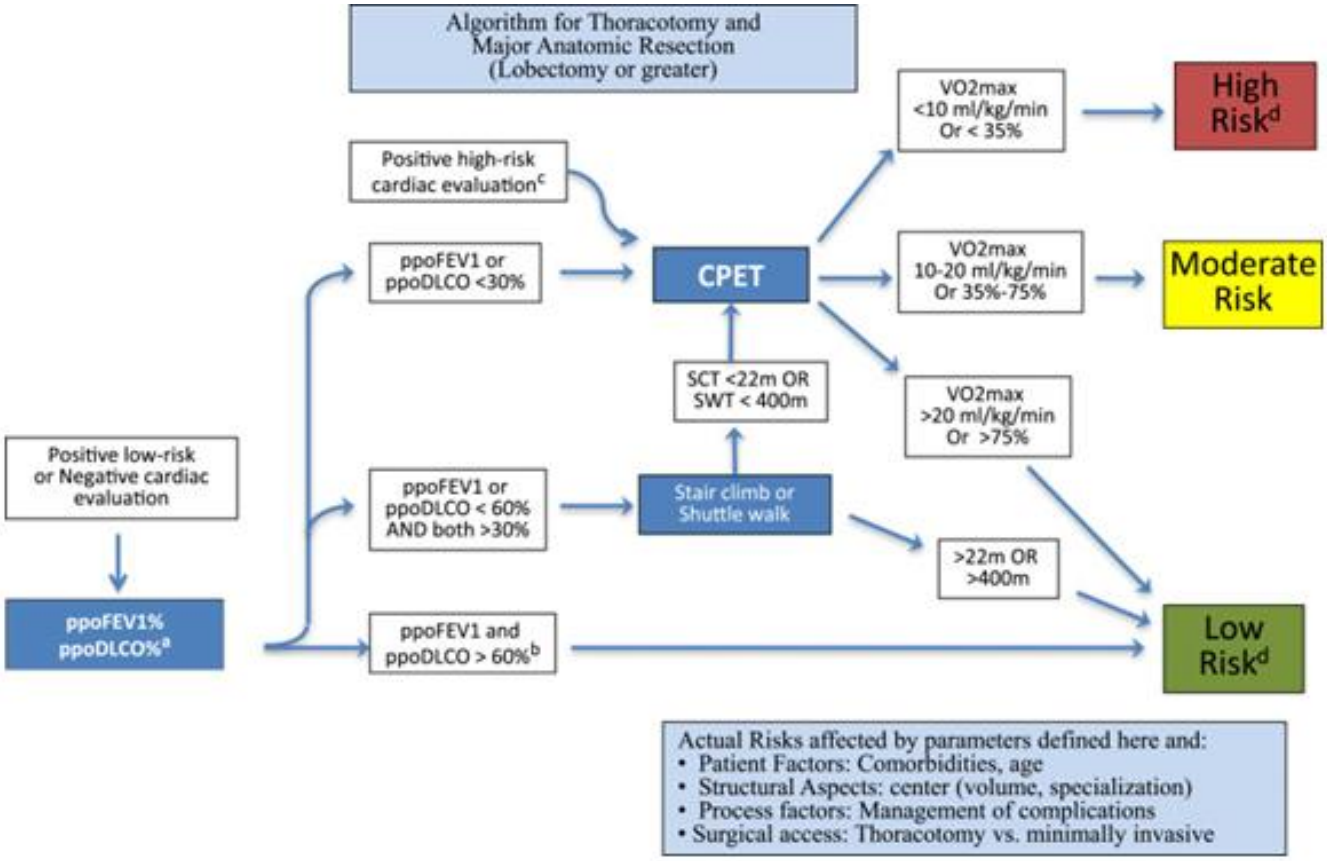
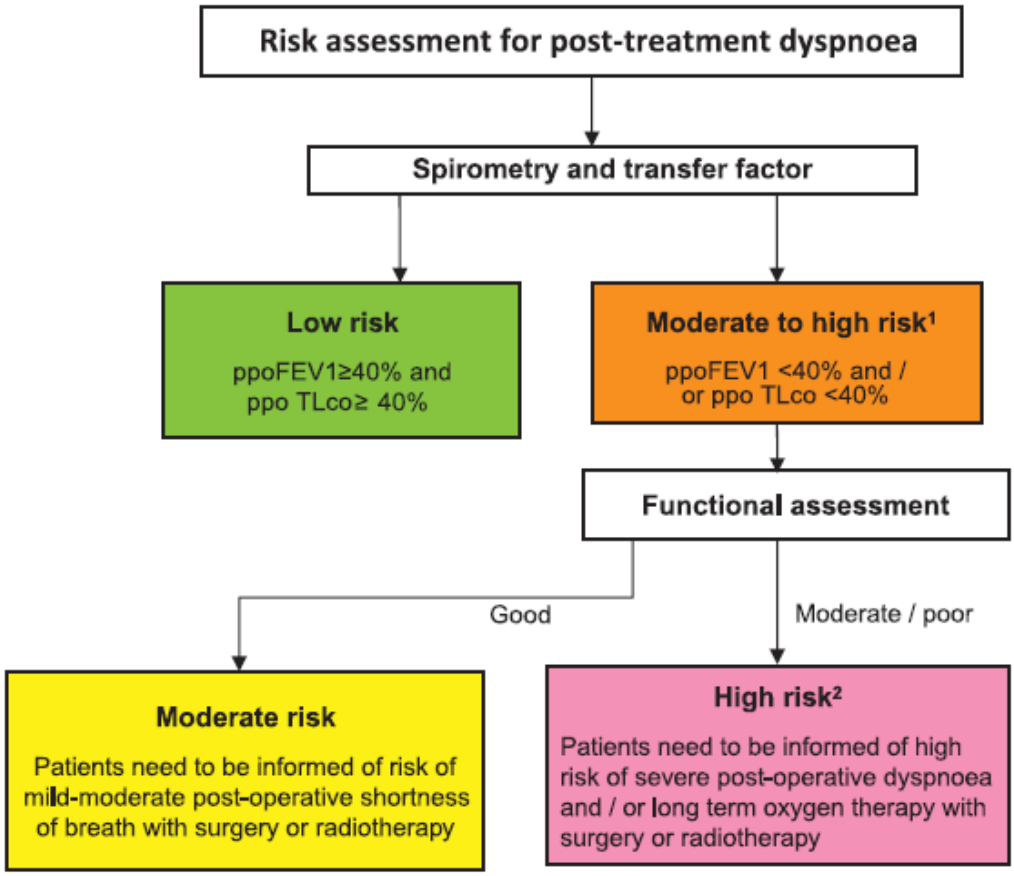


Figure 8 : processus d'évaluation préopératoire avant résection pulmonaire oncologique proposé par l'ATS/ACCP, d'après Brunelli et al. 2013 (57). FEV1 : volume expiratoire maximal en 1 seconde ; DLCO : capacité de diffusion du poumon pour le monoxyde de carbone ; CPET : épreuve fonctionnelle à l'exercice ; $\dot{V}O_2max$: consommation d'oxygène maximale ; ppo : prédictive postopératoire.



1. Consider split lung function testing for patients in this group if there is any suspicion of a ventilation perfusion mismatch (e.g. compression of a pulmonary artery or marked emphysema in the lobe with cancer) to allow more accurate estimation of post-operative values.

2. Patients in this sub-group are at high risk of ventilator dependency after surgery. It is important to ensure that criteria for LVRS have been considered as lung function can improve in appropriately selected patients.

Figure 9 : évaluation du risque de dyspnée post-chirurgie pulmonaire oncologique proposée par la BTS, d'après Lim et al. 2010 (58) ; FEV1 : volume expiratoire maximal en 1 seconde ; TLCO : capacité de diffusion du poumon pour le monoxyde de carbone ; LVRS : chirurgie de réduction du volume pulmonaire ; PPO : prédictive postopératoire.

Au regard de la sélection des patients à risque postopératoire, nous nous sommes intéressés dans le cadre de cette thèse à quelques points spécifiques liés à l'évaluation de la capacité à l'exercice :

En premier lieu, comme nous l'avons vu précédemment, la $\dot{V}O_2max$ étant un paramètre clé, sa validité chez l'ensemble des patients a retenu notre attention.

En second lieu, au regard de la difficulté matérielle et humaine pour réaliser cet examen auprès de tous les patients adressés en chirurgie, nous avons poursuivi l'évaluation de tests de terrain toujours plus accessibles pour filtrer l'identification des patients les plus à risque.

2.2. Etude n°1 : Analyse de la limitation à l'effort des patients atteints de CBNPC adressés en évaluation physiologique préopératoire et limites de la $\dot{V}O_2$pic.

2.2.1. Présentation et rationnel de l'étude

L'exploration fonctionnelle à l'exercice (EFX) est un test diagnostique global qui intègre des grandeurs cardio-respiratoires et métaboliques. L'EFX permet ainsi d'évaluer de façon qualitative et quantitative la réponse à l'exercice du patient.

L'EFX à puissance progressivement croissante, dite incrémentale, est le mode d'évaluation le plus décrit et utilisé en pratique courante (81, 82). Après une période de 3 minutes de repos, le patient réalise une période d'effort à charge constante de 3 minutes correspondant à environ 20% de sa puissance maximale aérobie (PMA) théorique avant une phase incrémentale par pallier d'environ 10% de sa PMA pour obtenir une phase incrémentale de 8 à 12 minutes, suivie d'une période de récupération. (Figure 10)

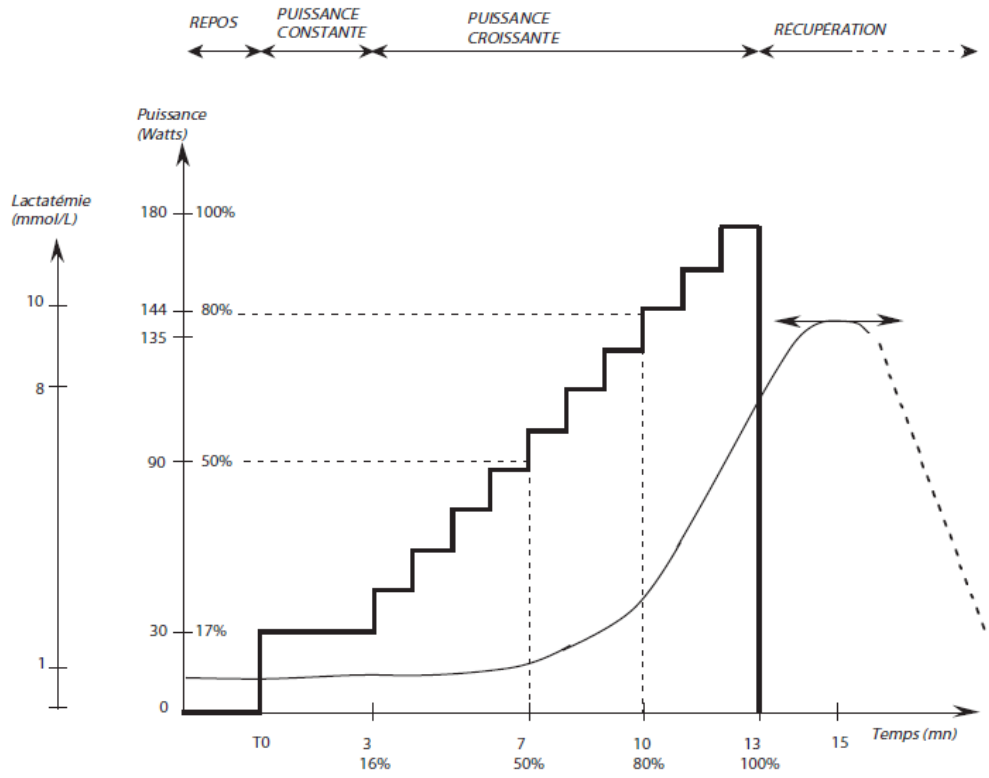


Figure 10 : schématisation du processus de l'EFX incrémentale selon Aguilaniu et al. (82)

Le débit maximal d'oxygène consommé, appelé $\dot{V}O_2max$, est lié à une limitation en un ou plusieurs points de la voie de transport de l'oxygène, de son entrée dans les voies respiratoires jusqu'au lieu de son utilisation que constitue la mitochondrie (Figure 11) (78).

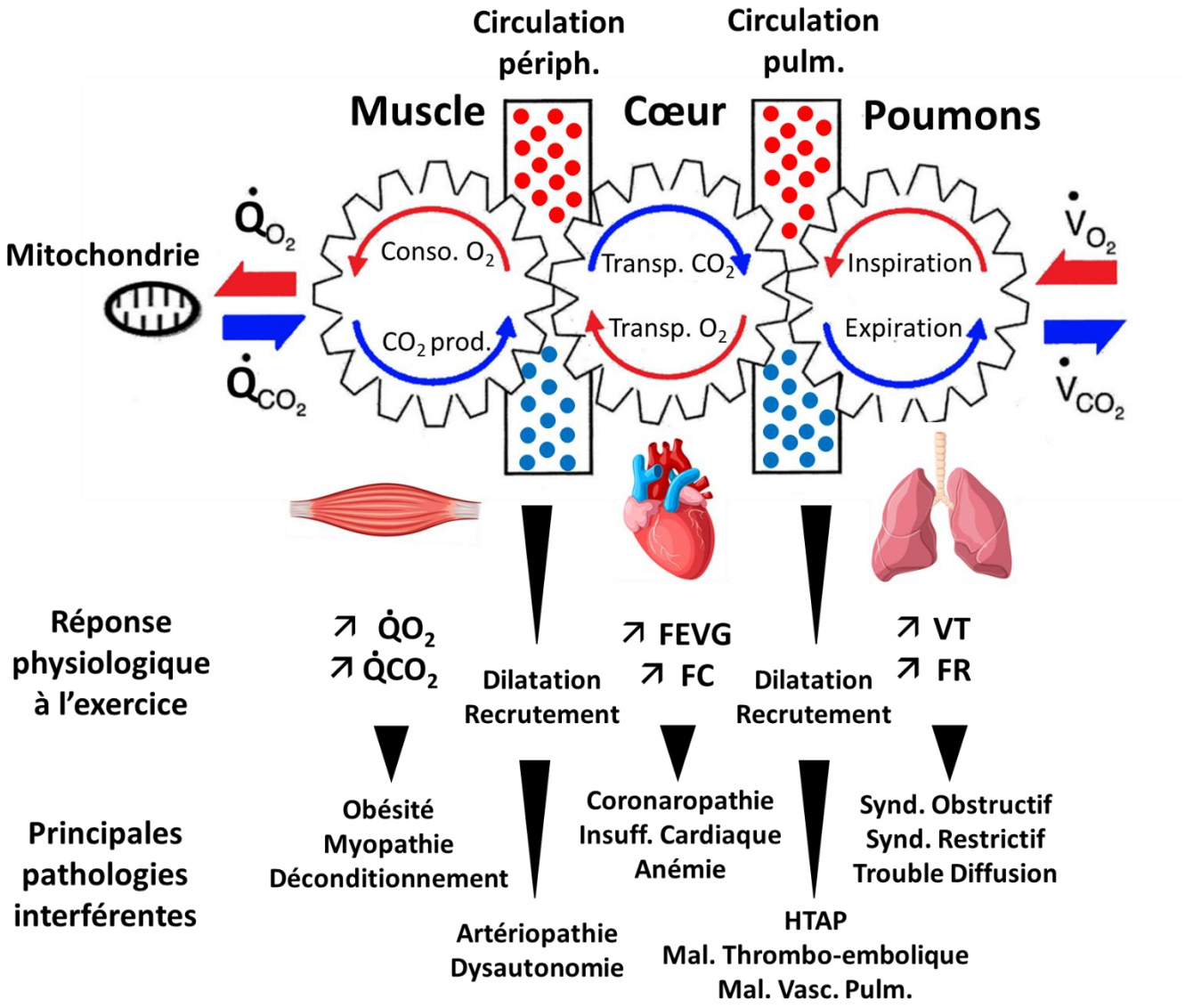


Figure 11 : modélisation de l'interaction entre les systèmes pulmonaires, cardio-vasculaires et musculaire, ainsi que leur réponse à l'exercice et les principales pathologiques interférentes pour chaque point d'étape, adapté des travaux de Wasserman et Whipp réédités par Sietsema et al. en 2020 (78). QO_2 et QCO_2 : débits d'absorption et d'extraction du dioxygène et dioxyde de carbone ; $\dot{V}O_2$ et $\dot{V}CO_2$: débit d'absorption du dioxygène et d'expiration du dioxyde de carbone mesurés dans les gaz expirés ; FEVG : fraction d'éjection du ventricule gauche ; FC : fréquence cardiaque ; VT : volume courant ; FR : fréquence respiratoire ; AOMI : artériopathie oblitérante des membres inférieurs ; HTAP : hypertension artérielle pulmonaire.

L'organisme présente nécessairement une limite physiologique relative à la capacité de chaque système à se démultiplier dans des proportions finies. Ces proportions sont inhérentes aux caractéristiques anatomophysiologiques individuelles et au niveau d'optimisation potentiellement obtenu à travers un entrainement physique. Cependant, comme présenté succinctement en figure 11, certaines conditions pathologiques peuvent créer des facteurs limitants en bridant la réponse d'un ou plusieurs systèmes.

Une détermination rigoureuse de la $\dot{V}O_2$max repose sur la mise en évidence d'un plateau de la courbe de $\dot{V}O_2$ au regard de l'augmentation de la charge de travail imposée. Une variation inférieure à 2,1 ml/kg/min ou environ 150 ml/min a été décrite dès 1955 et fréquemment reprise dans la littérature depuis (83).

Malheureusement, tous les individus, notamment les plus fragiles, ne présentent pas un plateau pendant un exercice progressif rapide. En l'absence de plateau observable au terme de l'effort, il est possible de retenir une valeur dite « pic », correspondant à la valeur maximale atteinte et qui se substitue à la $\dot{V}O_2$max. Des critères supplémentaires peuvent être utilisés pour aider à soutenir que la $\dot{V}O_2$pic obtenue représente bien un effort physiologiquement quasi maximal, on retrouve ainsi les « critères de maximalité » suivants (81, 82) :

1. Plateau de $\dot{V}O_2$ malgré deux incréments de la puissance (sur deux minutes habituellement) ;
2. Atteinte de la Fréquence cardiaque Maximale Théorique (FMT) (+/- 5%) ;
3. Atteinte de la puissance maximale théorique ;
4. Atteinte ou épuisement de la réserve ventilatoire (<15%) ;
5. Atteinte d'un pH < 7.30 et/ou d'une lactatémie de fin d'effort > 8 mmol.L-1 ;
6. Quotient respiratoire ou « *respiratory exchange ratio* » (RER) > 1,15 ;
7. Intolérance clinique du patient : dyspnée ou fatigue musculaire ≥ 9/10 sur l'échelle de Borg modifiée sur 10 points.

Il convient de noter que la pathologie ou les médications peuvent affecter certains de ces critères dans une population de patients. Ainsi, une incompétence chronotrope (réduction de la réponse cardiaque) peut être d'origine iatrogène liée à un traitement bêtabloquant, ou la limitation des débits ventilatoires peut entraver l'exercice avant la genèse d'une acidose métabolique chez certains patients obstructifs sévères... Ainsi, un effort peut être physiologiquement maximal sans que l'ensemble de ces critères ne soient atteints, et par conséquent ils doivent être interprétés avec prudence à la lumière de l'ensemble de la réponse à l'exercice.

L'exploration d'une capacité aérobie réellement poussée dans ses retranchements n'est peut-être pas une question majeure chez les sujets jeunes et en bonne santé ayant l'expérience de la pratique de l'exercice jusqu'à l'épuisement volontaire. En effet, ces derniers atteignent quasi-systématiquement ce fameux plateau de $\dot{V}O_2max$ indépendamment du protocole d'évaluation proposé (84). Cependant, chez les sujets sédentaires ou naïfs de la sensation d'un réel effort physique (tels que les populations de patients oncologiques), l'exercice peut être interrompu bien avant que leur $\dot{V}O_2max$ ne soit atteinte (85). De nombreuses raisons peuvent alors être invoquées : la motivation, des douleurs articulaires, la kinésiophobie…

A ce jour, bien que certaines équipes soulèvent la difficulté d'obtenir les durées d'évaluation d'effort préconisées ou l'obtention d'efforts maximaux, aucune étude ne rapporte le type de limitation à l'effort ainsi que le taux de patients concernés par une capacité aérobie potentiellement sous-estimée. Lorsque la $\dot{V}O_2max$ est un critère majeur pouvant guider en partie les options thérapeutiques proposées au patient, comme dans la population des patients atteints de CBNPC, cela représente une question de première importance.

Dans ce cadre nous avons souhaité analyser de manière rétrospective la population reçue en évaluation physiologique à l'effort dans le cadre d'un bilan d'opérabilité de chirurgie thoracique oncologique au cours de ces dernières années d'activité. Nous avons mis en place un screening de l'ensemble des dossiers du service de physiologie respiratoire et sportive du Centre Hospitalier Universitaire de Rouen de janvier 2014 à juillet 2019. Toutes les EFX

incrémentales des patients majeurs évalués dans le cadre d'un bilan d'opérabilité dans un contexte d'oncologie pulmonaire ont été sélectionnées puis analysées.

Les résultats de ce travail ont été rapportés sous la forme d'un poster au congrès de l'ERS 2020, ainsi que d'un article original publié dans la revue *Journal of Thoracic Disease*, dont l'impact factor était de 2.895 en 2020 (Rang D) (86).

Les annexes en ligne de l'article sont disponibles en Annexe 2.1.

Ma contribution dans ce travail a été :

- Identification de la question de recherche, rédaction du projet ;

- Démarches administratives liées à la recherche : déclaration du traitement des données selon la méthodologie de référence MR-003 auprès de la Commission Nationale Informatique et Liberté (CNIL) et demande d'avis auprès du Comité d'Ethique pour la Recherche sur Données Existantes (CERDE) du CHU de Rouen. Ce travail étant une recherche portant sur des données de santé et n'impliquant pas directement la personne humaine (hors RIPH) de par son caractère rétrospectif, il n'a pas été nécessaire de réaliser une demande d'avis auprès d'un comité de protection des personnes (CPP) ;

- Screening des dossiers informatisés et sélection des épreuves d'efforts incluables ;

- Extraction des données sous format Excel ;

- Participation à l'élaboration du plan statistique et à la réalisation des comparaisons ;

- Rédaction et soumission du poster et du manuscrit.

Original Article

Cardiopulmonary exercise testing in patients with non-small cell lung cancer: trust the $\dot{V}O_{2peak}$?

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Contributions: (I) Conception and design: FE Gravier, T Bonnevie, D Debeaumont; (II) Administrative support: JF Muir, JM Baste, A Cuvelier; (III) Provision of study materials or patients: D Debeaumont, JF Muir, JM Baste; (IV) Collection and assembly of data: FE Gravier, T Bonnevie, F Boujibar, D Debeaumont; (V) Data analysis and interpretation: FE Gravier, T Bonnevie, C Médrinal; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Maximal oxygen consumption ($\dot{V}O_{2max}$) is the most frequently used variable to determine postoperative risk in patients with non-small cell lung cancer (NSCLC), however patients frequently cannot provide the necessary maximum effort to ensure the validity of the $\dot{V}O_2$ measurements. The aim of this observational study was to assess exercise-limiting factors and the rate of achievement of the currently recommended maximality criteria in patients with NSCLC who had been routinely referred for cardiopulmonary exercise testing (CPET) to assess their postoperative risk.

Methods: Patient data, including peak exercise variables and markers used to designate the exercise test as maximal, were retrospectively analysed from 203 preoperative CPET assessments that were performed at Rouen University Hospital from January 2014 until July 2019.

Results: Ventilatory limitation was the most common physiological cause of exercise cessation. A total of 62 patients (or 30.5%) achieved either one, or no, markers of maximality. The mean duration of the incremental phase (after the 3-minute warm-up) was 5.1±2 minutes.

Conclusions: About 30% of the patients in this study did not generate maximum effort during CPET. As a result, it is likely that their $\dot{V}O_{2peak}$ was underestimated and that their post-operative risk was overestimated. It is therefore important to incorporate strategies to verify $\dot{V}O_{2peak}$ results for patients with $_{values}$ close to the risk threshold.

Keywords: Cardiopulmonary exercise testing (CPET); non-small cell lung cancer (NSCLC); lung resection; preoperative assessment; oxygen consumption

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Introduction

Lung cancer is now the most common form of cancer diagnosed and the leading cause of cancer death worldwide (1). Remarkable advances have been made in recent years regarding diagnosis and therapy (2). Lung resection is the primary curative treatment for the early stages of non-small cell lung cancer (NSCLC) (3). Resection may also be carried out in the more advanced stages, as part of a broader therapeutic strategy (4).

Cardiopulmonary exercise testing (CPET) is currently recommended by both the European Respiratory Society and the American Thoracic Society as part of the preoperative evaluation of patients with NSCLC who have respiratory comorbidities and/or functional limitations (5,6). CPET is a comprehensive physiological testing procedure that evaluates cardiovascular, respiratory and metabolic variables, as well as perceived exertion. The most commonly used method for CPET is the incremental test, which involves a gradual increase in load. The incremental test is standardized and has been shown to be reliable (7).

Maximum oxygen consumption ($\dot{V}O_{2max}$) has been described as a potent predictor of postoperative complications in patients with NSCLC (8) and thus is a key variable measured by CPET. The risk of complications is considered to be low for values above 20 mL/kg/min, moderate for values between 10 and 20 mL/kg/min and high for values below 10 mL/kg/min (5,6). The $\dot{V}O_{2max}$ results are therefore used in the surgical decision-making process and may be used to determine if preoperative rehabilitation is necessary.

However, it has recently been suggested that the use of a single incremental test for the evaluation of $\dot{V}O_{2max}$ may lead to an underestimation of $\dot{V}O_{2max}$ (9). Although the measurement of $\dot{V}O_{2max}$ is highly accurate in subjects who are experienced in performing exercise to volitional exhaustion, other populations, such as patients, inexperienced subjects or less motivated individuals, may stop exercising before their $\dot{V}O_{2max}$ is reached. For this reason, the $\dot{V}O_{2peak}$, which is the highest value reached during a clinically limited incremental CPET, is often used instead as a surrogate of their real $\dot{V}O_{2max}$. However, patients with low $\dot{V}O_{2peak}$ values may therefore be denied surgery, because of overestimation of their risk.

We hypothesized that a significant proportion of patients referred for physiological evaluation do not provide maximum effort. The aim of this study was to describe peak exercise variables and the achievement of markers used to consider CPET as maximal in patients with NSCLC. Secondly duration of the incremental ramp and load increments were analysed. The following article is presented in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" reporting checklist (10) (Available at http://dx.doi.org/10.21037/jtd-20-1528).

Methods

Patients and design

Patients with a diagnosis or suspicion of NSCLC and impaired pulmonary function or comorbidities, consecutively referred between January 2014 and July 2019, for CPET to determine surgical risks at the Rouen University Hospital respiratory and exercise physiology department, were retrospectively included. Incomplete records and tests without gas exchange analysis were not included. Only the first-ever CPET on a cycle-ergometer was considered to exclude learning effect. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional Rouen University Hospital ethics committee (n°E2019-47) and individual consent for this retrospective analysis was waived.

Data extraction

The following data were extracted: age, sex, height, weight, body mass index (BMI), pulmonary function, maximal capacity variables at the end of CPET, smoking status (never/former/current), exposure to tobacco (expressed as pack/years; 1 pack/year = one pack per day for one year), tumour histology and stage on the 7th Tumor Node Metastasis (TNM) classification (11).

Assessments

Pulmonary function

Pulmonary function tests (PFT) were carried out according to the American Thoracic Society and the European Respiratory Society guidelines using plethysmography (Masterscreen, Jaeger, Wittsburg, Germany). Values were expressed as percentages of established theoretical values for European populations (12). Predictive postoperative (PPO) forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) were calculated according to the equations recommended by the ERS/ESTS guidelines (5).

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CPET

CPET was performed on an electromagnetic ergometer (Ergoselect 200, Ergoline, Bitz, Germany) using a standardised, incremental protocol (7). Following a three-minute warm-up, load was increased by a constant amount each minute until exhaustion. The selected increment was individualized between 5 to 15 watts/min according to the predicted maximal capacity and estimated physical level during the consultation preceding the CPET). Heart rate (HR) was continuously monitored with a 12-lead electrocardiogram (Ergocard, Medisoft, Louvain Belgium). A face mask (Hans Rudolph, Inc., Kansas City, MO, USA), pneumotach and gas analyser (Ergocard, Medisoft, Louvain, Belgium) were used to measure breath-by-breath oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). Peak oxygen consumption ($\dot{V}O_{2peak}$) was the highest $\dot{V}O_2$ value during an average of three to five breath during the exercise ramp. The predicted maximal work rate (W_{max}) and $\dot{V}O_{2max}$ was derived from the equations reported by Wasserman *et al.* (13). Ventilatory threshold (VT) was manually determined as the average of the results obtained using the first break in VE, V-slope and ventilatory equivalents methods (7).

Markers used to designate the exercise test as maximal (7)

The end criteria for reaching maximal oxygen uptake were based on American Thoracic Society/American College of Chest Physicians' recommendations were:

(I) The patient achieved their predicted maximal $\dot{V}O_2$ (≥85% predicted) and/or a plateau was observed;

(II) Their predicted maximal work rate (W_{max}) was achieved;

Predicted maximal heart rate (HR) was achieved; with HR_{max} predicted = 208 – 0.7 × age (14);

Evidence of ventilatory limitation i.e. ventilatory reserve (VR) >85% with VR = $\dot{V}E_{max}$/MVV × 100 and maximal voluntary ventilation (MVV) = FEV1 × 35;

The patient overcame a respiratory exchange ratio (RER) value of 1.15;

Patient exhaustion/Borg scale rating of 9–10 on a 0 to 10 scale.

Statistical analysis

Categorial data were expressed as numbers (percentages). Continuous data were expressed as means (± standard deviation) or medians (25^{th}–75^{th} percentile) according to the data distribution. Normality was assessed using the D'Agostino & Pearson omnibus normality test. Correlation between the duration of the incremental phase of CPET and the number of markers achieved for the determination of a maximal exercise test were evaluated with a Spearman correlation test. A one-way analysis of variance with a Bonferroni multiple comparison test was used to compare the between-patient duration of the CPET incremental phase as assessed with minute-increments of 15, 10 or 5 watts. A P value <0.05 was considered statistically significant. GraphPad Prism 5.03 and R 3.6.1 software was used for all analyses.

Results

Patients

Over the data collection period, 217 patients who were either diagnosed, or being diagnosed, with NSCLC were referred for CPET to evaluate their risks for surgery although only 203 patients' CPET results were analysed for this study. *Table 1* summarizes patient characteristics, and comorbidities-medications are detailed in *Table S1*. Data from 14 patients from the original 217 were not included. Two patients were found to have cardiac disorders at the pre-CPET medical consultation which contradicted using the test. A further 10 patients did not undergo gas exchange analysis: 7 were receiving oxygen therapy, 2 could not have the analysis due to a lack of a tracheostomy-adapted equipment interfaces and 1 patient's mask had to be removed during the CPET. Finally, another 2 patients had to be excluded for reasons of consistency because their CPET was carried out on a treadmill and not cyclo-ergometer (see flow chart in *Figure 1*).

Peak exercise variables

The results showed a clear limitation of aerobic capacity in this population as demonstrated by a $\dot{V}O_{2peak}$ below 85% of the predicted $\dot{V}O_{2max}$, for 86.2% of the patients included. The whole peak exercise variables are reported in *Table 2*.

Physiological limitations

First, ventilatory limitation was the most frequent physiological cause of effort limitation. One hundred and four patients presented mechanical ventilatory limitation

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Table 1 Patient characteristics (n=203)

Variable (units)	Outcome
Female, n (%)	55 (27.1)
Age (years), median (IQR)	64 (59–69)
Height (cm), median (IQR)	170 (164–175)
Weight (kg), median (IQR)	71.0 (59.0–89.0)
BMI (kg/m^2), median (IQR)	25.5 (21.2–30.7)
FEV1 (liter), median (IQR)	1.8 (1.4–2.2)
$FEV1_{ppo}$ (liter), median (IQR)	1.4 (1.2–1.8)
FEV1 (% pred.), median (IQR)	66.0 (54.0–80.0)
$FEV1_{ppo}$ (% pred.), median (IQR)	52.0 (43.5–60.5)
FVC (liter), median (IQR)	3.0 (2.5–3.6)
FVC (% pred.), mean ± SD	87.5±17.3
FEV1/FVC, mean ± SD	61.6±12.2
FEV1/FVC <70, n (%)	144 (70.9)
RV/TLC, mean ± SD	51.4±10.6
DLCO (%Theo), median (IQR)	57.0 (47.0–70.0)
$DLCO_{ppo}$ (%Theo), median (IQR)	45.0 (39.0–56.0)
Tobacco	
Non-smoker, n (%)	4 (2.0)
Smoker, n (%)	62 (30.5)
Former, n (%)	137 (67.5)
Exposure (pack-years), median (IQR)	45.0 (34.5–60.0)
NSCLC stage, n (%)	
0	4 (2.0)
Ia	35 (17.2)
Ib	28 (13.8)
IIa	9 (4.4)
IIb	11 (5.4)
IIIa	28 (13.8)
IIIb	9 (4.4)
IV	18 (8.9)
NS	61 (30.0)
Histology, n (%)	
Large cell carcinoma	21 (10.3)
Squamous carcinoma	50 (24.6)
Adenocarcinoma	78 (38.4)
Other postoperative diagnosis	8 (3.9)
Large cell neuroendocrine carcinoma	2 (1.0)
NS	44 (21.7)

NS, not specified; BMI, body-mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; $\dot{V}O_{2peak}$, peak of oxygen consumption; W_{peak}, peak work rate; $\dot{V}E/\dot{V}CO_2$ slope, linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$); NSCLC, non-small cell lung cancer.

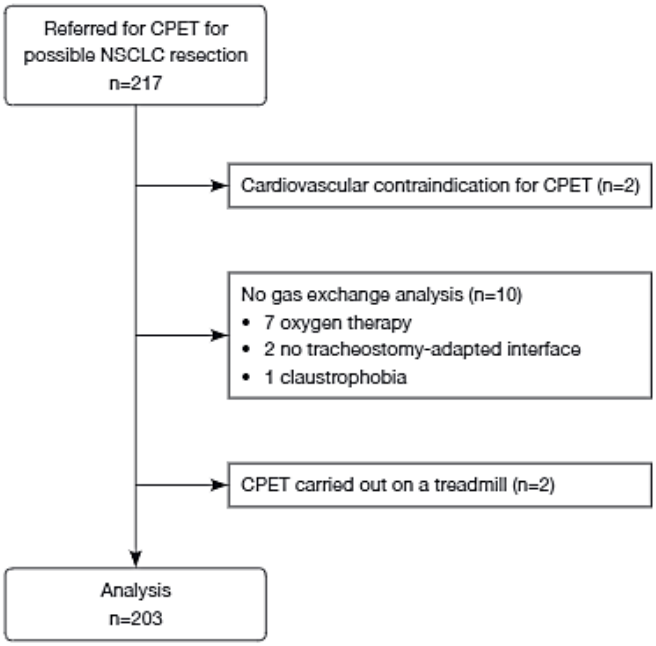

Figure 1 Flow chart of patients included in the study from January 2014 to July 2019. CPET, cardiopulmonary exercise testing; NSCLC, non-small cell lung cancer.

limitations with exhaustion of their VR. In addition, 37 patients presented gas-exchange impairment with desaturation ≥4% during the CPET. Most of them (34/37) were associated with an exhaustion of the VR, or deficit of diffusion observed on the PFT (3/37).

This was followed by peripheral muscle deconditioning, diagnosed on the basis of the conjunction of different factors such as an early ventilatory threshold, peripheral fatigue, poor performance in terms of power reached,

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Table 2 CPET outcomes (n=203)

Variable (units)	Outcome
$\dot{V}O_{2peak}$ (mL/kg/min), median (IQR)	14.6 (12.2–17.0)
$\dot{V}O_{2peak}$ (% pred.), median (IQR)	63.0 (54.0–74.0)
$\dot{V}O_{2VT}/\dot{V}O_{2max}$ (n=191), median (IQR)	46.0 (39.0–53.0)
W_{peak} (Watts), median (IQR)	80.0 (60.0–100.0)
W_{peak} (%pred.), median (IQR)	66.0 (52.0–79.0)
W_{peak}/kg, median (IQR)	1.1 (0.9–1.4)
$\dot{V}E/\dot{V}CO_2$ slope, median (IQR)	36.0 (31.6–41.0)
HR_{max} (% pred.), median (IQR)	81.0 (72.0–90.0)
$\dot{V}E_{max}$ (% MVV pred.), median (IQR)	85.0 (70.0–100.0)
Dyspnoea (Borg scale/10) (n=148), median (IQR)	5.0 (3.0–6.0)
Leg fatigue (Borg scale/10) (n=148), median (IQR)	4.0 (2.8–7.0)

$\dot{V}O_{2peak}$, peak of oxygen consumption; $\dot{V}O_{2VT}/\dot{V}O_{2max}$, oxygen consumption at ventilatory threshold on maximal predicted oxygen consumption; W_{peak}, peak work rate; $\dot{V}E/\dot{V}CO_2$ slope, linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO2$); HR_{max}, maximal heart rate; MVV, maximal voluntary ventilation.

Table 3 Markers of maximality (n=203)

Variable	n (%)
Markers used for the determination of a "maximal" exercise test (7)	
Predicted $\dot{V}O_{2peak}$ achieved (≥85% $\dot{V}O_{2max}$ pred.) and/or plateau observed	66 (32.5)
Predicted W_{max} achieved (≥90% pred.)	22 (10.8)
Predicted HR_{max} achieved (≥90% pred.)	51 (25.1)
VR >85%	104 (51.2)
RER >1.15	160 (78.8)
Borg score ≥9/10 (n=148)	17 (11.4)
Number of markers achieved, n (%)	
N=0	18 (8.9)
N=1	61 (30.0)
N=2	72 (35.5)
N≥3	52 (25.6)
Other markers, n (%)	
O_2 pulse at $\dot{V}O_{2peak}$ >80% pred.	102 (50.2)
pH <7.30 or lactatemia >8 mmol/L (n=85)	12/85 (14.1)
Decrease in SpO_2 ≥4%	37 (18.2)

Data are expressed as n (%). $\dot{V}O_{2peak}$, peak of oxygen consumption; W_{max}, maximal work rate; HR_{max}, maximal heart rate; VR, ventilatory reserve; RER, respiratory exchange ratio; O_2 pulse, $\dot{V}O_2/HR$.

muscle wasting, sedentary behaviour. Ventilatory threshold (VT) could not be measured for 12 patients and the ratio $\dot{V}O_2$ at VT/$\dot{V}O_{2max}$ predicted was below 40% for 49 patients. This reflects a limitation in O_2 supply to the tissues, compatible in part with deconditioning. Moreover, the median power/body-weight ratio was 1.1 watts/kilogram at peak exercise, which reflects poor performance in terms of power developed. Muscle deconditioning was rarely an isolated cause of limitation because it stemmed from health history.

Finally, cardiovascular function contributed to exercise limitation. Forty-two patients had peripheral arterial disease and 25 diagnosed heart disease (10 overlaps), which impacted their exercise performance. Although 35 patients were on beta-blocker, only 9 cases of chronotropic incompetence were highlighted as the main limiting factor. Fifteen patients presented an alteration of the ECG (sus/sub-ST, repolarization disorder, ventricular extrasystole) of which 7 required the early cessation of the effort, the others having occurred at near-maximum effort. Two cases of arterial hypertension (≥250/120 mmHg) necessitated to stop the CPET, one prematurely, and one at near-maximum effort. A pathological kinetics of the O_2 pulse were noted in 4 patients without diagnosed cardiac comorbidity, suggesting an unknown onset heart failure.

Maximality criteria

Using the strict marker of achievement of a $\dot{V}O_2$ plateau to designate maximality, only 49 patients (24%) achieved their "real" $\dot{V}O_{2max}$, the values reached by the other patients are therefore considered as $\dot{V}O_{2peak}$.

The analysis of maximality markers showed that tests were not performed to a real sustained effort for all patients. The median number of markers achieved for the determination of a maximal exercise test was 2 (range, 1–3) (*Table 3*, *Figure 2*). Although the RER was >1.15 in 78.8% of patients the other markers were less frequently achieved, in particular only around one-third of patients achieved a $\dot{V}O_{2peak}$ >84% of the $\dot{V}O_{2max}$ predicted and/or a $\dot{V}O_2$ plateau, and only around one-quarter achieved the predicted HR_{max}.

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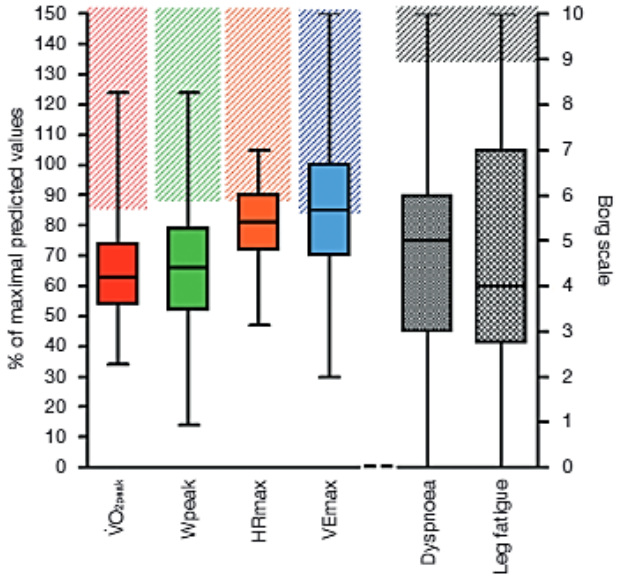

Figure 2 Percentage of maximal predicted values expressed as medians (25th–75th percentile) and ranges for peak oxygen consumption ($\dot{V}O_{2peak}$) in red, peak work rate (W_{peak}) in green, maximal heart rate (HR_{max}) in orange, maximal ventilation minute (VE_{max}) in blue, dyspnoea and leg fatigue in grey. Stripes indicate achievement of maximality for the criterion (7).

Few patients achieved a high Borg scale rating for dyspnoea.

A total of 79 patients presented only one or no maximality criterion. Taking into account the 9 cases of chronotropic incompetence as well as the 8 cases of premature cessation for an adverse cardiovascular event, then 62 patients (or 30.5%) were likely to have provided poor effort.

Incremental protocols used

The incremental protocols were set at 5, 10 or 15 watts per minute, according to the predicted maximal capacity and estimated physical level to theoretically last 8 to 12 minutes. The median load during the three minutes warm-up was 20 [10–30] watts, and the median load increment was 10 [10–15] watts per minute. The mean duration of the incremental phase (after warm-up) was 5.1±2.0 minutes. A significant, positive correlation was found between the duration of the incremental phase of the CPET and the number of maximality markers achieved: r=0.41, P<0.0001.

We compared the results obtained by patients who benefited from the three different load increments proposed. The mean duration of the incremental phase was significantly different between the three incremental load protocols (4.3±1.7, 5.7±2.0, and 5.1±2.6 min for 15, 10 and 5 W/min respectively, overall P<0.0001), and was mainly driven by a significant difference between 15 and 10 W/min increments (P<0.001) (*Table 4*).

Discussion

Limitation of exercise capacity

As expected, ventilatory factors were the main limitation of exercise capacity in this cohort of patients with NSCLC. More than 50% of the patients used over 85% of their VR, and 18% presented gas-exchange impairment. However, the definition of VR is debatable as some authors consider that patients begin to use their VR when ventilation exceeds 80% or even 70% of the predicted MVV (15,16). Using these cut-offs, the rate of patients finishing the CPET with a reduced ventilatory reserve in the present study would be (125/203) 62 % or (151/203) 74% respectively. It is important to note that many formulae have been proposed for the estimation of MVV based on the FEV1, although its validity is debatable, this indirect measure is widely used in clinical practice (17). Paradoxically, only a very small proportion of the patients achieved almost maximal or maximal rating dyspnoea. The median Borg rating for dyspnoea was 5, which is defined as "severe" but is far from a score of 9 or 10, which are defined as "almost maximal or maximal". This is likely due to the difficulty of rating dyspnoea or the perception of effort on a scale by patients who are not used to physical activity. However these results are similar to peak exercise dyspnoea ratings reported in other cohort of patients with chronic obstructive pulmonary disease (18). This preponderant ventilation limitation could explain a very early cessation of effort without maximum cardiological or muscular solicitation.

The second limitation of exercise capacity demonstrated by CPET was the effect of deconditioning. Poor patient performance was associated with a rapidly reached inability to continue pedalling and an abnormally early ventilatory threshold. This was unsurprising given the sedentary lifestyle reported by the vast majority of patients during the pre-CPET consultation, and is consistent with other reports in the literature (19).

Cardiovascular comorbidities were the third limitation of exercise capacity, as described in the results. To go further, we noted that few patients achieved their predicted

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Table 4 Comparison of CPET between patients assessed with an increment per minute of 15, 10 or 5 watts

Variable (units)	15 W/min (n=80)	10 W/min (n=112)	5 W/min (n=11)	P
Women, n (%)	17 (21.2)	30 (26.8)	8 (72.7)	0.06
Age (years)	65 (59–69)	64 (59–69)	64.0 (59–71)	0.99
Height (cm)	171 (165–176)	169 (164–174)	161 (154–170)	0.07
Weight (kg)	76 (63–92)	70 (59–87)	66 (54–75)	0.15
BMI (kg/m^2)	26.2 (22.5–31.1)	24.4 (21.1–29.7)	23.4 (19.7–30.4)	0.44
FEV1 (%)	68.0 (56.3–83.5)	64.0 (53.0–78.0)	63.0 (37.0–75.0)	0.05
FVC (%)	88.0 (80.0–102.0)	84.0 (72–97.5)†	82.0 (72.8–99.8)	0.04*
FEV1/FVC	63.0 (53.7–71.5)	61.7 (53.2–71.6)	50.9 (41.7–60.0)	0.06
RV/TLC	47.6±10.7	53.6±9.3†	58.3±12.7‡	0.0002*
DLCO (%)	59 (48–72)	58 (48–67.5)	46 (28–50)‡,§	0.0015*
$\dot{V}O_{2peak}$ (mL/kg/min)	14.9 (12.2–17.8)	14.5 (12.2–16.8)	11.9 (8.1–15.6)‡	0.03*
$\dot{V}O_{2peak}$ (%)	64 (55.5–74.5)	62.0 (54.0–78.8)	58.0 (42.0–62.0)	0.13
W_{peak} (Watts)	90 (75.0–116.3)	70.0 (60.0–90.0)†	40.0 (30.0–45.0)‡,§	<0.0001*
W_{peak} (%)	72.1±19.3	63.5±18.5†	39.6±16.8‡,§	<0.0001*
Incremental phase (min)	4.3±1.7	5.7±2.0†	5.1±2.6	<0.0001*

Values expressed as medians (IQR) or means ± SD according to distribution; Chi-square test was used for contingency comparison; Kruskal Wallis test or a One-way analysis of variance with Dunn's or Bonferroni post-hoc test respectively were used according to distribution. *Overall P<0.05; †<0.05 between 15 and 10 W/min; ‡<0.05 between 15 and 5 W/min; §<0.05 between 10 and 5 W/min. CPET, cardiopulmonary exercise testing; BMI, body-mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; $\dot{V}O_{2peak}$, peak of oxygen consumption; W_{peak}, peak work rate.

HR_{max}. This can simply means poor effort, but patients with lung hyperinflation have been shown to have poor cardiovascular responses during symptom-limited cycling exercise (20). It is also noteworthy that some patients in the present study were being treated with beta-blockers and experienced bradycardia during the exercise test. The O_2-pulse at the $\dot{V}O_{2peak}$ was less than 80% of the predicted value in almost half of the patients. A low O_2-pulse suggests a lack of skeletal muscle oxygen extraction; this can indicate either peripheral deconditioning or, in some patients with cardiovascular comorbidities, a limitation of stroke volume (7).

Risk of under-estimation of cardio-respiratory fitness

As mentioned in the introduction, there may be various physical or mental reasons why patients are either unable or unwilling to achieve maximal effort e.g., osteoarthritis, arteriopathy, anxiety, kinesiophobia or a lack of motivation. A previous study reported that individuals with NSCLC engage in less physical activity, are weaker and more depressed than healthy individuals (21). As a result of the difficulties in measuring maximal effort in these patients, several objective physiological criteria are measured along with $\dot{V}O_{2peak}$ (as a surrogate for $\dot{V}O_{2max}$) to determine the level of patient effort generated (7).

Plateauing of $\dot{V}O_2$ at the end of the CPET is considered as an unambiguous sign of maximum oxygen uptake (9). This occurred in 49 (24%) in the present study. It has also been suggested that an RER value >1.15 is associated with a maximal effort. Unfortunately, there is currently no single agreed value that defines what RER value constitutes maximal effort (7,9). Therefore, in order to increase the certainty that maximal effort had been achieved, we considered that a CPET result could only be considered as indicative of maximal effort if at least two markers had been achieved. Based on this definition and taking into account adverse events, about 30% of the patients in this study did

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not achieve a physiologically maximal CPET.

Another factor potentially related to the underestimation of $\dot{V}O_{2max}$ was the duration of the test. The mean duration of the incremental phase in the present cohort was 5.1± 2.0 minutes. Moreover, as expected there was a positive correlation between the duration of the incremental exercise and the number of maximality criteria achieved. According to a previous study, cycle ergometer incremental exercise of less than 7 minutes can lead to an underestimation of cardiorespiratory fitness measured by $\dot{V}O_{2max}$ (22).

As a result, it is reasonable to suggest that the $\dot{V}O_{2peak}$ results were lower than the value of the $\dot{V}O_{2max}$. Care must therefore be taken in the use of $\dot{V}O_{2peak}$ to determine the risk of post-operative complications in patients with NSCLC, particularly if the $\dot{V}O_{2peak}$ values are close to the thresholds of risk determined by the decisional algorithms (5,6).

Strategies to reduce the risk of underestimation

Low-intensity incremental protocols to increase the duration of the CPET

As indicated above, strategies that could be used to reduce the risk of underestimation of $\dot{V}O_{2max}$ include increasing the duration of the incremental exercise. Current guidelines suggest that CPET should last for between 8 and 12 minutes (7). This guidance, however, is based on a 1983 study of 5 healthy subjects (23). More recent data has suggested that a minimum of 7 minutes and a maximum of 26 minutes of incremental effort on a cyclo-ergometer is more appropriate in order for patients to achieve maximal effort (22). We would therefore suggest that smaller load increments should be used to increase the duration of the exercise. In clinical terms, increments of 5 to 10 watts per minute would seem to be sufficient to obtain a suitable ramp for the vast majority of patients with NSCLC referred for CPET to determine their risk-benefit ratio ahead of surgery. This suggestion is supported by secondary analysis from this study which indicated that patients who underwent CPET with increments of 15 watts, rather than 10 watts, per minute did reach higher levels of $\dot{V}O_{2peak}$ despite the higher work rate (*Table 4*). We believe that this was due to the significantly shorter duration of the incremental phase: 4.3±1.7 minutes for the 15-watt/min group, versus 5.7± 2.0 minutes for the 10-watt/min group. This duration may not have allowed adequate physiological adaptation in this cohort of older individuals with respiratory comorbidities and reduced $\dot{V}O_2$ kinetics (24,25). Furthermore, less than 10% of patients exceeded a power of 120 watts and so the risk of prolonging the effort disproportionately with increments of 5 to 10 watts is very low, since the maximal expected power for a CPET with an increment of 15 watts per minute is about 150 watts. In clinical practice it is likely that patients who are able to reach this level of power would already have been identified as having a low postoperative risk during pre-CPET preliminary tests such as stair climbing or the shuttle test and so would not require CPET (6).

Validation $\dot{V}O_{2peak}$ through a second evaluation

Jones *et al.* recently have questioned the reliability of the measurement of $\dot{V}O_{2peak}$ and suggested that a more appropriate strategy would be to validate the patient's $\dot{V}O_{2max}$ through the addition of a second supra-maximal constant-load test (9). This method is physiologically robust and has already been validated for several pathologies (26). However, it is difficult to apply in current clinical practice, mostly because it doubles the evaluation time due to the necessary rest period between the two tests (27,28). The use of this second supra-maximal constant-load test may further reduce the number of patients accessing to CPET, since access is already limited in many hospitals due to increasing numbers of patients being referred for testing.

Incorporation of submaximal postoperative predictive factors

The low reliability of the $\dot{V}O_{2peak}$ as an evaluation of outcomes following pulmonary resection surgery has led some teams to evaluate other physiological indicators that are considered to be less affected by volition and duration of the exercise. Kasikcioglu *et al.* evaluated the oxygen uptake efficiency slope (OUES) during incremental CPET, calculated from the ratio of the $\dot{V}O_{2peak}$ value and logarithmic equivalent of the ventilatory volume ($\dot{V}E$). They found almost identical predictive values for the risk of post-operative complications for the OUES and the $\dot{V}O_{2peak}$ (29). More recently Yakal *et al.*, showed that the OUES is significantly correlated with $\dot{V}O_{2peak}$ and does not require the performance of maximal exercise (30). In parallel Torchio *et al.* and Brunelli *et al.* assessed ventilatory efficiency in patients with NSCLC who were eligible for surgery. They showed that the $\dot{V}E/\dot{V}CO_2$ slope, which is the linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$), was not only an accurate and independent predictive factor of mortality, but that it was also a more reliable predictor of postoperative complications than

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$\dot{V}O_{2peak}$ (31-33). The $\dot{V}E/\dot{V}CO_2$ slope may represent a useful complementary indicator to stratify the postoperative complication risk independent of the $\dot{V}O_{2peak}$.

Limitations

This study has limitations that were inherent in its retrospective design. The first is that there may have been selection bias and due to the long period of data collection, some data may have been lost. Secondly, the comparison of data between patients who carried out different incremental protocols should be considered with caution because the study was not powered for these outcomes. Even if all tests were undertaken with the same team and the same equipment throughout in accordance with guidelines, which strengthens internal validity, the monocentric design limit the generalisability (external validity) of the study results. Despite these limitations, this work provides a concrete insight into the limitations of $\dot{V}O_{2peak}$ in patients with NSCLC evaluated outside clinical trials. The difficulty in achieving the recommended duration for incremental CPET (or simply a sustained effort) has been reported by several teams, but, until now, there had been no objective report of the number of patients with NSCLC who failed to reach these maximum criteria.

Finally, as suggested by some authors "clinical $\dot{V}O_{2peak}$ is part of the deal" (27). It is possible that although the raw value of $\dot{V}O_2$ was underestimated, this peak value includes the painful or motivational component, and remains predictive of perioperative complications. Unmotivated or painful patients, even at CPET assessment, may have an impact on their post-operative recovery and outcomes. To date, this question remains unanswered and future works are needed to further refine our assessment methods in an increasingly large and severe population of candidates for pulmonary surgery.

Conclusions

This study showed that CPET prior to NSCLC surgery was mainly limited by ventilatory factors. About 30% of the patients in the present study did not achieve maximal effort during their CPET, therefore, the values of $\dot{V}O_{2peak}$ possibly underestimated their cardio-respiratory fitness, leading to the potential overestimation of the risk of post-surgical complications. To overcome this issue, we suggest several strategies: (I) low-intensity incremental protocols (5 to 10 watts per minute) to increase the duration of the CPET, (II) validation through a second evaluation, or (III) the incorporation of submaximal postoperative predictive factors. These strategies must however be validated in order to help to ensure that appropriate surgical and therapeutic decisions are made for patients with NSCLC.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional Rouen University Hospital ethics committee (n°E2019-47) and individual consent for this retrospective analysis was waived.

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2.2.2. Discussion de l'étude n°1

Résultats principaux

Tout d'abord, la limitation ventilatoire a été objectivement identifiée comme principal facteur limitant chez les patients atteints de CBNPC adressés en évaluation physiologique préopératoire. Comme reporté dans le Tableau 2 de l'article ci-dessus, la ventilation minute au maximum de l'exercice ($\dot{V}E_{max}$) atteignait une médiane (25^{e}-75^{e} percentile) de 85 % (70-100) de la valeur individuelle attendue sur la base du VEMS. En conséquence, la limitation ventilatoire concernait 50 à 75% des individus évalués, selon la définition retenue pour qualifier la limitation ventilatoire (82, 87, 88). Cette observation quant à l'origine ventilatoire de la limitation à l'exercice était attendue. En effet, l'évaluation physiologique étant initialement motivée par une altération de la fonction pulmonaire (56-58).

De plus, nous avons à présent une confirmation objective du ressenti clinique soulevé par les cliniciens quant à la difficulté d'obtenir des durées d'effort incrémental adéquates, et en conséquence un taux non négligeable d'environ 30% d'EFX sous-maximales. Concernant l'évolution de la sévérité des patients adressés en EFX avant la chirurgie thoracique, la question de la méthode d'évaluation et de ses limites chez certains d'entre eux nous semble d'actualité. Cette étude reste limitée quant à son niveau de preuve en raison de son aspect rétrospectif et de l'absence de suivi qui aurait permis d'évaluer les impacts sur les données postopératoires.

Au-delà des points déjà abordés dans la discussion de l'article publié, certains éléments peuvent encore soulever des interrogations.

La limite de la $\dot{V}O_2pic$ est-elle déjà intégrée dans les algorithmes actuels ?

Nous avons identifié de manière objective que la capacité aérobie réelle est potentiellement sous-estimée chez 30% des patients adressés en évaluation physiologique préopératoire. Cependant, bien que certains patients aient développé une valeur de $\dot{V}O_2pic$

dont la validité est douteuse, il est possible que les patients inclus dans les études à l'origine de la détermination des seuils de risques actuellement admis aient présenté les mêmes difficultés à fournir des efforts assez soutenus pour les considérer comme maximaux ou assimilables. Ceci a fait notamment l'objet du questionnement des relecteurs lors de la soumission du manuscrit de l'étude.

Comme suggéré, nous avons donc vérifié les critères d'évaluation de la capacité aérobie dans les études compilées dans la méta-analyse de Benzo et al. publiée en 2007 (80), dont la synthèse est présentée dans l'Annexe 2.2. Sur les 14 études incluses (77, 89-101) dans cette méta-analyse, six d'entre elles se réfèrent uniquement au concept de $\dot{V}O_2$max (77, 90, 91, 94, 95, 99). Parmi celles-ci, une seule d'entre elles (90) mentionne clairement le maximum atteint chez la grande majorité des patients. Quatre mentionnent l'utilisation de la $\dot{V}O_2$max, mais dont la définition n'est pas suffisamment claire, laissant penser à une utilisation mixte avec la $\dot{V}O_2$pic (97, 98, 100, 101). Trois expriment clairement l'utilisation de $\dot{V}O_2$pic dans leur protocole (89, 93, 96). Enfin, concernant la dernière étude aucune valeur réelle de $\dot{V}O_2$ n'a été mesurée, puisque les valeurs obtenues sont des estimations dérivées de la performance au test de montée d'escalier (92). Au total, les méthodologies de validation des mesures au pic de l'effort ne sont presque jamais clairement rapportées et l'ambiguïté entre les valeurs prédictives de $\dot{V}O_2$pic ou $\dot{V}O_2$max reste présente.

Quelle valeur pronostique donner à un effort sous-maximal ?

Grâce aux progrès des techniques chirurgicales et de l'anesthésie, une catégorie de patients polypathologiques sévères est aujourd'hui potentiellement éligible sous réserve d'une évaluation physiologique favorable. Ceci se confirme au travers du recueil de comorbidités et de médications dans le tableau supplémentaire joint à notre étude (Annexe 2.1.), avec une médiane de 3 (2 – 4) antécédents chroniques associée au CBNPC, et 4 (2 – 6) traitements quotidiens par patient.

La capacité à générer un effort intense ou maximal sur le plan physiologique peut être fluctuante parmi cette population, comme nous l'avons rapporté. Dans le cadre du suivi de l'insuffisance cardiaque, une valeur de $\dot{V}O_2$pic basse est jugée comme d'autant plus péjorative

si elle est associée à des marqueurs de maximalité par rapport à un patient qui aurait fourni un moindre effort objectif (102). Concernant les patients avant chirurgie pour CBNPC, la valeur pronostique à donner à cette sous-évaluation peut être double. D'une part, il pourrait être considéré sur ce principe que dans la situation où le patient est sous-évalué sur le plan cardiorespiratoire et métabolique, alors sa capacité réelle est supérieure. Dans ce cadre, le niveau de risque à terme est moindre que ne pourrait le laisser supposer la $\dot{V}O_2$pic mesurée. D'autre part, l'incapacité à pouvoir tout simplement engager un effort intense pourrait d'emblée être un marqueur prédictif aggravant. Le patient pourrait présenter des difficultés à coopérer aux soins postopératoires, dont la remobilisation précoce et la récupération d'un niveau fonctionnel adéquat.

En l'absence de suivi des patients dans le cadre du présent travail, il ne nous est pas possible de répondre à cette interrogation qui serait un axe de futurs travaux.

Faut-il modifier les protocoles incrémentaux ?

Les protocoles d'EFX proposés dans la présente cohorte comprennent des paliers d'incréments allant de 5 à 15 watts par minute. Ces niveaux d'incréments correspondent aux recommandations développées récemment par une nouvelle société savante anglo-saxonne centrée sur l'évaluation et la réhabilitation périopératoire « Perioperative Exercise Testing and Training Society (POETTS) » (103).

Nous avons soulevé dans notre discussion la question de privilégier des paliers d'incrément minimes pour augmenter la durée d'effort. Une évaluation à l'aide d'une méthodologie robuste comparant les $\dot{V}O_2$pic obtenues selon différents niveaux d'incréments est nécessaire afin de mesurer la réalité voire la pertinence clinique de cette hypothèse.

Enfin, une part importante des patients nécessiterait potentiellement une seconde évaluation physiologique. Celle-ci est souvent réalisée en contrôle post-réentrainement préopératoire. Malheureusement, la multiplication de la programmation des EFX auprès de centres évaluateurs déjà surchargés n'est pas humainement et matériellement possible. De plus, l'hétérogénéité de l'accès à cet examen en fonction des centres hospitaliers reste forte comme le démontrent certaines études anglo-saxonnes, dans lesquelles les chirurgiens

américains déclarent intégrer l'évaluation de la $\dot{V}O_2max$ dans 57% des cas (104), ou encore la disponibilité du matériel d'évaluation dans environ un tiers des centres hospitaliers réalisant des chirurgies majeures en Angleterre (105). A notre connaissance, bien que des difficultés d'accès à l'EFX soit couramment soulevées dans les réseaux professionnels, cette donnée n'est pas disponible en France.

Dans ce cadre, le recours à des tests de terrains pour identifier les patients les plus à risque et ainsi adapter précocement leur parcours de soins, en intégrant une éventuelle préhabilitation, est nécessaire.

2.3. Etude n°2 : Intérêt du test de lever de chaise de 3 minutes (TLC-3) dans le cadre de l'évaluation préopératoire des patients atteints de CBNPC.

2.3.1. Présentation et rationnel de l'étude.

La $\dot{V}O_2$max est retenue comme un indicateur majeur du risque postopératoire, comme nous l'avons précédemment abordé. Cependant, l'accès à l'évaluation des réserves physiologiques via l'EFX peut être compromise dans certains centres en raison de limitations d'équipements et de ressources. De plus, au fur et à mesure de la diffusion de cet examen dans de nombreux hôpitaux, son utilité tant pour son intérêt diagnostique ou pronostique vis-à-vis de l'ensemble des pathologies chroniques, s'accompagne d'une explosion des programmations.

En conséquence, l'utilisation de tests fonctionnels permettant d'estimer plus simplement la capacité à l'exercice peut être une alternative afin d'identifier les patients les plus fragiles. La validation des tests de terrain en tant qu'outils de repérage des patients à risque a été envisagée de deux manières : en corrélant leur performance directement au taux de complications postopératoires, ou en les corrélant à l'outil de référence qu'est la $\dot{V}O_2$pic ou max ; la seconde méthode indirecte étant la plus explorée.

Le test navette (SWT) et le test de montée d'escalier (SCT) sont tous deux actuellement recommandés, préalablement ou à défaut d'accès à l'EFX (56, 57). Les recommandations européennes intègrent pour leur part le SCT comme une alternative par défaut en cas d'impossibilité de recourir à l'EFX (56). Le seuil recommandé par l'ACCP et l'ATS pour identifier les patients les plus à risque de complications à l'aide du SWT est fixé à 400 m (57). L'étude de Singh et al. avait déterminé qu'une performance de plus de 25 navettes (soit 5 minutes ou 250 mètres) était associée à une $\dot{V}O_2$pic ≥ 15 ml/kg/min chez des patients atteints de syndrome obstructif (106). Cette valeur seuil de 250 mètres avait été retenue dans les recommandations britanniques de 2001 (107), avant d'être à nouveau reconsidérée à 400 mètres dans la nouvelle version de 2010 (58). Pour le SCT, une ascension de plus de 22 mètres a été associée à une $\dot{V}O_2$pic ≥ 15 ml/kg/min et moins de complications postopératoires (108, 109).

Bien que le SWT et le SCT soient des tests relativement simples d'exécution, ils nécessitent toujours respectivement un espace assez conséquent ou une cage d'escalier assez haute et à disposition proche de la salle de consultation. Le développement de tests de terrain complémentaires pour la pratique clinique est donc pertinent.

Le test de lever de chaise semi-rythmé de 3 minutes (TLC-3) a récemment été standardisé et validé chez des patients atteints de BPCO (110). Il a l'avantage de ne nécessiter que très peu d'espace et seulement une chaise, un oxymètre de pouls et un chronomètre. Par conséquent, le TLC-3 peut être effectué dans presque tous les lieux de soins, y compris des espaces limités tels qu'une salle de consultation. Cependant, les résultats du TLC-3 n'ont pas encore été comparés aux données définitives obtenues au cours de l'EFX chez les patients atteints de CBNPC, comme cela a été fait pour les SWT et SCT.

Le but de cette étude était donc d'étudier la relation entre la mesure de la puissance métabolique que représente la $\dot{V}O_2$pic et la mesure de la puissance mécanique développée par le travail de déplacement répété au cours du TLC-3 chez les patients atteints de CBNPC. Plus spécifiquement, l'objectif était d'évaluer la possibilité de prédire la $\dot{V}O_2$pic sur la base de la performance au test et/ou sa capacité à identifier les patients avec une $\dot{V}O_2$pic < ou ≥ 15 ml/kg/min.

Les résultats de ce travail ont été rapportés sous la forme d'un poster au congrès de l'ERS 2020, ainsi que d'un article original publié dans la revue *Thoracic Cancer*, dont l'impact factor était de 3.500 en 2020 (Rang D) (111).

Dans le cadre de ce travail, à l'initiative des Dr Mathilde AZZI et Dr David DEBEAUMONT, ma contribution dans ce travail a été :

- Démarches administratives liées à la recherche : déclaration du traitement des données selon la méthodologie de référence MR-003 auprès de CNIL et demande d'avis auprès du CERDE du CHU de Rouen. Ce travail étant une recherche portant sur des données de santé et

n’impliquant pas directement la personne humaine (hors RIPH) de par son caractère rétrospectif, il n’a pas été nécessaire de réaliser une demande d’avis auprès d’un CPP ;

- Participation à l’élaboration du plan statistique et à sa réalisation ;

- Rédaction et soumission du poster et du manuscrit.

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ORIGINAL ARTICLE

Evaluation of the 3-minute chair rise test as part of preoperative evaluation for patients with non-small cell lung cancer

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Cardiopulmonary exercise testing; field test; lung surgery; non-small cell lung cancer; preoperative assessment.

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Abstract

Background: Peak oxygen uptake ($\dot{V}O_{2peak}$) measured by a cardiopulmonary exercise test (CPX) is the gold-standard for predicting surgical risk in patients with non-small cell lung cancer (NSCLC). The 3-minute chair rise test (3CRT) is a simple test requiring minimal resources. This study aimed to determine the ability of 3CRT to predict $\dot{V}O_{2peak}$ in patients with NSCLC.

Methods: Retrospective data from CPX and 3CRT carried out in 36 patients with NSCLC between March 2018 and February 2019 were included. A multivariate analysis was undertaken to derive a predictive $\dot{V}O_{2peak}$ equation based on performance on the 3CRT. In addition, sensitivity-specificity analysis was carried out to estimate a threshold 3CRT value for the prediction of $\dot{V}O_{2peak} \geq 15$ mL/kg/minute.

Results: The following equation was obtained: $\dot{V}O_{2peak}$ predicted = (0.04765 × FEV1) - (0.207 59 × BMI) - (0.115 89 × age) + (0.386 09 × vertical distance) + 16.628 69; $r^2 = 0.75$, $P < 0.01$. The bias between the $\dot{V}O_{2peak}$ values predicted and measured during CPX was 0.0 ± 1.7 mL/kg/minute (95% limits of agreement [−3.5 to 3.5]). A performance ≥49 chair rises predicted $\dot{V}O_{2peak} \geq 15$ mL/kg/minute with a sensitivity of 0.75 and a specificity of 0.81.

Conclusions: The level of error in the prediction of $\dot{V}O_{2peak}$ from 3CRT performance was too great to recommend that 3CRT should replace CPX as the sole measurement of $\dot{V}O_{2peak}$. Nevertheless, the 3CRT could help to identify those patients that require CPX prior to lung resection surgery for NSCLC, larger prospective study is needed to confirm this hypothesis.

Key points

Significant findings of the study: Cardiopulmonary exercise tests can stratify the surgical risk. Prediction of the peak oxygen uptake ($\dot{V}O_{2peak}$) value from the

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3CRT yields an unacceptable level of error. However, a performance of 49 chair rises or more during the 3CRT could indicate a $\dot{V}O_{2peak} \geq 15$ mL / kg / minute.

What this study adds: The 3CRT is a useful screening tool to determine the necessity for a comprehensive cardiopulmonary exercise test, whose access is limited in clinical practice. It could also allow early screening of patients requiring specific prehabilitation programs.

Introduction

Pulmonary resection is the most effective treatment for non-small cell lung cancer (NSCLC).[1] Unfortunately, many patients with lung cancer also have numerous comorbidities that increase the risk of postoperative complications.[2] The incidence of postoperative complications after lung cancer surgery is very heterogeneous according to the studies, it is estimated to be around 5% to more than 40%.[3] These complications are associated with significantly poorer long-term outcomes.[4] For this reason, all patients with NSCLC undergo comprehensive preoperative assessment to determine the benefits and risks of surgery in order to make appropriate therapeutic decisions.

Cardiopulmonary exercise test (CPX) is an important part of the preoperative assessment. It is used to measure and calculate variables that have been shown to be powerful indicators of the postoperative risk of morbidity and mortality. These variables include maximal oxygen uptake ($\dot{V}O_{2max}$) or, if maximal effort is not achieved, peak oxygen uptake ($\dot{V}O_{2peak}$).[5, 6] Although the oxygen uptake capacity is now considered as the gold standard measurement to determine postoperative risk, access to CPX may be limited in some centres due to limitations in equipment and resources. As a result, other simpler tests have been developed.

The shuttle walking test (SWT) and the stair climbing test (SCT) are both currently recommended as screening tools to determine the necessity to perform CPX.[7] Performance of 25 shuttles (ie, 5 minutes or 250 meters) in the SWT has been shown to be predictive of a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute.[8] For the SCT, an ascension of more than 22 meters has been associated with a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute and fewer postoperative complications.[9, 10] Therefore, these tests are useful to identify patients at low risk of postoperative complications. Patients who are at higher risk of postoperative complications and who do not achieve these test results often have a $\dot{V}O_{2peak} < 15$ mL/kg/minute.[6, 11] Those patients require CPX in order to determine their risk more precisely; a $\dot{V}O_{2peak} < 10$ mL/kg/minute is considered a high surgical risk.[7, 12]

Although the SWT and SCT are relatively simple tests, they still require space and stairs respectively. A new test, the semi-paced 3-minute chair rise test (3CRT), has recently been standardized and validated in patients with chronic obstructive pulmonary disease.[13] It has the advantage of requiring very little space and only a chair and a pulse oximeter. Therefore, the 3CRT can be performed in nearly any care setting, including very limited spaces such as consultation rooms. However, the results of 3CRT have not yet been compared with the definitive data obtained by CPX in patients with NSCLC, as has been undertaken for the SWT and SCT methods. This could allow the method to be used as a practical preoperative screening tool.

The aim of this study, therefore, was to investigate the relationship between the measurement of metabolic power by CPX ($\dot{V}O_{2peak}$) and the measurement of mechanical power developed during the 3CRT. More specifically, the aim was to determine the ability of 3CRT to predict the $\dot{V}O_{2peak}$ in patients with NSCLC and/or its ability to identify patients with a $\dot{V}O_{2peak} < \text{or} \geq 15$ mL/kg/minute in order to provide indications regarding either suitability for surgery, or the need for further testing.

Methods

Population and design

All patients in this paper were retrospectively included in the analysis. The institutional ethics committee of the Rouen University Hospital approved the data extraction for this study (n°E2019-67). Patients all had been diagnosed with NSCLC and had either a predicted postoperative forced expiratory volume in 1 second (ppoFEV1) or a predicted postoperative diffusing capacity for carbon monoxide (ppoDLCO) < 60%,[7] and been referred for complementary tests by thoracic surgeon or pneumologist. The predicted postoperative values of FEV1 and DLCO were estimated by preoperative value/total number of functioning segments before the operation, and× the residual number of functioning segments after the operation.[12] The patients had undergone CPX as part of their preoperative assessment for pulmonary resection between March 2018 and February 2019. In addition, they had all also been assessed using 3CRT in

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the physiology department of Rouen university hospital, France, since the department was trialing the test to determine if it was clinically feasible. All tests were carried out by the physiology medical team trained in carrying out stress assessment tests.

Assessments

Pulmonary function

Pulmonary function tests were carried out according to the American Thoracic Society and the European Respiratory Society guidelines[14] using plethysmography (Masterscreen, Jaeger, Wittsburg, Germany). Values were expressed as percentages of established theoretical values for European populations.[15]

Cardiopulmonary exercise test

The CPX room was air-conditioned and kept at a constant temperature of 19°C for all tests, and the hygrometry was not controlled in current practice. The measuring instruments were recalibrated every half day with a reading of the atmospheric pressure. Patients were advised to avoid strenuous exercise and the consumption of alcohol, tobacco or caffeine for 24 hours prior to examination. CPX was performed on an electromagnetic ergometer (Ergoselect 200, Ergoline, Bitz, Germany) using a standardized, incremental protocol.[16] Following a three-minute warm-up, incremental ramp exercise (5 to 15 W/minute) was maintained until exhaustion. Markers used to consider the CPX as maximal were determined accorded to current guidelines.[16] A face mask (Hans Rudolph, Inc., Kansas City, MO), pneumotach and gas analyzer (Ergocard, Medisoft, Louvain, Belgium) were used to measure breath-by-breath oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). Heart rate (HR) was continuously monitored with a 12-lead electrocardiogram (Ergocard, Medisoft, Louvain, Belgium).

3-minute chair rise test (3CRT)

The 3CRT was performed in the same condition (CPX room) according to the methodology validated by Aguilaniu *et al*[13] Test instructions and instructions for rating the 0 to 10 points Borg scale (dyspnea and fatigue) were given while the patient was sitting at rest on a standard chair (floor to seat height 48 cm); this chair was then used for the test: "The aim of the exercise is to stand up and sit down repeatedly for three minutes. You must keep your hands on your hips all the time. I'll give you the pace for the first minute by saying: "sit", "stand" or by doing the sit-to-stand with you. During the last two minutes try to stand up and sit down as many times as possible. I'll let you know how much time is left, for example: "1 minute and 30 seconds to go", "1 minute to go", "30 seconds to go". You can slow down or speed up at any time. If the exercise is too difficult, you can have a little rest then continue. You can also stop the test before the end of three minutes if you feel too tired or breathless to finish it." A chair rise was defined as one complete movement from sitting to standing and then sitting again (Fig 1).

Depending on the patient's FEV1 value, the pace during the first minute was set to ensure that either 12 (FEV1 < 1200 mL) or 20 (FEV1 ≥ 1200 mL) rises were performed, in order to reduce interindividual variability at the start of the test.[13] At the end of the test, physiological data

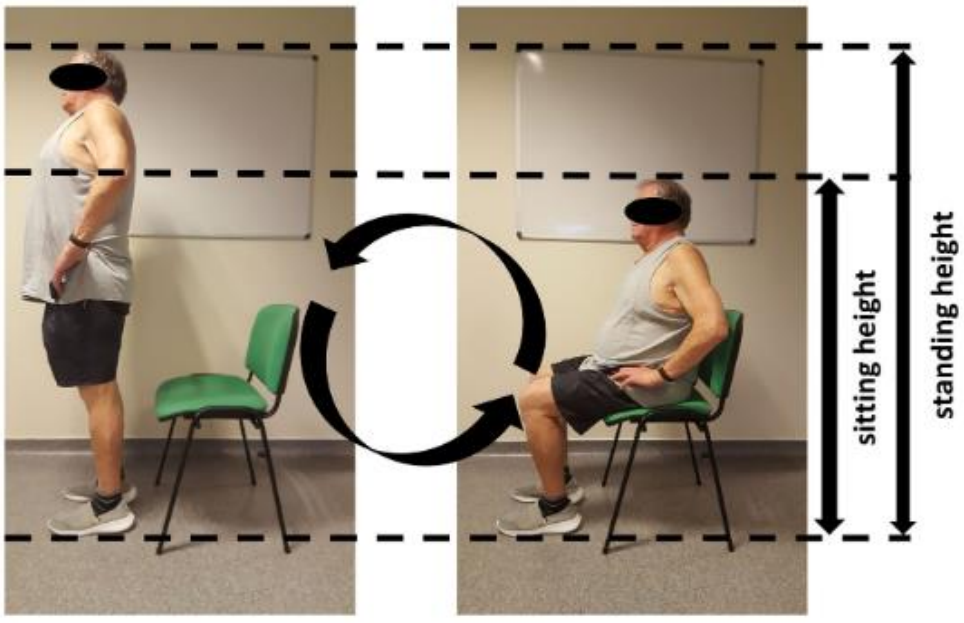

Figure 1 Installation and execution of the 3-minute chair rise test (3CRT). The patient was asked to stand up and sit down repeatedly for three minutes keeping their hands on their hips all the time. In the study the number of rises and the vertical distance reached (= [patient's standing height - sitting height] x number of chair rises) were recorded.

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(SpO_2, HR) and symptoms (dyspnea and leg fatigue with the Borg scale) were recorded. The number of chair rises was also recorded and two variables were calculated: (i) the vertical distance reached (in meters) = (patient's standing height - sitting height) x number of chair rises and (ii) the weight displaced (patient's weight x the number of chair rises).

Statistical analysis

Categorial data are expressed as numbers (percentages). Continuous data are expressed as means ± standard deviation or medians (interquartile range) according to their distribution; normality was assessed using the Shapiro-Wilk test. Paired *t*-tests or Wilcoxon matched-pairs signed rank tests were used for the comparison of continuous data depending on the normality of the distributions.

In order to predict the $\dot{V}O_{2peak}$, a multiple regression was undertaken using $\dot{V}O_{2peak}$ as the dependent variable. First, the univariate relationships between the $\dot{V}O_{2peak}$ measured during CPX and each demographic variable (age, BMI and FEV1) and each performance outcomes of the 3CRT (number of rises, vertical distance reached and weight displaced) were assessed using a Pearson's correlation test. The variables identified as related to $\dot{V}O_{2peak}$ with a *P*-value <0.10 were assessed for interrelationships and entered in a multivariate analysis. In the case of a strong interrelationship ($r > 0.80$), only the variable most related with $\dot{V}O_{2peak}$ was used. Finally, a multivariate forward/backward stepwise regression was used to derive the best model to predict $\dot{V}O_{2peak}$. Agreement between the measured $\dot{V}O_{2peak}$ (during CPX) and predicted $\dot{V}O_{2peak}$ was evaluated using a Bland-Altman analysis and the mean absolute difference (MAD) between both results was calculated. Clinical equivalence between measured and predicted $\dot{V}O_{2peak}$ was defined a priori as: limits of agreements (upper and lower bounds) < 1.5 mL/kg/minute, corresponding to less than 10% of risk of bias.

The ability of the 3CRT to predict a cutoff $\dot{V}O_{2peak} \geq 15$ mL/kg/minute was evaluated by sensitivity, specificity and receiver operating characteristic (ROC) curve analyses. A *P*-value <0.05 was considered statistically significant in all cases. GraphPad Prism 5.03 and R 3.6.1 software were used for all analyses.

Results

Patients

Between March 2018 and February 2019, 51 patients were referred for CPX as part of a preoperative evaluation for NSCLC. Of these, 13 did not undergo the 3CRT because of orthopedic limitations associated with disabling pain. A further two CPXs were uninterpretable due to submaximality of effort. The flow chart of these results is presented in Fig 2. Patient characteristics for the 36

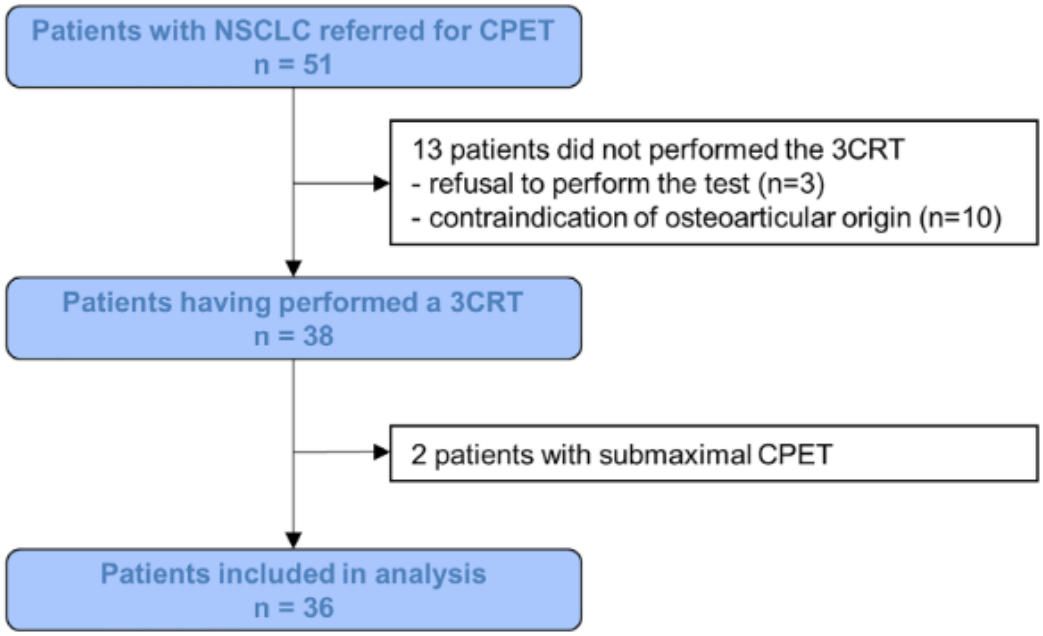

Figure 2 Flow-chart of patients included in the study; NSCLC, non-small cell lung cancer; CPX, cardiopulmonary exercise test; 3CRT, 3-minute chair rise test.

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Table 1 Patient characteristics ($n = 36$)

Variable (units)	
Age (years), mean ± SD	65.6 ± 7.7
Male, *n (%)*	27 (75%)
BMI (kg/m2), mean ± SD	25.4 ± 5.4
Lung function	
FEV1/FVC (%), mean ± SD	54.1 ± 13.4
FEV1 (L), median (Q1 to Q3)	1.7 (1.2 to 2.0)
FEV1 (% predicted), mean ± SD	58.4 ± 18.6
RV/TLC (%), median (Q1 to Q3)	49.5 (43.3 to 60.0)
DLCO (%), mean ± SD	60.7 ± 20.3
mMRC, mean ± SD	1.5 ± 1.0
Tobacco	
Pack-years, median (Q1 to Q3)	50.0 (36.3 to 60.0)
Former, n (%)	24 (66%)

BMI, body-mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; mMRC, modified Medical Research Council dyspnea scale.

participants are shown in Table 1. Comorbidities and treatments are shown in Table S1. The CPX and 3CRT results are summarized in Table 2.

Correlation between $\dot{V}O_{2PEAK}$ and 3CRT

There was a significant correlation between the $\dot{V}O_{2peak}$ and the number of chair rises in three minutes ($r^2 = 0.37$, $P < 0.01$) as well as the vertical distance reached during the 3CRT ($r^2 = 0.62$, $P < 0.01$) (Fig 3). The other variables that were significantly correlated with $\dot{V}O_{2peak}$ were: age ($r^2 = 0.29$, $P < 0.01$), BMI ($r^2 = 0.18$, $P = 0.01$) and FEV1 ($r^2 = 0.12$, $P = 0.04$).

Capacity of the 3CRT to predict $\dot{V}O_{2PEAK}$

The best model determined by the multivariate analysis to predict $\dot{V}O_{2peak}$ was: $\dot{V}O_{2peak}$ predicted = (0.04765 × FEV1 in % predicted) − (0.20759 × BMI in kg/m2) − (0.11589 × age in years) + (0.38609 × vertical distance in m) + 16.62869; $r^2 = 0.75$, $P < 0.01$. The mean $\dot{V}O_{2peak}$ measured during CPX and predicted by the previous equation was not significantly different 14.6 ± 3.6 vs. 14.6 ± 3.1, $P = 0.99$ (Table 2).

The bias between the $\dot{V}O_{2peak}$ predicted using this equation and the measured $\dot{V}O_{2peak}$ was 0.0 ± 1.7 mL/kg/minute, but the 95% limits of agreement were −3.5 to 3.5. The corresponding Bland-Altman (B&A) plots are presented in Fig 4. The mean absolute difference (MAD) was 1.5 ± 1.0 mL/kg/minute. These results indicate that even if the r-square of the predictive model was high, it did not provide an adequate fit for our data.

Capacity of the 3CRT to predict a $\dot{V}O_{2PEAK}$ > 15 mL/kg/minute

During CPX, there were 16 patients with a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute and 20 who did not reach this capacity. The ROC curve analysis is presented in Fig 5 and detailed in Table S2.

Table 2 Cardiopulmonary exercise testing (CPET) and 3-minute chair rise test (3CRT) ($n = 36$)

	CPET	3CRT	*P*-value
Number of chair rises (n), mean ± SD	-	51.0 ± 11.7	
Vertical distance reached (m), mean ± SD	-	20.9 ± 4.7	
$\dot{V}O_{2peak}$ (mL), mean ± SD	1048.0 ± 280.0	-	
$\dot{V}O_{2peak}$ (mL/kg/minute), mean ± SD	14.6 ± 3.6	14.6 ± 3.1 (predicted)	0.99
$\dot{V}O_{2peak}$ (% predicted), mean ± SD	61.6 ± 14.1	61.6 ± 11.6 (predicted)	1.00
W_{peak} (watts), mean ± SD	81.6 ± 23.9	-	
W_{peak} (% predicted), mean ± SD	65.9 ± 18.7	-	
$\dot{V}E/\dot{V}CO_2$ slope, mean ± SD	37.3 ± 7.7	-	
HRmax (bpm), mean ± SD	127.0 ± 21.4	115.9 ± 18.9	< 0.01 *
HRmax (%predicted), mean ± SD	75.7 ± 11.7	69.0 ± 11.0	< 0.01 *
Δ HR (bpm), mean ± SD	45.2 ± 17.7	33.0 ± 15.4	< 0.01 *
Δ SpO_2 (%), median (Q1 to Q3)	−2.0 (0.0 to −3.0)	−2.0 (−1.0 to −5.0)	0.28
Rest dyspnea (Borg), median (Q1 to Q3)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.5)	0.65
Δ dyspnea (Borg), mean ± SD	5.0 ± 1.8	3.7 ± 2.2	< 0.01 *
Rest fatigue (Borg), median (Q1 to Q3)	0.0 (0.0 to 0.1)	0.0 (0.0 to 1.0)	0.19
Δ fatigue (Borg), mean ± SD	4.8 ± 2.3	4.0 ± 2.1	0.12

$\dot{V}O_{2peak}$, peak of oxygen consumption during CPET; W_{peak}, peak power reached during CPET; $\dot{V}E/\dot{V}CO_2$ slope, linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$); HR, heart rate; Δ, delta between rest and the end of the test; SpO_2, pulsed oxygen saturation.

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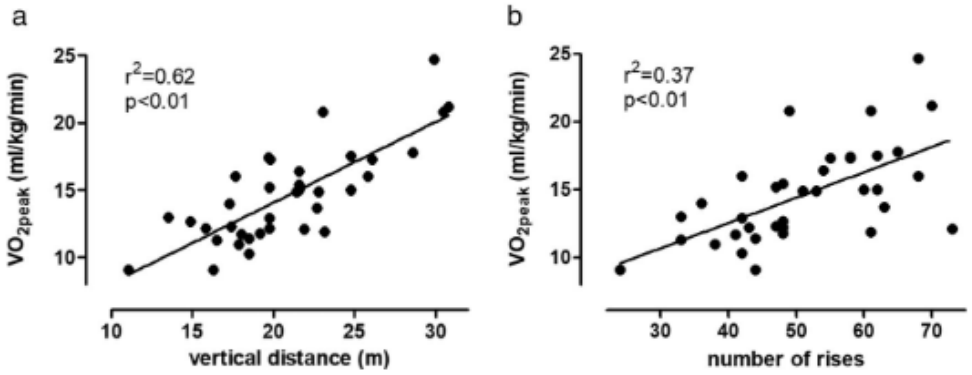

Figure 3 Correlation between the peak oxygen uptake ($\dot{V}O_{2peak}$) measured during cardiopulmonary exercise test with (a) the vertical distance reached, and (b) the number of chair rises, duringthe 3CRT.

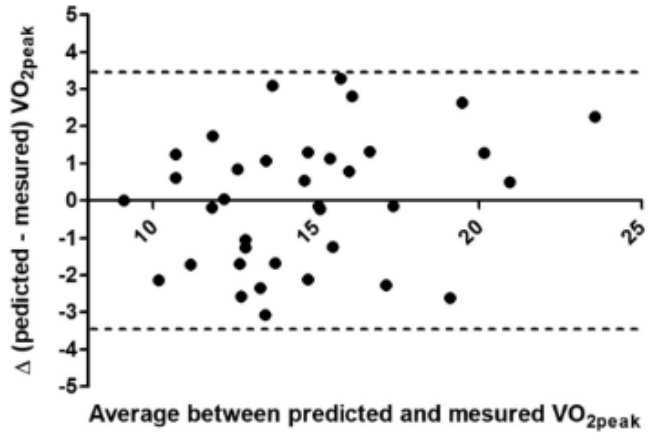

Figure 4 Bland-Altman plots for the estimation of the peak oxygen uptake ($\dot{V}O_{2peak}$) using the predictive equations derived from the 3-minute chair rise test (3CRT) performance. The point-to-point difference (Δ) between the two values (actually predicted minus measured) is plotted against the mean of the two values; bias = 0.0, 95% CI limits of agreement (lower and upper bounds) were − 3.5 to 3.5 mL/kg/minute.

The area under the curve (AUC: 95% CI) was 0.82 (0.67 to 0.96). A number of chair rises ≥49 predicted a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute with a sensitivity of 81% and a false-positive rate of 25% (specificity: 75%). The false-positive rate reduced to 15%, 10% and 5% for patients who achieved 54, 62 and 65 rises, respectively.

In this cohort, the threshold of 49 chair rises was associated with a positive predictive value (PPV) and a negative predictive value (NPV) to detect a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute of 72% and 83%, respectively.

Discussion

The incidence of lung cancer is increasing worldwide.[17] Access to curative surgical treatment for patients with NSCLC requires an assessment of functional capacity in order to identify patients at risk.[7, 12] Since $\dot{V}O_{2peak}$ is a powerful predictive marker in many chronic pathologies, the demand for CPX is exploding in many institutions. The need to develop field tests to estimate oxygen uptake is particularly topical. This study demonstrated a significantly positive relationship between performance on the 3CRT and $\dot{V}O_{2peak}$ measured during CPX in patients with NSCLC. The vertical distance reached during 3CRT was particularly strongly correlated with $\dot{V}O_{2peak}$ results. According to the multivariate analysis, the four independent variables related to $\dot{V}O_{2peak}$ during the 3CRT were the vertical distance reached, age, BMI and FEV1. Although the equation derived from the multivariate regression did not accurately predict specific $\dot{V}O_{2peak}$, the number of 49 or more rises performed during the 3CRT predicted a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute with a sensitivity of 81% and a specificity of 75%.

To our knowledge, this is the first study to assess the ability of the 3CRT method as a tool to determine the need for presurgical CPX in patients with NSCLC. The 3CRT is one of a set of many sit-to-stand-tests (STST). Although they all evaluate the ability to get up from a chair without using the upper limbs as a measure of physical capacity, the specific aims and methods of each differ. The 1-minute STST (1-STST) particularly is used in patients with COPD. It is well correlated to quadriceps strength,[18] as well as distance walked during the 6-minute walk test (6MWT), thus providing an estimate of functional capacity with less hemodynamic stress.[19, 20] However, such quick tests do not reflect cardiorespiratory capacity, especially as $\dot{V}O_2$ kinetics are known to be slowed and related to the severity of the respiratory disease.[21, 22] For patients with NSCLC, a longer evaluation over 3 minutes seems more appropriate since respiratory function is often altered and it may take 3 minutes for cardiorespiratory function to adapt to a constant load test.

We believe this test is valuable since it can easily be performed during a consultation to provide data to guide further therapeutic decisions. Similarly, to tests such as the SWT, the SCT and CPX, the main contraindication to its use is disabling lower limb pain. Patients with peripheral arteriopathy and hip prostheses were able to perform the 3CRT in the present study.

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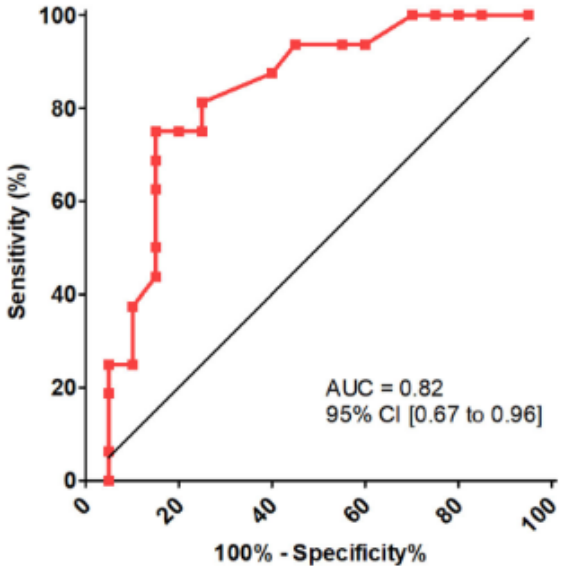

Figure 5 Receiver operating characteristic curve (ROC curve) performed to determine a threshold of the number of chair rises to predict a $\dot{V}O_{2peak} > 15$ mL/kg/minute: sensitivity (% of patients positively considered with a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute) is plotted against 100%-specifity% (% of patients with a $\dot{V}O_{2peak} < 15$ mL/kg/minute falsely considered positive) at each possible threshold. Accuracy is measured by the area under the curve (AUC). An area of 1 = perfect; an area of 0.5 = inadequate.

The lack of accuracy of the prediction of specific $\dot{V}O_{2peak}$ value by the multivariate regression equation prohibit its use in clinical practice to predict $\dot{V}O_{2peak}$. The fact HR_{max} and Borg rating of dyspnea were significantly higher during the CPX suggests that the 3CRT was physiologically less stressful, or the evaluators did not motivate the patient as much as during the CPX during this new test. It is also possible that the sample size was too small and thus the dispersion of the data was relatively high. Larger studies should therefore be conducted to refine the equation and assess the influence of the evaluation conditions.

The ROC analysis showed that performance of 49 rises or more during the 3CRT was predictive of a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute, with a high level of sensitivity (81%) and a moderate false-positive rate (25%) (specificity: 75%). To compare with other field tests used in screening NSCLC patients in the preoperative assessment, the PPV and NPV for the threshold of 49 rises during the 3CRT were calculated (72% and 83%, respectively). A study of the SWT found higher PPV and NPV (90% each) for a distance ≥250 meters to predict a $\dot{V}O_{2peak} > 15$mL/kg/minute.[8] For the SCT, a high PPV (86%) was found for a climb ≥22 meters to predict a $\dot{V}O_{2peak} > 15$ mL/kg/minute; however, the NPV was only 62%.[10]The SWT is therefore the most accurate of these tests in determining which patients need to be referred for CPX. However, it is also the most difficult to carry out in everyday practice, as none of the thoracic surgeons interviewed in a recent American survey prescribe a SWT.[23] Comparatively to the SWT and SCT, the 3CRT can be performed in nearly any care setting, including very limited spaces such as consultation rooms by surgeons themselves, or allied health professionals, and could be sufficient to determine the need for presurgical CPX in patients with NSCLC.

During the 3CRT validation study in COPD patients, Aguilaniu *et al.* reported that patients who were able to perform more than 50 rises during the 3 minutes had a lower score on the disability related to COPD tool (DIRECT) questionnaire, suggesting less impaired function.[13] Similarly, Lévesque *et al.* reported a mean number of 51.9 ± 13.1 rises during the 3CRT in patients with COPD whose BODE index score was in the first favorable quartile (0–2 /10).[24] These results are consistent with the threshold of 49 rises found in the present study to predict a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute in the present cohort.

This study had several limitations. First, there may have been selection bias due to the retrospective design. Second, even if the multivariate regression analysis model (r2 = 0.75, $P < 0.01$) and ROC curve analyses (AUC 0.82 [0.67 to 0.96]) were statistically significant, the study was not powered a priori and was probably underpowered. The measurement of post hoc statistical power is questionable and has not been recommended by several authors.[25] We took the option not to include this measure in the present paper, as we felt that it would not strengthen the level of evidence of this preliminary retrospective study. Third, a separate validation with an independent cohort of patients is necessary to confirm the PPV and NPV for the threshold of 49 rises during the 3CRT to predict a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute. Finally, this study only focused on the evaluation of performance on the 3CRT in relation to the $\dot{V}O_{2peak}$ as a postoperative risk factor, and did not directly evaluate postoperative complications.

Nevertheless, the results of this preliminary, retrospective study suggest that this simple tool is promising as a screening test prior to CPX in patients with NSCLC and thus larger, prospective studies are justified. Moreover, the data relating to the relationship between 3CRT performance and $\dot{V}O_{2peak}$ can be used to determine the appropriate design of a prospective study with a larger number of patients.

In conclusion, performance of at least 49 chair rises during the 3CRT indicated a $\dot{V}O_{2peak} \geq 15$ mL/kg/minute, similar to results from the SCT and the SWT. However, prediction of the specific $\dot{V}O_{2peak}$ value based on the 3CRT performance was insufficiently accurate or sensitive to be used as a standalone method for determining the specific

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$\dot{V}O_{2peak}$ value. The 3CRT is a simple field test that could be very useful as a screening test to indicate patients with NSCLC who require further testing with CPX and those who can be safely referred for surgery. Prospective studies with larger sample sizes are needed to validate these results.

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Disclosure

The authors report having no conflict of interest to disclose in relation to the present study.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1: Comorbidities and treatments (n = 36).**Table S2:** Receiver operating characteristic analysis of the number of chair rises versus peak oxygen consumption ($\dot{V}O_{2peak}$) ≥15 mL/kg/minute; binary outcome.

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2.3.2. Discussion de l'étude n°2

Résultats principaux

Tout d'abord, la performance réalisée au cours du TLC-3, notamment mesurée en déplacement vertical, est fortement corrélée à la $\dot{V}O_2$pic mesurée à l'EFX ($r^2 = 0.62$, $p < 0.01$) chez les patients atteints de CBNPC en cours de bilan préopératoire.

En second lieu, sur la base de cette forte corrélation et l'utilisation d'un modèle multivarié prenant en compte d'autres facteurs clés, nous avons dérivé une équation prédictive de la $\dot{V}O_2$pic :

$$\dot{V}O_2\text{pic prédite} = (0{,}04765 \times \text{VEMS}) - (0{,}20759 \times \text{IMC}) - (0{,}11589 \times \text{âge}) + (0{,}38609 \times \text{distance verticale}) + 16{,}62869 \; ; \; r^2 = 0{,}75 \; ; \; P < 0{,}01.$$

Où le VEMS est exprimé en % théorique, l'IMC en kg/m^2, l'âge en années, et la distance verticale en mètres.

A l'échelle de la population étudiée, la forte corrélation de cette équation prédictive s'exprime par un biais de précision négligeable au niveau de l'analyse de Bland et Altman (Biais moyen entre la $\dot{V}O_2$pic prédite par l'équation et la valeur mesurée = 0.0 ml/kg/min). Cependant, la dispersion des données à l'échelle individuelle [IC 95% -3.5 à 3.5 ml/kg/min] ne permet pas son utilisation en pratique clinique.

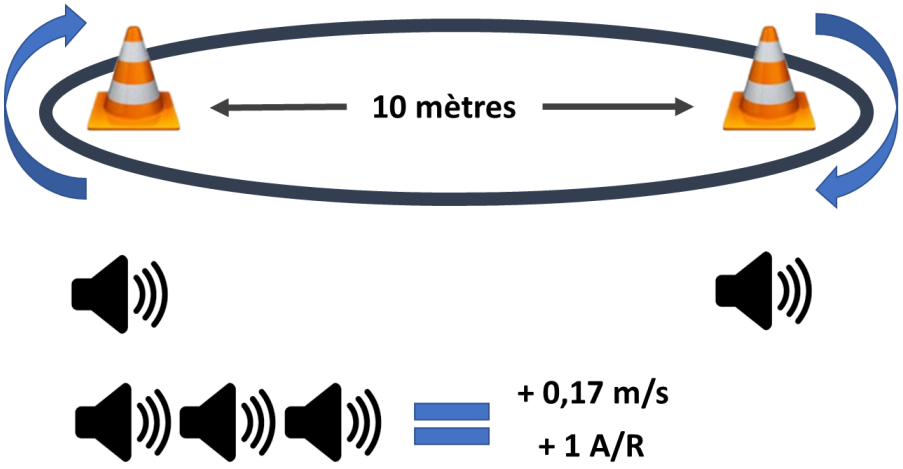
Enfin, à défaut de pouvoir prédire une valeur précise, le TLC-3 semble être un outil intéressant d'identification des patients présentant une $\dot{V}O_2$pic < 15 ml/kg/min sur la base d'une performance ≥ 49 levers de chaise. Cette dernière caractéristique identifiée de manière exploratoire nécessite d'être retestée de manière prospective sur une population indépendante.

Autres tests de terrain évalués avant résection pulmonaire oncologique

Parallèlement à ce présent travail, la thématique des tests de terrains dans le cadre de l'évaluation du niveau fonctionnel des patients avant chirurgie thoracique pulmonaire est très innovante et influencera certainement de nouvelles recommandations à venir.

Test navette (SWT)

La version du SWT adaptée aux patients atteints de pathologies respiratoires a été développé et validée en 1992 par Singh et al. (112). Ce test consiste à réaliser le plus grand nombre d'allers-retours entre deux plots espacés de 10 mètres, avec une vitesse croissante guidée via une bande son émettant des signaux sonores de plus en plus rapprochés jusqu'à épuisement. Le test compte 12 paliers, avec une augmentation de 0,17 m/s (soit environ 0,6 km/h) et un aller-retour en plus, chaque changement de palier est notifié par un triple signal sonore. A titre indicatif, le nombre d'allers-retours est de 3 au premier pallier dont vitesse est de 1,8 km/h, pour atteindre 14 allers-retours au 12^{e} et dernier pallier à environ 8,5 km/h (112). (Figure 12)



	Vitesse (m/s)	Allers-retours (n)
Palier 1	0,50	3
Palier 2	0,67	4
Palier 3	0,84	5
Palier 4	1,01	6
Palier 5	1,18	7
Palier 6	1,35	8
Palier 7	1,52	9
Palier 8	1,69	10
Palier 9	1,86	11
Palier 10	2,03	12
Palier 11	2,20	13
Palier 12	2,37	14

Figure 12 : modélisation du SWT validé auprès des patients atteints de pathologies respiratoires chroniques d'après Singh et al 1992 (112).

Bien que SWT rapporte des capacités prédictives pertinentes de la $\dot{V}O_2$pic avec une valeur seuil de performance validée à 400 mètres et plus (57, 58), son utilisation en pratique courante est peu répandue. Comme le montre une enquête de pratique récente auprès des chirurgiens américains, le SWT n'est utilisé en pratique courante par aucun des 203 centres ayant répondu (104). Malgré la fiabilité étayée du test, la simplicité de mise en œuvre d'un test de terrain semble donc cruciale pour son utilisation en pratique clinique.

Test de montée d'escaliers (SCT)

Dans ce test le patient est invité à monter la plus grande hauteur possible jusqu'à se sentir limité par ses symptôme (Figure 13). Une méta-analyse récente publiée en 2020 par Boujibar et al. ayant standardisé les différentes hauteurs atteintes dans les études publiées rapporte un seuil d'environ 10 mètres d'ascension comme facteur prédictif de complications postopératoires (113). L'évolution des techniques chirurgicales, comme de l'ensemble des soins péri-opératoire est un marqueur explicatif possible de la diminution du niveau de risque initialement évalué à 22 mètres d'ascension (56, 57).

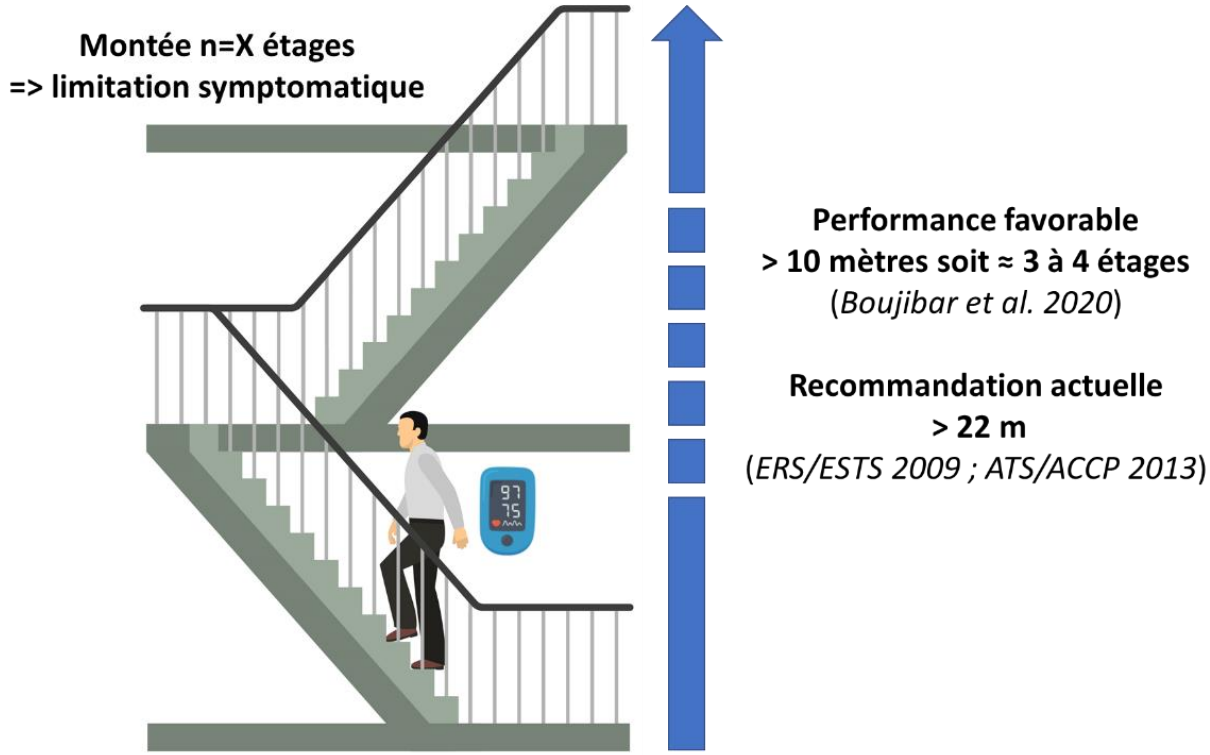


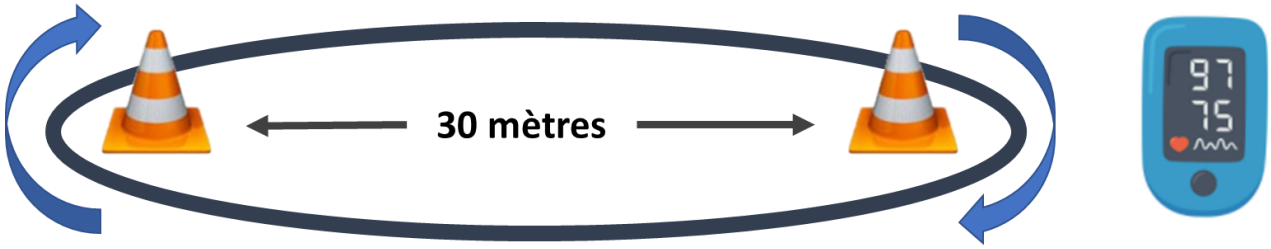
Figure 13 : modélisation du SCT.

D'un point de vue pratique, cette hauteur standardisée de 10 mètres correspond environ à la hauteur de 3 à 4 niveaux dans un établissement de soins. Malgré une standardisation des normes relatives d'accessibilité au niveau national et européen, des spécificités propres à chaque établissement quant à la hauteur de marche, la position des

rambardes, la présence ou non de paliers intermédiaires… font que la validité externe des données acquises dans chaque hôpital est potentiellement limitée.

Test de marche de 6 minutes (TDM6)

Le TDM6 est un test de référence dans le suivi des pathologies respiratoires chroniques. Ce test consiste à réaliser la plus grande distance possible sur une durée de 6 minutes, la vitesse de marche est libre selon le ressenti du patient, les arrêts sont autorisés (sans arrêt du chronomètre). Les conditions des réalisations standardisées incluent des encouragements types chaque minute, un espace dégagé permettant de modéliser une zone de marche de 30 mètres, le monitorage continu de la fréquence cardiaque et de la saturation en oxygène (Figure 14) (114).



Temps	Phrase standard
1 min	« Bien. Il reste 5 minutes. »
2 min	« Bon travail, continuez. Il reste 4 minutes. »
3 min	« Bien. Vous avez réalisé la moitié. »
4 min	« Bon travail, continuez. Il ne reste que 2 minutes. »
5 min	« Bien. Il ne reste qu'une minute. »
5min 45s	« Dans un instant, je vais vous dire d'arrêter. Quand je le ferai, arrêtez-vous où vous êtes et je viendrai à vous. »
6 min	« Stop »

Figure 14 : modélisation du TDM6 validé auprès des patients atteints de pathologies respiratoires chroniques d'après les recommandation de l'ATS (114).

Le TDM6 ne présentait pas assez de données convergentes et fiables pour être retenu dans les dernières recommandations publiées en 2013 (57). Des travaux publiés depuis cette date remettent en avant l'utilité de ce test. Tout d'abord, Marjanski et al. ont rapporté une augmentation du risque de complications postopératoires chez les patients présentant une distance au TDM6 < 500 m (P < 0,01; OR : 2,60 [IC 95% 1,28 à 5,30]) (115). Deux études récentes européenne et coréenne, chacune sur une cohorte d'environ 1000 patients, apportent de nouvelles données venant étayer une augmentation du risque de complications postopératoires pour les patients présentant une distance au TDM6 < 400 m (116, 117). Au-delà du marqueur prédictif de TDM6 pourrait permettre de faciliter l'accès rapide à un entrainement préopératoire personnalisé en l'absence d'accès à l'EFX. En effet, Bonnet et al. ont rapporté que la fréquence cardiaque au seuil ventilatoire était corrélé à la fréquence cardiaque du plateau des 3 dernières minutes d'effort de marche (118). Bien que le TDM6 soit un test plus fréquemment réalisé que le SWT les contraintes d'espace pour la réalisation de ce dernier demeurent.

Test de levers de chaises d'une minute (TLC-1)

Le test de levers de chaise peut se décliner sous différentes variantes comme nous l'avons exposé dans la discussion de notre article ci-dessus. Le test de levers de chaise de 1 min (« One-minute *Sit To Stand Test* » 1-STST ou TLC-1) est un test validé et utilisé en pratique courante de réhabilitation respiratoire, notamment auprès des patients atteints de BPCO (119). Les consignes et la réalisation sont simples en pratique courante. En effet, de même que pour le TLC-3 précédemment décrit (Figure 1 de l'article), le patient est invité à réaliser le plus grand nombre de levers complet et retour assis sur une chaise de hauteur standard (46 à 48 cm), mains sur les hanches, les genoux à 90°, seuls les cycles complets sont comptés et le patient est informé de l'atteinte des 15 dernières secondes.

Le TLC-1 a récemment été évalué auprès des patients en chirurgie thoracique oncologique (120). Ce travail réalisé par Boujibar et al. a l'avantage, par rapport à notre étude sur le TLC-3, d'évaluer directement la capacité prédictive de complications sans intermédiaire

de la $\dot{V}O_2$pic. Ainsi, un nombre de levers < 19 levers au TLC-1 est prédictif de complications postopératoires (120).

Test stepper de 6 minutes (TS6M)

Le TS6M est un test dérivé du TDM6, les consignes en étant directement inspirées. Cependant, l'effort a l'avantage d'être réalisé sur un appareil stationnaire permettant de s'affranchir d'un espace dégagé de plus de 30 mètres linéaires. Ce test a été validé chez les patients atteints de BPCO et/ou d'autres insuffisances respiratoires (121). Le patient est positionné face à un mur à une distance permettant de poser les mains lors des pauses (si nécessaire), et/ou ajuster l'équilibre (Figure 15). Dans la mesure du possible il est demandé au patient de ne pas s'appuyer sur le mur lors du test, les consignes sont standardisées sur le même modèle que le TDM6 (114). Le nombre de pas réalisé au terme des 6 minutes est relevé sur le compteur du dispositif à la fin du test, 1 pas équivaut à 1 aller-retour complet.

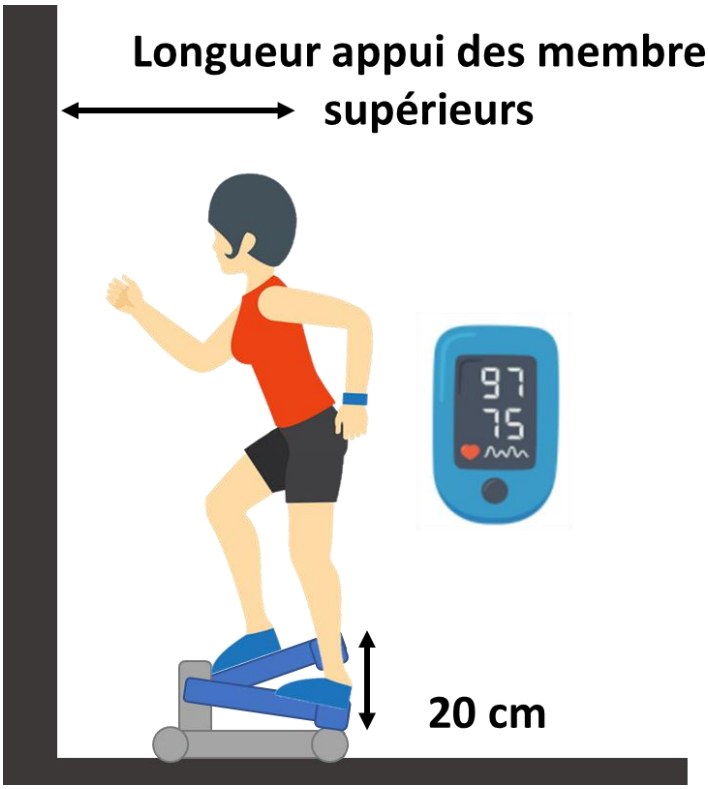


Figure 15 : modélisation du TS6M.

Boujibar et al. se sont aussi intéressés à l'évaluation du TS6M auprès des patients atteints de CBNPC, et ont déterminé qu'un nombre de pas < 140 au TS6M est prédictif de complications postopératoires majorée (120). De même que pour le TDM6, Bonnevie et al. ont rapporté que la fréquence cardiaque moyenne, cette fois-ci des 3 premières minutes au TS6M, était corrélée à la fréquence cardiaque obtenue au seuil ventilatoire chez les patients atteints de BPCO (122). Ce test pourrait donc permettre de concilier évaluation et initiation rapide d'un programme de réentrainement à l'effort.

2.4. Conclusion de la première partie

Dans cette première partie, dédiée à la thématique de l'évaluation à l'effort des patients atteints de cancer pulmonaire en attente de chirurgie, nous avons proposé deux travaux originaux. Le premier nous a permis d'identifier qu'environ 30% des patients reçus en EFX préopératoire fournissaient des efforts sous-maximaux, et dans le second nous avons évalué un nouveau test de terrain permettant d'identifier les patients avec une $\dot{V}O_2$pic supérieure ou inférieure à un seuil de 15 ml/kg/min.

L'évaluation de la capacité à l'exercice avant la chirurgie s'ancre de plus en plus dans la pratique courante, tant pour sa valeur pronostique que pour prescrire une réhabilitation préopératoire efficace. Sur ce point nos deux travaux sont donc complémentaires pour notre pratique clinique. Le premier nous encourage à potentiellement réduire les paliers d'incrément, voire re-tester certains patients, pour maximiser la validité de la capacité à l'effort mesurée. Ceci peut impacter le volume de patients qui accèdent à l'EFX dans un contexte déjà limité. C'est pourquoi l'identification de tests de terrains aisément réalisables en pratique clinique tient une importance capitale. Notre seconde étude fait donc écho à la première, le TLC-3 pouvant éventuellement, sous couvert d'une contre-validation prospective, discriminer les patients les plus fragiles et ainsi réduire la pression de programmation vers les plateaux techniques d'évaluation physiologique. D'autres tests de terrain étant en cours de validation, la comparaison de ces tests et leurs corrélations avec les paramètres de l'EFX sont autant de futurs travaux nécessaires.

Enfin, la rapidité comme la validité de l'évaluation sont des conditions implicites à la mise en place d'un programme de réhabilitation préopératoire adapté aux besoins du patient et dans les délais impartis par le contexte oncologique. Nous aborderons le contenu et les effets de cette intervention, qualifiée de préhabilitation, dans la seconde partie.

3. Deuxième partie : La préhabilitation, composantes et effets

3.1. La Préhabilitation

Le concept de la préhabilitation a émergé dans les années 2000 en lien avec le développement de l'ensemble des soins physiques et psychologiques apportés aux patients atteints de cancer et nécessitant des thérapies lourdes pour lesquelles une préparation et un accompagnement spécifique sont nécessaires. Il a été défini par Silver et al. (2013) comme « un processus sur le continuum de soins du cancer qui arrive entre le diagnostic de cancer et le début du traitement aigu, et qui inclut les évaluations physiques et psychologiques qui établissent un niveau fonctionnel de base, identifient les déficits et fournissent les interventions qui promeuvent la santé physique et psychologique, pour réduire l'incidence et/ou la gravité de déficits futurs. » (123).

Nous avons exposé dans l'introduction de cette thèse les grandes classes de facteurs de risque modifiables que sont des capacités cardio-respiratoire et fonctionnelle altérées, le tabagisme et la dénutrition. Dans le cadre de la préparation à la chirurgie thoracique pour CBNPC, les principales interventions relatives à cet ensemble appelé « préhabilitation » ayant été évaluées dans la littérature sont le réentrainement à l'effort, et bien sûr l'aide au sevrage tabagique, qui en sont les constantes majeures. La plupart des programmes évalués intègrent aussi des exercices respiratoires et une éducation à la période postopératoire où le patient est mobilisé précocement dans le cadre des protocoles de RAAC. Les travaux évaluant les effets d'une intervention nutritionnelle sont rares. Malheureusement, dans les données actuellement à notre disposition, l'évaluation du soutien psycho-social n'a jamais pu être relevée.

3.2. Accessibilité à la préhabilitation ; exemple d'un fonctionnement local

Malgré les recommandations concernant la réhabilitation respiratoire pour les patients atteints de pathologies respiratoires chroniques hors cadre oncologique, telles que notamment la BPCO (124), le nombre de structures ainsi que leur capacité d'accueil restent limitées. Ainsi en France, une proportion inférieure à 10% des patients souffrant de pathologies respiratoires invalidantes peut bénéficier chaque année d'une prise en charge globale de réhabilitation respiratoire (125). Face à cette situation, rares sont les centres de soins à proposer une prise en charge systématique des patients en attente de résection pulmonaire pour CBNPC en dehors de protocoles de recherche clinique.

Depuis 2014, les services de pneumologie, chirurgie thoracique et de physiologie respiratoire du CHU de Rouen ont développé un partenariat avec l'association d'Aide à Domicile aux Insuffisants Respiratoires (ADIR), afin de créer une filière de préhabilitation pour les patients à risques postopératoires nécessitant une chirurgie thoracique (Figure 16).

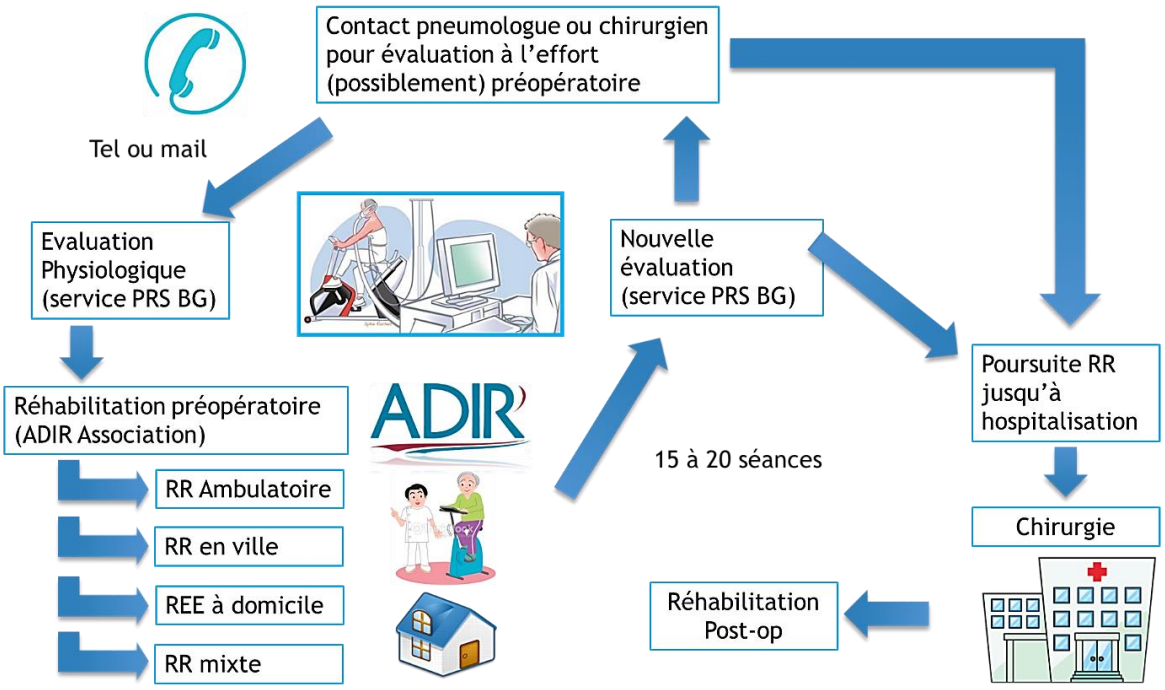


Figure 16 : Schéma du parcours de préhabilitation proposé par le CHU de Rouen et l'association ADIR.

3.3. Programme de préhabilitation proposé à l'association ADIR

3.3.1. Planification

Les patients sont adressés de façon privilégiée vers le centre de réhabilitation de l'ADIR Association qui joue un rôle de coordination locale. En cas d'éloignement géographique important, le prêt d'un matériel à domicile ou un relais chez un kinésithérapeute de ville peut avoir lieu au décours de la séance d'initiation au programme, qui continue d'être coordonné par l'association ADIR (Figure 16).

La fréquence des séances proposées à tous les patients adressés en réentrainement préopératoire est par défaut de 3 à 5 fois par semaine, jusqu'à l'hospitalisation en service de chirurgie thoracique. Celle-ci est modulée selon les semaines, en fonction des thérapeutiques associées (notamment radio-chimiothérapie néoadjuvante) et des examens complémentaires.

Chaque séance ambulatoire, supervisée par un kinésithérapeute, dure environ 1h30 et se compose des éléments abordés ci-dessous.

3.3.2. Réentrainement en endurance

Les exercices aérobies sont proposés sur cyclo-ergomètre ou tapis de marche, et s'inspirent des données de la littérature associées à la pratique clinique du centre.

La première séance d'exercice aérobie est le plus fréquemment de 15 à 20 min en fonction de la tolérance du patient, toute situation d'échec à la première séance devant être évitée. Dans un premier temps, l'objectif consiste à augmenter la durée de l'effort, pour obtenir un minimum 30 minutes et plus d'activité physique modérée à intense à raison de 3 à 5 fois par semaine, tel que recommandé par *l'American College of Sports Medicine* (ACSM) pour stimuler et maintenir la capacité aérobie chez l'ensemble des individus (126). Après explication du protocole, la durée de l'effort en endurance est donc augmentée de 5 à 10

minutes à chaque séance on fonction de la tolérance, pour atteindre un total de 45 min. Cette durée totale comprend donc 35 minutes d'effort calibré, précédées de 5 minutes d'échauffement équivalent à la montée en charge pour atteindre la puissance souhaitée, et enfin 5 minutes de récupération active à une puissance libre.

	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min
Objectif 1	Ech	SV1	RA						
Objectif 2	Ech	SV1	SV1	RA					
Objectif 3	Ech	SV1	SV1	SV1	RA				
Objectif 4	Ech	SV1	SV1	SV1	SV1	RA			
Objectif 5	Ech	SV1	SV1	SV1	SV1	SV1	RA		
Objectif 6	Ech	SV1	SV1	SV1	SV1	SV1	SV1	RA	
Objectif 7	Ech	SV1	SV1	SV1	SV1	SV1	SV1	SV1	RA
Objectif 8	Ech	SV1	SV1	SV1	SV1	SV1	SV1	+ 10 W	RA
Objectif 9	Ech	SV1	SV1	SV1	SV1	SV1	+ 10 W	+ 10 W	RA
Objectif 10	Ech	SV1	SV1	SV1	SV1	+ 10 W	+ 10 W	+ 10 W	RA
Objectif 11	Ech	SV1	SV1	SV1	+ 10 W	+ 10 W	+ 10 W	+ 10 W	RA
Objectif 12	Ech	SV1	SV1	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	RA
Objectif 13	Ech	SV1	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	RA
Objectif 14	Ech	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	RA
Objectif 15	Ech	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 20 W	RA
Objectif 16	Ech	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 20 W	+ 20 W	RA
Objectif 17	Ech	+ 10 W	+ 10 W	+ 10 W	+ 10 W	+ 20 W	+ 20 W	+ 20 W	RA
Objectif 18	Ech	+ 10 W	+ 10 W	+ 10 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	RA
Objectif 19	Ech	+ 10 W	+ 10 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	RA
Objectif 20	Ech	+ 10 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	RA
Objectif 21	Ech	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	RA
Objectif 22	Ech	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 30 W	RA
Objectif 23	Ech	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 30 W	+ 30 W	RA
Objectif 24	Ech	+ 20 W	+ 20 W	+ 20 W	+ 20 W	+ 30 W	+ 30 W	+ 30 W	RA
Objectif 25	Ech	+ 20 W	+ 20 W	+ 20 W	+ 30 W	+ 30 W	+ 30 W	+ 30 W	RA

Figure 17 : principe d'incrémentation de durée et de charge de l'entrainement en endurance inspiré de Debigaré et al. (127). Ech : échauffement ; SV1 : premier seuil ventilatoire ; RA : récupération active ; W : puissance en watts.

Dans un second temps, une fois la durée d'effort planifiée atteinte, la charge de travail peut être augmentée à son tour. L'intensité du réentrainement est initialement fixée au premier seuil ventilatoire (SV1) déterminé au cours de l'EFX. Un incrément de charge est ensuite réalisé par palier d'environ 10 watts selon la tolérance évaluée via l'échelle de Borg (128). Cet incrément est toujours débuté par la fin de la phase d'effort afin de préserver la durée de stimulation cardio-respiratoire.

Ce protocole modélisé en figure 17, est inspiré de celui établi par Debigaré et al. auprès de patients en attente de chirurgie de réduction de volume pulmonaire pour emphysème (127). L'objectif est de proposer une évolution progressive, mais systématiquement supérieure à la séance précédente, si les constantes (fréquence cardiaque, saturation en oxygène et tension artérielle) le permettent.

3.3.3. Renforcement musculaire

Le renforcement musculaire est précédé d'une évaluation de la charge maximale pouvant être mobilisée une seule fois sur l'ensemble de l'amplitude définie (1-RM). Cette 1-RM permet d'étalonner la charge du renforcement proposé.

La mesure de la 1-RM, a été décrite comme bien tolérée pour évaluer la fonction d'extension des membres inférieurs sur presse chez les patients atteints de BPCO au cours d'un programme de réhabilitation respiratoire (129). En pratique, le thérapeute installe le patient sur la presse à quadriceps à 90° de flexion de genou et demande la réalisation d'une extension complète (en veillant à éviter le recurvatum et toute compensation). Deux tests de familiarisation à charge faible sont recommandés avant d'incrémenter la charge. L'examinateur augmente ou diminue ensuite la charge pour s'approcher de la 1-RM avec une minute d'intervalle entre chaque contraction. Cette méthode d'évaluation a été évaluée comme fiable et reproductible chez des patients atteints de pathologies respiratoires et cardiologiques et peut donc être tout à fait transposable aux patients accueillis en réhabilitation dans un cadre préopératoire de cancer pulmonaire (130, 131). Bien que principalement décrite concernant la chaine d'extension des membres inférieurs, le principe

de la 1-RM peut s'appliquer à divers muscles ou fonctions de façon fiable chez des patients sportifs ou sédentaires de tous âges (132). L'utilisation d'une presse à quadriceps et d'un banc de musculation multifonction permet de réaliser une évaluation globale des différentes grandes fonctions musculaires des membres inférieurs comme supérieurs selon un mode isotonique.

Figure 18 : renforcement musculaire en résistance sur presse à quadriceps et banc multifonction chez une patiente en attente de résection pulmonaire pour CBNPC.

Suite à l'évaluation préalable, le renforcement musculaire est calibré à 60-70% de la 1-RM sur trois composantes principales : presse à quadriceps, extension et traction des membres supérieurs (Figure 18), à raison de 3 séries de 12 mouvements. Ces niveaux de résistances ont été établis sur la base des protocoles de renforcement musculaire évalués chez des patients atteints de BPCO dans le cadre de la réhabilitation respiratoire conventionnelle (133). La charge est augmentée régulièrement selon la tolérance (objectif de 4/10 « effort un peu difficile » à 6/10 « effort difficile à très difficile » sur l'échelle de Borg modifiée) (128). La conjonction de cette planification de renforcement musculaire en résistance à un

entrainement aérobie à charge modérée rapporte des bénéfices supérieurs à un entrainement en endurance seul chez les patients atteints de BPCO (134).

3.3.4. Education aux techniques de kinésithérapie respiratoire.

Lors de la séance d'initiation, les patients sont éduqués aux différentes techniques de kinésithérapie respiratoire.

Drainage bronchique

L'éducation au drainage bronchique autonome consiste dans un premier temps à faire prendre conscience au patient de son possible encombrement bronchique par des expirations à glotte ouverte. En effet, la plupart des patients présentant une hypersécrétion chronique sont habitués à vivre avec un encombrement sans nécessairement ressentir le besoin de se drainer. Des rappels réguliers sont réalisés au cours des séances suivantes afin de vérifier l'assimilation. Savoir évaluer la présence d'un encombrement bronchique est donc une première nécessité.

En ce qui concerne les techniques de drainage bronchique comme d'auto-drainage, elles sont basées sur la « modulation du flux expiratoire », terme synthétisant une large part des techniques reconnues dans la dernière conférence de consensus en kinésithérapie respiratoire (135). Synthétiquement, la modulation du flux expiratoire a pour objectif de créer un flux turbulent au niveau des différents étages bronchiques, afin d'améliorer la clairance des sécrétions. Ainsi, le kinésithérapeute et le patient utilisent les bruits expiratoires émis selon différents débits associés à une ouverture plus ou moins importante de la glotte. La mobilisation efficace des sécrétions bronchiques est perçue lors de la genèse de crépitants expiratoires de plus en plus précoces ou forts sur le temps expiratoire, jusqu'à leur évacuation à l'aide d'une expiration forcée à glotte ouverte ou d'une toux dirigée (136). Il n'existe à ce jour aucune preuve scientifique valide de l'effet d'un drainage bronchique réalisé de manière répété au cours de la période préopératoire sur les résultats postopératoires. L'objectif est

d'obtenir une maîtrise préalable des techniques de désencombrement bronchique, et de développer la capacité à percevoir un encombrement bronchique potentiel en postopératoire.

Toux protégée

Bien que l'analgésie postopératoire soit aujourd'hui mieux maitrisée, la toux reste fréquemment un effort induisant des surpressions intrathoracique et abdominale. La contention pariétale manuelle au moment des efforts de toux, aussi appelée toux protégée, est une manœuvre pouvant être facilement répétée avant la chirurgie pour être reproduite en postopératoire. L'objectif de la toux protégée est de limiter les mouvements et l'étirement douloureux en regard de la zone d'intervention et du drain thoracique.

Travail inspiratoire et spirométrie incitative (SI)

L'apparition d'atélectasies (plus ou moins importantes) est un phénomène quasi inévitable au cours de la période postopératoire immédiate en raison des effets physiopathologiques de l'anesthésie, de la ventilation mécanique, et des modifications de la pression thoraco-abdominale (29). En chirurgie thoracique cardiaque, la kinésithérapie respiratoire postopératoire, incluant diverses techniques d'exercices inspiratoires telles que la SI et les respirations profondes (« *deep breathing* »), limite l'installation des atélectasies et des complications pulmonaires qui en découlent (137). Cependant, leur mise en place systématique en période préopératoire versus postopératoire uniquement n'a pas montré de supériorité quant au développement de complications postopératoires (138).

Les deux dernières revues Cochrane concernant une thérapie préalable par SI ne rapportent pas de diminution des complications après chirurgie thoracique ou chirurgie abdominale (139, 140). Plutôt que d'exclure cette thérapie, ces deux dernières revues pointent le manque d'essais randomisés de qualité méthodologique suffisante pour statuer sur l'effet réel de cette technique. Bien que la SI n'ait pas fait ses preuves d'efficacité comparativement à une autre technique inspiratoire, l'utilisation d'une SI en volume semble supérieure par rapport à une SI en débit, notamment versus à des exercices de ventilation

profonde (141). Une utilisation commune de l'ensemble des techniques inspiratoires en fonction du degré d'adhésion du patient semble par ailleurs la plus pertinente (142).

Une explication de l'efficacité de l'ensemble des techniques préopératoires d'inspiration profonde pour réduire les complications pulmonaires reposerait sur la préparation et la motivation préopératoire, permettant une initiation postopératoire des exercices ventilatoires dès le retour à l'état de conscience lors de la phase de réveil. Dans un service de chirurgie conventionnel (hors soins intensifs postopératoires), l'intervention du kinésithérapeute débute avec un potentiel délai d'une journée, alors que plus de la moitié des complications respiratoires se développent dans les 48 heures après chirurgie (143). L'étude de Boden et al. illustre parfaitement ce concept dans le cadre des soins de kinésithérapie respiratoire péri-opératoire de chirurgie abdominale (144). Cet essai randomisé compare une sensibilisation à la kinésithérapie postopératoire à l'aide d'un livret expliquant les exercices respiratoires et la déambulation précoce, versus une consultation de 30 minutes avec un kinésithérapeute spécialisé. Les résultats rapportent une diminution de moitié des complications pulmonaires dans le groupe de patients ayant bénéficié de la séance unique avec un kinésithérapeute (144).

3.3.5. Entrainement des muscles inspirateurs (EMI)

L'EMI ne doit pas être confondu avec la SI volumétrique inspiratoire destinée à stimuler une inspiration profonde et non à renforcer la musculature inspiratoire. L'EMI est une technique de renforcement musculaire à part entière réalisée à l'aide à un appareil résistif type valve à seuil, ou un dispositif d'hyperpnée isocapnique. Dans le cadre du présent programme, le recours à une valve à seuil (Threshold IMT®, Respironics), visible en figure 19, a été privilégié pour une question de coût moindre du dispositif et une gestion de l'hygiène plus maitrisable grâce à un matériel à patient unique.

Figure 19 : dispositif de renforcement des muscles inspirateurs utilisé au cours du programme de réentrainement préopératoire ; valve à seuil (Threshold IMT®, Respironics)

La force des muscles inspiratoires peut être estimée de façon non invasive sur la base de mesures statiques des pressions maximales inspiratoires à la bouche (Pimax). Cette Pimax peut alors à son tour être utilisée pour calibrer le renforcement des muscles inspirateurs en résistance, calqué sur un renforcement musculaire conventionnel comme nous l'avons vu précédemment. La mesure de la Pimax a été réalisée à l'aide d'un matériel de type manomètre électronique (POWERbreathe® KH2), l'embout buccal étant positionné à la bouche de façon hermétique, avec l'utilisation d'un pince nez. L'examinateur incite le sujet à faire des efforts inspiratoires maximaux et soutenus à des niveaux pulmonaires proches du volume résiduel. Le patient réalise 5 à 8 essais et la meilleure valeur de 3 essais consécutifs avec une variabilité de moins de 10% est retenue (145).

La résistance initiale proposée est calibrée au minimum à 30% de la Pimax et augmentée régulièrement selon la tolérance avec un objectif de sensation en fin d'entrainement compris entre 4/10 « effort un peu difficile » et 6/10 « effort difficile à très difficile » sur l'échelle de Borg modifiée (128). Un entrainement quotidien en autonomie de 15 min est encouragé après l'initiation à l'utilisation du matériel sur une durée de 2 à 4 semaines minimum et encouragé jusqu'à la chirurgie si le délai est plus long.

Ainsi, l'Entrainement des Muscles Respiratoires (EMR) en force, et plus spécifiquement l'EMI, réalisé avant chirurgie majeure est probablement la technique de kinésithérapie présentant l'un des plus forts niveaux de preuve avec la préhabilitation. En effet, la dernière méta-analyse publiée en 2018 par Ge et al. (146), estime un risque relatif de 0.59 [IC 95% 0.47

à 0.74] de développer une complication pulmonaire, ainsi qu'une différence moyenne sur la durée de séjour hospitalier de -1.15 jours [IC 95% -2.10 à 0.20], en faveur du renforcement inspiratoire avant chirurgie thoracique cardiopulmonaire et abdominale haute. L'analyse séquentielle des essais, complétant la méta-analyse réalisée, amène les auteurs à encourager l'intégration de cette technique dans la pratique clinique (146).

3.3.6. Aide au sevrage tabagique

Le tabagisme est un facteur de risque prépondérant de complications postopératoires. Comme nous l'avons abordé dans l'introduction, le risque de complications est multiplié par trois à six chez les patients fumeurs en comparaison aux non-fumeurs (42, 43).

Les données relatives au sevrage tabagique dans les semaines précédant l'intervention chirurgicale sont contradictoires dans des travaux plus anciens (147). Cependant dans les travaux plus récents on retrouve une diminution de moitié du taux de complications postopératoires dans la catégorie des ex-fumeurs par rapports aux fumeurs actifs (148). Les récents travaux de Fukui et al. rapportent une diminution progressive du risque de complications pulmonaires à chaque tranches de délai de sevrage par rapport aux non-fumeur : fumeur actif Odds Ratio (OR) = 12,9 ; sevrage < 1 mois OR = 10,3 ; entre 1 et 3 mois OR = 8,5 ; entre 3 et 6 mois OR = 6,3 ; entre 6 et 12 mois OR = 6,0 ; > 12 mois OR = 5,0 (42). Une éducation incluant des informations objectives basées sur la science doit donc être apportée pour favoriser un sevrage le plus rapide possible. Une prudence doit cependant être de mise dans la délivrance de ce soutien au sevrage tabagique afin de ne pas induire une situation d'échec humiliante pour le patient qui pourrait aller jusqu'à la mise en retrait de l'ensemble de la préhabilitation (149).

La consultation kinésithérapique initiale inclut un temps de discussion dédiée, précédée d'une évaluation destinée à (re)déterminer les niveaux de dépendance nicotinique (à l'aide du questionnaire Fagerström en deux questions), psychologique (effets positifs associés à la consommation tabagique) et comportementale (relatif à l'automatisation de la consommation en fonction des habitudes de vie) (150, 151). La fréquence et la durée des

séances de réentrainement permet d'aborder fréquemment le sujet avec le patient et de prescrire ou ajuster des traitements nicotiniques de substitutions afin d'accompagner les patients dans leur démarche (152).

3.3.7. Surveillance nutritionnelle et soutien psychologique

Le parcours de préhabilitation proposé à ce jour à l'association ADIR est uniquement dispensé par des kinésithérapeutes. Ainsi, la prise en charge nutritionnelle et psycho-sociale s'apparente à des conseils généraux et une veille permettant d'alerter le prescripteur initial en cas de difficulté.

Une chirurgie majeure telle que la chirurgie thoracique expose de fait le patient à un risque de dénutrition (48). Ainsi, en accord avec les indications de l'équipe médicale une surveillance du poids et de la prise des compléments nutritionnels oraux éventuellement prescrits est régulièrement réalisée au cours du programme.

Le projet chirurgical et le contexte oncologique peuvent exposer le patient à un niveau d'anxiété important pouvant influencer les résultats eux-mêmes de la chirurgie (153). Malgré un niveau de preuve encore faible, une préparation psychologique avant chirurgie favorise une diminution de la douleur et un meilleur vécu de la période postopératoire (154). Bien que la kinésithérapie ne puisse remplacer une prise en charge psychologique spécialisée, voire médicamenteuse en cas de d'anxiété non maitrisée, les techniques de respiration profonde ainsi que l'activité physique sont préconisées pour leurs effets potentiels dans la gestion du stress (155, 156).

3.4. Etude n°3 : Effets de la préhabilitation sur l'efficience ventilatoire des patients atteints de CBNPC.

3.4.1. Présentation et rationnel de l'étude.

Nous avons exposé précédemment la construction du programme de préhabilitation proposé à l'association ADIR. L'évaluation des résultats générés au terme de ce programme a été l'un des projets à l'origine de cette thèse.

Plusieurs travaux ont intégré une évaluation cardio-respiratoire d'effort de patients atteints de CBNPC bénéficiant de programmes de réhabilitation préopératoire innovants. La $\dot{V}O_2$pic, en tant que marqueur permettant la stratification du risque postopératoire est un critère de jugement ayant attiré l'attention de nombreuses équipes. Leurs résultats convergent en faveur du recours à l'exercice physique préopératoire pour optimiser la $\dot{V}O_2$pic avant chirurgie de résection pulmonaire (157-166). Au-delà d'une présomption clinique, l'évaluation de notre pratique et de sa cohérence avec la littérature semblait nécessaire.

Parallèlement à la corrélation importante entre la $\dot{V}O_2$pic et le risque de complications postopératoires, certains travaux se sont intéressés à l'évaluation de l'efficience ventilatoire des patients atteints de CBNPC éligibles à la chirurgie (167-169).

Au cours de l'effort, la ventilation ($\dot{V}E$) a pour rôle dans un premier temps de réguler la pression artérielle en dioxyde de carbone ($PaCO_2$) générée par l'oxydation des substrats énergétiques pour un effort modéré aérobie ainsi que de compenser l'acidose métabolique qui s'engage au cours d'un effort à charge plus élevée.

L'efficience ventilatoire peut s'appréhender par l'évaluation du débit ventilatoire total engagé pour évacuer l'accroissement de CO_2 produit par la charge de travail (rapport $\dot{V}E/\dot{V}CO_2$). Ainsi, on observe typiquement une diminution du rapport $\dot{V}E/\dot{V}CO_2$ dans une première portion d'un effort incrémental jusqu'à une valeur minimale (nadir). Cette valeur nadir intervient entre le seuil anaérobie (« *Anaerobic Threshold* » AT) associé au premier seuil ventilatoire (SV1), où la lactatémie commence à augmenter tout en étant tamponnée

transitoirement par les ions bicarbonates (HCO_3-), et le seuil de compensation ventilatoire (« *Ventilatory Compensation Point* » VCP ou SV2), où la VE augmente une seconde fois brutalement pour compenser l'acidose métabolique induite par l'accroissement de la lactatémie (78).

Au cours d'une EFX croissante, l'analyse de ce rapport $\dot{V}E/\dot{V}CO_2$ peut être appréhendée sous différents angles : 1) au moment du seuil de compensation ventilatoire (SV2) ; 2) à sa valeur dite « nadir » (ou asymptotique, intervenant conventionnellement entre le SV1 et le SV2) ; 3) à travers le coefficient de pente $\dot{V}E/\dot{V}CO_2$, correspondant à la régression linéaire du rapport entre l'augmentation de la ventilation minute ($\Delta\dot{V}E$) et l'augmentation du débit de dioxyde de carbone expiré ($\Delta\dot{V}CO_2$). Ces trois valeurs issues de l'analyses du rapport $\dot{V}E/\dot{V}CO_2$ ont été décrites comme des méthodes valides d'évaluation de l'efficience ventilatoire, avec un intérêt dans l'interprétation de l'EFX (78). Un exemple de la mesure de ces trois valeurs est proposé en Figure 20.

Chez les individus déconditionnés ou présentant une pathologie limitant l'effort, le SV1 comme le SV2 ne sont pas toujours discernables, ou peuvent intervenir pendant la phase descendante du rapport $\dot{V}E/\dot{V}CO_2$, et donc compromettre l'interprétation du vrai nadir, ce qui enjoint à privilégier l'utilisation du coefficient de pente pour apprécier l'efficience ventilatoire.

Une valeur de pente $\dot{V}E/\dot{V}CO_2$ >35 a été déterminée comme un seuil péjoratif au-delà duquel les complications respiratoires et la mortalité postopératoires sont majorées (167-169). Cet indicateur est d'autant plus pertinent qu'il est corrélé de manière indépendante aux complications postopératoires indépendamment des autres facteur communément retenus (167, 169). Certains auteurs proposent son intégration dans les algorithmes de stratification du risque postopératoire (170).

A l'inverse de la $\dot{V}O_2$pic ayant suscité l'intérêt de nombreuses équipes comme évoqué précédemment, la sensibilité de la pente $\dot{V}E/\dot{V}CO_2$ à l'entrainement n'avait pas été décrite dans la littérature. Dans ce contexte, la problématique soulevée dans l'étude présentée ci-dessous était d'évaluer si un programme de réhabilitation préopératoire pouvait modifier de façon favorable l'efficience ventilatoire évaluée par la pente $\dot{V}E/\dot{V}CO_2$ chez les patients en attente de chirurgie de résection pulmonaire pour CBNPC. Nous avions émis l'hypothèse que

le coefficient de pente $\dot{V}E/\dot{V}CO_2$ serait significativement diminué après réhabilitation préopératoire, ce qui signerait une amélioration de l'efficience ventilatoire des patients.

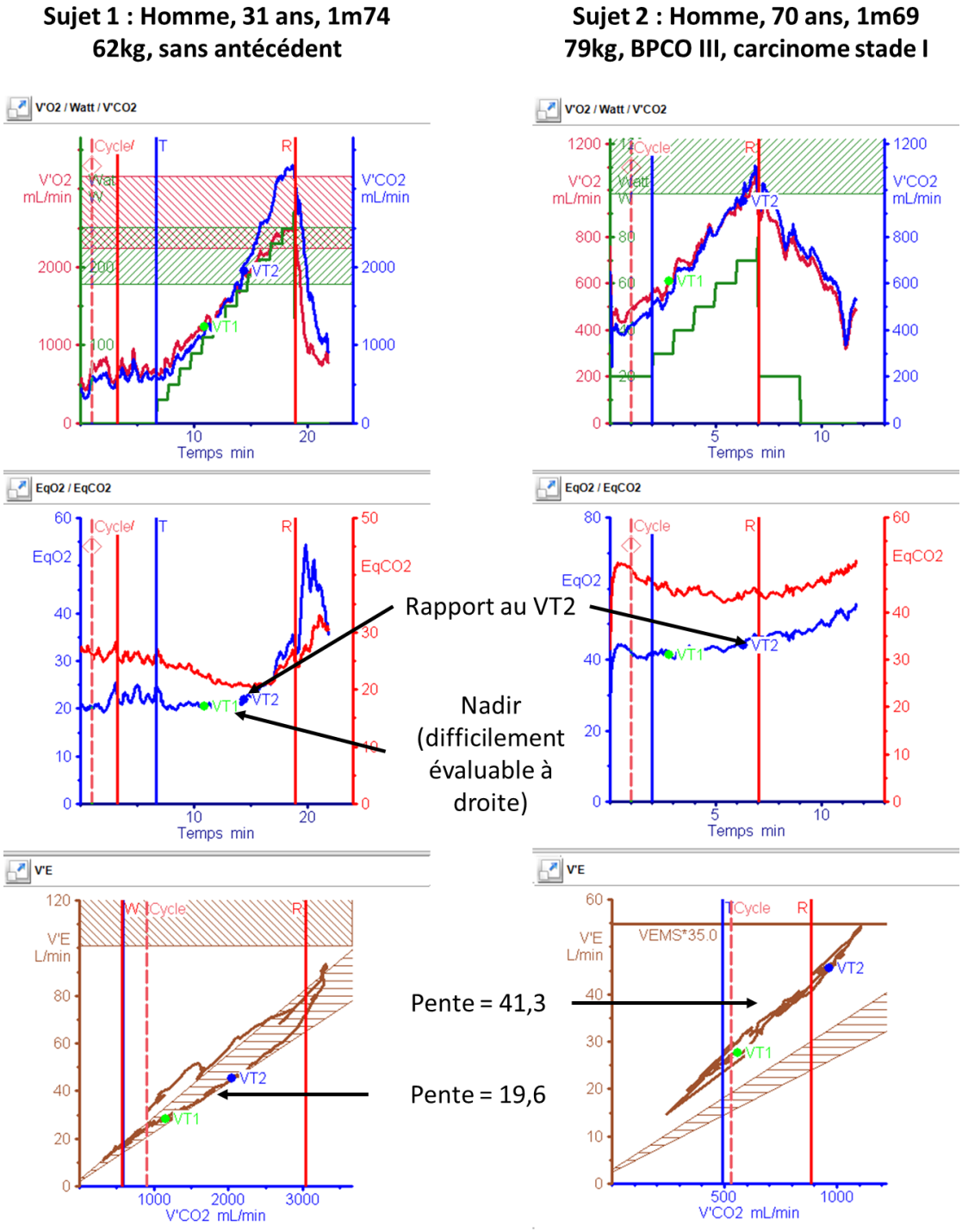


Figure 20 : exemple de l'évolution du rapport $\dot{V}E/\dot{V}CO_2$, repérage du nadir, et mesure de la pente au cours d'une EFX incrémentale, chez un sujet sans antécédent et un patient atteint de BPCO et cancer pulmonaire.

Les résultats de ce travail ont été rapportés sous la forme d'un article original publié dans la revue Journal of Thoracic and CardioVascular Surgery (JTCVS), dont l'impact factor était de 4.45 en 2019 (Rang B) (171).

Ma contribution dans ce travail a été :

- Identification de la question de recherche, rédaction du projet ;

- Démarches administratives liées à la recherche : déclaration du traitement des données selon la méthodologie de référence MR-003 auprès de la CNIL et demande d'avis auprès du CERDE du CHU de Rouen. Ce travail étant une recherche portant sur des données de santé et n'impliquant pas directement la personne humaine (hors RIPH) de par son caractère rétrospectif, il n'a pas été nécessaire de réaliser une demande d'avis auprès d'un CPP ;

- Screening des dossiers patients d'ADIR Association et récupération des données manquantes dans les bases de données informatiques ;

- Extraction des données sous format Excel ;

- Participation à l'élaboration du plan statistique et à la réalisation des comparaisons ;

- Rédaction et soumission du manuscrit.

Version publiée non-libre de droit :

Gravier FE, Bonnevie T, Boujibar F, Medrinal C, Prieur G, Combret Y, et al. Effect of prehabilitation on ventilatory efficiency in non-small cell lung cancer patients: A cohort study. J Thorac Cardiovasc Surg.2019 Jun;157(6):2504-12 e1.

Lien Pubmed : https://pubmed.ncbi.nlm.nih.gov/30982587/

3.4.2. Discussion de l'étude n°3

Résultats principaux

Sur l'ensemble de la cohorte des patients ayant bénéficié du programme de préhabilitation, nous avons mesuré une amélioration de la capacité maximale à l'exercice d'environ 10 watts (moyenne 73,16 ± 21,64 watts, versus 82,76 ± 23,98 watts, p<0,01), et de 10% de la $\dot{V}O_2$pic initiale (médiane 13,2 ml/kg/min (11,9-14,7) versus 14,8 ml/kg/min (13,1-16,4), p<0,01). Ces effets observés à l'issue du programme de préhabilitation sont cohérents avec les effets décrits dans la littérature concernant la $\dot{V}O_2$pic et la puissance développée à l'EFX (164, 166). Cependant, contrairement à notre présomption, nous n'avons pas constaté d'optimisation de l'efficience ventilatoire mesurée grâce à la pente $\dot{V}E/\dot{V}CO_2$.

Le second résultat développé grâce aux analyses exploratoires réalisées est l'identification d'une charge totale d'entrainement approximative de 15 séances du programme de préhabilitation ambulatoire proposé pour obtenir des bénéfices physiologiques significatifs. Bien que la validité de de la courbe ROC pour déterminer ce seuil ne soit pas suffisante (aire sous la courbe = 0,63 [IC 95 %, 0,47 - 0,79] ; Figure 3 de l'article), nous avons choisi arbitrairement de tester cette hypothèse sur la base d'une présomption clinique. Nous avons mis en évidence que les patients ayant réalisé 15 séances présentaient en moyenne des bénéfices significativement supérieurs à ceux ayant réalisé un nombre de séance moindre avec une amélioration de $\dot{V}O_2$pic de 1,9 ± 1,9 ml/kg/min versus 0,1 ± 1.4 ml/kg/min (p<0.01).

Enfin, les analyses exploratoires réalisées selon le stade du CBNPC montrent que les patients adressés à des stades plus avancés (IIIB et plus), bénéficient tout autant des programmes de préhabilitation que les patients de stade plus précoce (Tableau 4 de l'étude précédente). Ainsi, la préhabilitation tient toute son importance pour maintenir et optimiser le niveau fonctionnel des patients de stade avancé bénéficiant d'un projet chirurgical dans le cadre d'une thérapie multimodale incluant notamment une chimiothérapie néoadjuvante.

Comparaison à des résultats discordants

Suite à notre étude publiée en juin 2019, nous avons noté la publication d'une seconde étude portant sur la même thématique. L'équipe de Perrotta et al. a réalisé une évaluation rétrospective de 25 patients atteints de BPCO participant à un programme de réhabilitation préopératoire avant résection pulmonaire pour CBNPC, entre décembre 2015 et janvier 2017 (172). Bien que ce travail s'intéresse spécifiquement aux patients présentant une BPCO comme comorbidité, les caractéristiques de la population étudiée étaient semblables à celles de notre étude avec 68% d'hommes, un âge moyen de 62 ans, un IMC moyen de 26 kg/m^2 et un VEMS moyen d'environ 61% de la théorique. A l'inverse de nos résultats, cette équipe retrouve une amélioration significative du coefficient de pente $\dot{V}E/\dot{V}CO_2$ (Figure 21). Cette divergence entre nos résultats peut se discuter sous différents points.

Table 2. Spirometry and cardiopulmonary exercise test parameters before and after the three-week pulmonary rehabilitation program.

Parameter	Before	After	p
FEV_1, % predicted	61.5 ± 22.0	61,9 ± 21.1	ns
VC, % predicted	81.1 ± 19.0	82.0 ± 17.8	ns
FEV_1/VC	54.1 ± 13.1	54.5 ± 14.1	ns
DLCO, % predicted	67.2 ± 18.1	67.5 ± 13.2	ns
VO_{2peak}, mL/kg per min	14.7 ± 2.5	18.2 ± 2.7	< 0,001
VO_{2peak}, % predicted	64.0 ± 19.2	81.1 ± 18.0	< 0,001
V_E/VCO_2 slope	32.0 ± 2.8	30.1 ± 4.0	< 0,01
Peak HR, % predicted	92.1 ± 1.8	92.3 ± 2.0	ns
Peak RER	1.2 ± 0.3	1.3 ± 0.2	ns
Breathing reserve, %	24.3 ± 6.1	24.7 ± 6.4	ns

ns: not significant; VO_{2peak}: peak oxygen uptake; V_E: minute ventilation; VCO_2: carbon dioxide output; and RER: respiratory exchange ratio.

Figure 21 : évaluation de la fonction respiratoire et cardiopulmonaire de la cohorte de Perrotta et al. 2019 (172)

Tout d'abord, malgré des caractéristiques générales proches, la cohorte de Perrotta et al. présente cependant un trouble de diffusion pulmonaire moins sévère que dans notre étude avec une DLCO d'environ 67.2 ± 18.1 vs 54.7 ± 17.0 % de la théorique respectivement. De même, l'efficience ventilatoire initiale était moins péjorative dans cette seconde cohorte étant donné que le coefficient de pente $\dot{V}E/\dot{V}CO_2$ initial moyen était de 32.0 ± 2.8, et en médiane de 37.1 (33.8-43.4) dans notre étude. En conséquence, la cohorte de patients que nous avons observée présentait un risque postopératoire en lien avec une inefficience ventilatoire

notable, avec une médiane supérieure au seuil de risque de 35 précédemment décrit (167, 169). Il est possible qu'une inefficience plus marquée soit d'autant plus figée car intrinsèquement liée à des facteurs structurels, tels que la distension thoracique, ou la capacité de diffusion pulmonaire.

Deuxièmement, les programmes proposés sont différents dans leurs modalités d'application. Le programme proposé par Perrotta et al. est en moyenne plus dense, car systématisé à raison de 5 fois par semaine sur une période de 3 semaines, contre 3 à 5 fois par semaine sur une période de 3 à 6 semaines environ dans notre étude (bien qu'indéterminée dans les faits car allant jusqu'à la chirurgie). Le protocole d'entrainement italien était basé sur un entrainement à haute intensité (>70% de la Pmax), contre un entrainement à intensité modérée au premier seuil ventilatoire (50 à 60% de la Pmax) dans notre pratique. Notons qu'une augmentation systématique d'environ 10 watts était pratiquée de part et d'autre, sur la base de la perception de l'effort. Enfin, les séances de réentrainement étaient d'environ 3h00 par jour contre 1h30 dans notre travail ce qui implique nécessairement un volume d'entrainement plus conséquent en faveur de la cohorte italienne. Le volume d'entrainement étant un facteur essentiel de l'optimisation physiologique, ceci peut expliquer la supériorité des bénéfices retrouvés tant sur l'efficience ventilatoire que sur la $\dot{V}O_2$pic (+3.5 points) dans la cohorte italienne.

Troisièmement, malgré nos différences quant à l'interprétation des résultats, les valeurs absolues obtenues dans chacune des études sont relativement proches avec une diminution du coefficient de pente $\dot{V}E/\dot{V}CO_2$ de 1.9 points de moyenne dans l'expérience de Perotta et al. et une diminution de 1.7 points de médiane dans notre étude (bien que non significative, p=0.09). En ne retenant que les patients ayant bénéficié d'une charge d'entrainement minimale de 15 séances dans notre analyse exploratoire, cette diminution de la pente $\dot{V}E/\dot{V}CO_2$ s'affirme dans des proportions significatives (p=0.02). Cette sous-analyse soutient l'hypothèse selon laquelle les patients qui auraient bénéficié de moins de 15 séances n'auraient pas reçu un volume d'entrainement suffisant pour optimiser leur efficience ventilatoire.

Enfin, au-delà de la possible diminution du coefficient de pente, la significativité clinique de ce changement reste inconnue. Le seuil de 35 étant reconnu comme un facteur de risque, nous avions donc proposé d'analyser la variation de la proportion de patients de part et d'autre de cette valeur seuil avant et après le programme de préhabilitation. Un total de 26 patients (52%) avait une pente $\dot{V}E/\dot{V}CO_2$ > 35 avant préhabilitation et n'ont pas changé de classe de risque post-programme. A l'inverse, 14 patients (28%) présentaient une pente $\dot{V}E/\dot{V}CO_2$ inférieure 35 avant et après la préhabilitation. Sept patients ont diminué leur pente $\dot{V}E/\dot{V}CO_2$ et sont passés en dessous du score de 35 à la suite de la prise en charge, et à l'opposé 3 patients ont détérioré leur coefficient qui a dépassé le score de 35. Au final, il n'y a pas de différence dans la proportion de patients avec une pente $\dot{V}E/\dot{V}CO_2$ inférieure ou supérieur au seuil de risque postopératoire évalué à 35 avant et après la préhabilitation proposée (McNemar's test, p = 0,34).

Au total, bien que les interprétations soient contradictoires, l'efficience ventilatoire est probablement un marqueur de risque moins modifiable. Comme nous l'avons soulevé dans notre article, ceci est certainement dû au fait que l'efficience ventilatoire est liée à des éléments structuraux de la fonction respiratoire (obstruction, distension, capacité de transfert), qui ne sont pas ou peu modifiés par l'entrainement dans la littérature (164, 173-175).

Au regard du faible niveau de preuve de ces deux études rétrospectives exploratoires, de futurs travaux prospectifs sont nécessaires pour répondre à cette problématique.

3.5. Etude n°4 : Effets du réentrainement préopératoire avant chirurgie de résection pour cancer broncho-pulmonaire : une revue systématique et méta-analyse.

3.5.1. Présentation et rationnel de l'étude.

Les données de la littérature commencent à se développer depuis le milieu des années 2000 sur la préhabilitation des patients en attente de chirurgie de résection pulmonaire pour CBNPC. Comme nous l'avons vu précédemment, la préhabilitation agrège tout un panel d'interventions destinées à l'optimisation physique et psychologique du patient avant l'échéance chirurgicale. Dans le cadre de cette thèse principalement axée sur l'entrainement des patients avant chirurgie thoracique pour CBNPC, la question de l'efficacité du réentrainement à l'effort a été l'une des interrogations majeures.

A l'initiation de ce projet de thèse, les deux dernières méta-analyses proposées par l'équipe de Sebio-Garcia et al. en 2016 et celle de Cavalheri et al. en 2017, apportaient des éléments de réponses préliminaires quant à l'efficacité de ces interventions (176, 177). Ces deux travaux, les plus cités dans la littérature sur la thématique de la préhabilitation en oncologie thoracique, rapportaient des résultats très favorables sur plusieurs critères de jugements importants comme le risque relatif de complications postopératoires ou la durée de séjour hospitalier rapportés dans le tableau II.

Malgré les résultats encourageants développés précédemment, il est important de rappeler que peu d'essais randomisés contrôlés (« *randomized controlled trial* » RCT) avaient été menés sur la préhabilitation des patients oncologiques dans le cadre de la chirurgie thoracique.

Tableau II : résultats principaux des méta-analyses disponibles dans la littérature à l'initiation du projet de thèse.

Critères de jugement	Sebio-Garcia et al. 2016 (176)	Cavalheri et al. 2017 (177)
RR de développer CPO	0,45 [IC 95% 0,28 à 0,73]	NE
RR de développer CPO pulmonaire	0,55 [IC 95% 0,34 à 0,89]	0,33 [IC 95% 0,17 à 0,61]
Durée de séjour hospitalier	-4,83 [IC 95% -5,90 à -3,76]	- 4,34 jours [IC 95% -5,35 à -3.03]

RR : risque relatif ; CPO : complication postopératoire CI : intervalle de confiance ; NE : non évalué.

En effet, la méta-analyse de Sebio-Garcia et al. (2016) ne compte que cinq RCT sur les 14 études retenues pour analyse (176). Les autres études étant des suivis de cohortes rétrospectives ou prospectives mais comparées à des données rétrospectives. Dans ce cadre, la méta-analyse Cochrane menée par Cavalheri et Granger en 2017 ne retient méthodologiquement que quatre RCT et ne conclut donc qu'avec un niveau de preuve faible en suivant la méthodologie de groupe de travail GRADE (*The Grading of Recommendations Assessment, Development and Evaluation*), concernant les effets de la préhabilitation sur le risque relatif de complications, la durée de séjour hospitalier, la durée de maintien du drain thoracique, ainsi que la capacité à l'exercice postopératoire (177).

Depuis ces travaux, de nouvelles études randomisées contrôlées ont été publiées dans le domaine de la préhabilitation, et notamment du réentrainement à l'effort comme composante majeure, ainsi que deux méta-analyses incluant uniquement des RCT (178, 179). La lecture de ces deux travaux a cependant soulevé certains écueils méthodologiques remettant en cause la validité des résultats publiés ; tels que la compilation de populations identiques de patients issues de sous-analyses ou de suivis de mêmes cohortes (178), ou l'inclusion non souhaitée d'essais non-randomisés (179). Enfin, une revue systématique

publiée en 2020 a exploré la littérature à la fois pré et postopératoire, mais les auteurs n'ont pas procédé à la réalisation d'une méta-analyse (180).

Au regard du niveau de preuve actuel et des nouvelles données depuis 2017, notre équipe s'est engagée dans la réactualisation d'une revue systématique et méta-analyse ciblée sur le thème du réentrainement à l'effort préopératoire.

Ce travail a été réalisé en se basant sur la méthodologie du *Cochrane Handbook for Systematic Reviews of Interventions* (181) et du PRISMA statement (182), et préalablement enregistrée publiquement sur le site dédié de l'université de York PROSPERO (www.crd.york.ac.uk/prospero: CRD42021224192).

Notre question de recherche principale était : « Quel est l'effet du réentraînement à l'effort préopératoire sur les complications postopératoires chez les patients atteints de cancer pulmonaire non à petites cellules avant résection pulmonaire ? », et secondairement « Quels sont les effets du réentraînement à l'effort préopératoire sur les paramètres cardio-respiratoires, fonctionnels, et de qualité de vie chez les patients atteints de cancer pulmonaire non à petites cellules avant résection pulmonaire ? ». Ceci peut être modélisé sur la base d'un PICOS, et ainsi exprimé de la façon suivante :

- **P**opulation : *patients with non-small cell lung cancer*
- **I**ntervention : *preoperative exercise training*
- **C**ontrol : *usual care*
- **O**utcomes : *postoperative complications (main outcome) / cardio-respiratory, functional, and quality of life parameters (secondary outcomes)*
- **S**tudy type : *only RCT*

Nous avons souhaité entreprendre une recherche de la littérature assez large incluant les principales bases de données médicales, la littérature grise et les résumés de congrès des principales sociétés savantes en lien avec le sujet. Les bases de données suivantes ont été explorées jusqu'à décembre 2020 : MEDLINE, CENTRAL, ScienceDirect, Scopus, PEDro et OpenGrey sans restriction de langage appliqué. Des recherches manuelles supplémentaires ont été effectuées à travers les résumés des congrès annuels de *l'European Respiratory Society* annual congress de 2011 à 2020; l'*American Thoracic Society* de 2009 à 2020 ; l'*European*

Society of Medical Oncology de 2016 à 2020; the *International Association for the Study of Lung Cancer* de 2008 à 2019. Les références des revues systématiques précédemment publiées sur le sujet ont aussi été manuellement explorées.

Ce travail intitulé « *Effects of exercise training in patients with non-small cell lung cancer before lung resection: a systematic review and meta-analysis*. » (Effets du réentrainement à l'effort chez les patients atteints de cancer pulmonaire non à petites cellules avant résection pulmonaire : une revue systématique et méta-analyse.), a été modélisé sous la forme d'un poster reprenant le critère de jugement principal présenté au congrès de l'ERS 2021 sous forme de communication orale, ainsi que d'un article original publié en ligne en aout 2021 dans la revue Thorax dont l'impact factor en 2020 était de 9,139 (Rang A) (183).

Les données supplémentaires en ligne de cet article sont disponibles en Annexe 3.

Ma contribution dans ce travail a été :

- Identification de la question de recherche ;

- Rédaction du projet et des équations de recherche avec deux co-auteurs (TB et PS) ;

- Démarches administratives liées à la recherche : enregistrement du protocole de la revue systématique et méta-analyse sur le site dédié de l'Université de York PROSPERO (www.crd.york.ac.uk/prospero: CRD42021224192) ;

- Exploration des bases de données et sauvegarde des listes dans le logiciel EndNote, effacement des doublons et premier filtre sur la base du titre ;

- Evaluation indépendante de l'éligibilité des études retenues avec un des co-auteurs (TB) ;

- Synthèse/Conciliation de l'évaluation des biais réalisée par deux co-auteurs (TB et PS) ;

- Participation à l'élaboration du plan statistique et à la réalisation des analyses ;

- Rédaction et soumission du poster et du manuscrit.

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3.5.2. Discussion de l'étude n°4

Résultats principaux

En premier lieu, cette revue systématique et méta-analyse sur les effets de l'entrainement préopératoire avant chirurgie pulmonaire oncologique rapporte une réduction conséquente des complications postopératoires par rapport aux soins courants, tant sur le plan général (10 études, 617 participants, RR 0.54 [IC 95% 0.42 à 0.69]) que concernant les complications cliniquement pertinentes objectivées par la classification de Clavien-Dindo (5 études, 453 participants, Clavien-Dindo ≥ 2 RR 0.56 [IC 95% 0.41 à 0.76])

Cette diminution des complications postopératoires s'exprime également par une diminution significative de la durée de séjour postopératoire (10 études, 617 participants, différence moyenne -2.29 jours [IC 95% -0.98 à -3.59]).

Enfin, les effets sur les fonctions cardio-respiratoire et pulmonaire, la capacité à l'exercice ou encore la qualité de vie, ne sont pas établis sur le plan clinique.

Il est important de noter qu'aucun événement indésirable n'a été relevé.

La nécessité d'une intégration au parcours de soins courants

Ainsi que nous l'avons souligné dans l'article précédent, la force de nos résultats se base dans la méthodologie appliquée en comparaison aux deux dernières méta-analyses sur cette thématique. D'autre part, nos résultats confortent ceux de la dernière Cochrane de 2017 grâce à une large augmentation de l'effectif des nouveaux RCT et participants.

Nous avons complété l'analyse de notre critère principal (complications postopératoires et déclinaison de celles-ci), par une analyse séquentielle des essais cliniques (« *Trial sequencial analysis* » TSA). Cette analyse complémentaire réalisée au cours du reviewing de l'article nous a permis de déterminer la taille de l'échantillon requis pour limiter l'inflation de l'erreur statistique de type 1 lors de la remise à jour régulière de la méta-analyse (184). Bien que l'intervalle de confiance ajusté de l'effet sur les complications postopératoires soit légèrement plus large, il n'en demeure pas moins significatif. D'autre part, la courbe z

cumulée dépasse la borne supérieure de mesure séquentielle relative au bénéfice (cf Figure 3 de l'article), en faveur d'un niveau de preuve suffisant pour recommander une intégration de l'entrainement préopératoire en pratique clinique en vue de diminuer les complications postopératoires chez les patients ayant une indication à une résection pulmonaire oncologique.

Il est intéressant de noter que nos résultats sont en concordance avec une méta-analyse récente publiée par l'équipe de Assouline et al. ayant élargi leurs recherches à l'ensemble des chirurgies majeures, dont la résection pulmonaire (185). Leurs résultats rapportent des résultats systématiques en faveur des patients préhabilités, avec des pertinences cliniques assez similaires :

- Complications postopératoires : RR 0.52 [IC 95% 0,41 à 0,66] sur la base de 23 études compilant 1864 participants ;
- Durée de séjour hospitalier : différence moyenne de -2.3 jours [IC 99% -3.82 à -0.75], sur la base de 11 études compilant 1176 participants ;
- $\dot{V}O_2$pic : différence moyenne +1.72 ml/kg/min [IC 99% 0.33 à 3.11] sur la base de 5 études compilant 301 participants ;
- Distance au TDM6 : différence moyenne +30.7 m [IC 99% -2.3 à 63.6] sur la base de 7 études compilant 523 participants.

Cette concordance a l'avantage de renforcer la pertinence de notre message clinique. Cependant, notre travail apporte des éléments plus spécifiques sur la chirurgie pulmonaire oncologique, avec une sous-analyse plus robuste sur le plan méthodologique dans notre catégorie d'intérêt. En effet, on retrouve dans les 10 études sélectionnées par Assouline et al. ciblant la chirurgie pulmonaire la même erreur de compilation de cohorte que nous avions relevée dans la méta-analyse de Rosero et al. (178), à savoir les études de Lai et al. de 2016 à 2017 (186-188).

Au regard des résultats de notre méta-analyse, des RCT en cours, ainsi que de la cohérence des faisceaux de preuves entre toutes les publications relatives à la préhabilitation, il semble à présent nécessaire d'intégrer la préparation physique au parcours de soins préopératoires.

3.6. Conclusion de la 2e partie

Dans cette seconde partie traitant de la préhabilitation, nous avons tout d'abord présenté le programme que nous avons développé depuis 2014. La littérature assez abondante sur la thématique de la réhabilitation respiratoire et de la préhabilitation dans les années 2000 et 2010 nous a permis de construire ce programme sur des bases scientifiques solides.

Le premier travail exposé dans cette partie est venu confirmer l'efficacité du programme proposé sur une cohorte rétrospective. Nous avons pu objectiver des bénéfices physiologiques significatifs, cohérents avec ce que rapportaient les expériences d'autres équipes à l'international. Nos résultats nous ont aussi permis de constater que l'efficience ventilatoire, facteur prédictif de complications plus récemment identifié, semble moins sensible à la préhabilitation que la $\dot{V}O_2$pic. Nos données sont cependant en opposition avec celles d'une seconde étude récente.

L'exploration de la littérature autour du réentrainement préopératoire nous a incité à proposer une revue systématique et méta-analyse actualisée des essais randomisés contrôlés disponibles fin 2020. Les résultats de cette revue systématique viennent appuyer l'efficacité des programmes de réentrainement évalués par de nombreuses équipes à l'international. Ces résultats sont cohérents avec une hétérogénéité statistique faible quant à l'analyse des résultats, avec un $I^2 < 50\%$ dans la majorité des méta-analyses (voir figures dans l'article précédent). L'analyse séquentielle des essais vient par ailleurs renforcer le niveau de preuve quant à la diminution des complications postopératoires. Ces résultats plaident pour l'intégration systématisée de la préhabilitation dans les parcours préopératoires.

Malgré ces résultats qui attestent d'une bonne validité externe de la préhabilitation, les programmes d'entrainement sont hétérogènes en termes de méthodes et de programmation. Nous aborderons dans la troisième partie les pistes d'optimisation des programmes de préhabilitation.

4. Troisième partie : Optimiser la préhabilitation

4.1. « *Prehab or not Prehab ?...* Telle n'est plus la question ? »

La préhabilitation a été une thématique de recherche active au cours des années 2010. Comme nous l'avons exposé dans notre méta-analyse dans la deuxième partie de cette thèse, le niveau de preuve en faveur de cette intervention se renforce, en particulier sur le plan des complications postopératoires.

L'intérêt de la préhabilitation par rapport aux soins courants, majoritairement des conseils hygiéno-diététiques standards éventuellement associés à une kinésithérapie respiratoire préopératoire, est de moins en moins discutable. Il est fort probable que les essais cliniques prospectifs en cours actuellement (Tableau III) viendront étayer les preuves déjà disponibles.

Il est intéressant de noter que la dernière revue Cochrane sur la réhabilitation respiratoire publiée en 2015, sur laquelle a été construit le modèle de la préhabilitation, rapporte un niveau de preuve suffisant pour conclure sur ses bénéfices cliniques et encourage à présent à basculer les efforts de recherche vers les modalités les plus optimales de prise en charge (189).

Le parallèle entre la réhabilitation respiratoire et la préhabilitation peut être envisagé. Nous avons souligné ce sentiment dans le cadre d'une réponse aux lettres à l'éditeur qui ont été adressées suite à notre article publié en 2019 dans le *Journal of Thoracic and Cardiovascular Surgery* (171), présentée en Annexe 4. Ainsi, l'évaluation scientifique des différents paramètres communément utilisés pour planifier un entrainement physique semble nécessaire.

Tableau III : identification des essais randomisés contrôlés prospectifs en cours ou en attente de publication des résultats (exploration des bases d'enregistrement Clinicaltrial.gov, Anzctr.org, Chictr.gov)

Titre (enregistrement)	Effectif	Pays/institution	Intervention
Effects of Preoperative Rehabilitation in Patients Resected for Lung Cancer (REXOCHIR) NCT03020251	90	France, Centre Hospitalier Universitaire de Clermont-Ferrand (PHRC)	15 séances de réentrainement à l'effort préopératoire à domicile + Kinésithérapie respiratoire versus Kinésithérapie Respiratoire seule.
Pulmonary Resection And Intensive Rehabilitation (PUREAIR) NCT02405273	140	Italie, Hôpital Santa Maria, Reggio Emilia	10 séances de réentrainement préopératoire ambulatoire en centre versus soins courants (conseils)
Multimodal Prehabilitation to Enhance Functional Recovery After Lung Surgery NCT02938104	120	Canada, Montréal, Centre Hospitalier Universitaire McGill	Réentrainement à l'effort préopératoire 4 semaines + réhabilitation postopératoire versus uniquement réhabilitation postopératoire.
Preoperative Exercise for Patients Undergoing Complex Cancer Surgery (PRE-HIIT) NCT03978325	79	Irlande, Université de Dublin, Trinity College	Réentrainement à l'effort préopératoire 2 semaines versus soins courants. (*Chirurgie pulmonaire et œsophagienne*)

4.2. Définition des principaux paramètres applicables aux programmes de préhabilitation

La programmation d'un entrainement s'appuie sur plusieurs paramètres qu'il est possible de moduler en fonction de la condition physique initiale des sujets et des objectifs visés. La préhabilitation, en particulier oncologique, tient une spécificité complémentaire dans le cadre du délai imparti avant l'échéance chirurgicale. La programmation d'un entrainement physique du sujet sain ou sportif est définie par un ensemble de paramètres codifiés (126). Dans le cadre de la préhabilitation, il est possible de s'inspirer de cette programmation pour structurer l'entrainement physique des patients en vue de l'échéance chirurgicale, tout en l'adaptant aux spécificités de ce parcours préopératoire.

4.2.1. Volume et charge totale d'entrainement

Ces deux paramètres représentent chacun une quantité d'entrainement observée selon deux temporalités différentes.

La charge totale d'entrainement peut être perçue dans le cadre de la préhabilitation comme la quantité totale de stimuli à laquelle sera exposé le patient pendant la durée de quelques semaines qui le sépare de la chirurgie. Elle cumule l'ensemble du volume de chaque séance.

Le volume correspond à la quantité de stimuli au cours d'une séance d'entrainement. On estime le volume grâce à l'intensité des efforts réalisés vis-à-vis de leur durée.

Sur un exercice d'endurance il peut s'agir d'un objectif de durée ou de distance parcourue. Concernant un exercice de renforcement musculaire, d'un nombre de contractions, la durée de ces contractions pouvant éventuellement être prise en compte dans le cadre d'une programmation avancée.

4.2.2. Intensité

L'intensité correspond au niveau de difficulté auquel le patient réalise l'exercice par rapport à la performance maximale préalablement mesurée, conventionnellement de manière incrémentale (Tableau IV). Ainsi, pour un exercice d'endurance, il est possible de calibrer l'intensité de l'effort, grâce à l'EFX, en fonction de la puissance, de la $\dot{V}O_2$pic, ou de l'adaptation ventilatoire. En l'absence d'une EFX préalable, il est possible de considérer un certain pourcentage prédéfini de la fréquence cardiaque maximale théorique (FMT), ou de se référer à des échelles de perception de l'effort. Pour un exercice de renforcement musculaire en résistance, l'intensité peut être calibrée sur la 1-RM, ou sur la Pimax concernant les muscles inspirateurs.

Tableau IV : représentation des niveaux d'intensité d'exercice sur la base de la $\dot{V}O_2$max, de la fréquence cardiaque maximale théorique et de la perception de l'effort d'après les recommandations de l'ACSM (126) et Sietsema et al. (78).

	Exercice cardio-respiratoire en endurance			**Exercice en résistance**	**Perception effort**
	% $\dot{V}O_2$max	% FMT	% Pmax	% 1-RM	Echelle de 6–20
Très léger	< 37	< 57	< 37	<30	RPE < 9
Léger	37-45	58-63	37-45	30-49	RPE 9–11
Modéré	46 - 65	64-76	46 - 65	50-69	RPE 12–13
Intense	66 - 90	77-95	66 - 90	70-84	RPE 14–17
Maximal	> 90	> 95	> 90	≥ 85	RPE ≥ 18

$\dot{V}O_2$max : débit de consommation maximale en oxygène ; FMT : fréquence cardiaque maximale théorique ; Pmax : puissance maximale : 1-RM : charge maximale correspondant à 1 répétition ; RPE : notation de la perception de l'effort (« *rate of perceived exertion* ») sur l'échelle de Borg (190).

4.2.3. Fréquence et Densité

La fréquence correspond au nombre de séances réalisées sur un temps donné. Dans le cadre de la réhabilitation et de la préhabilitation, la définition de la fréquence est communément basée sur le nombre de séances par semaine.

La densité correspond au rapport entre les alternances de périodes d'efforts et de récupération. Ce paramètre est communément utilisé à l'échelle d'une séance d'entrainement, et contribue au volume d'entrainement de la séance en question : moins il y a de temps de repos, plus le patient enchaine les différents exercices. A titre d'exemple, sur les premières séances du programme que nous avons présenté dans la partie 2 de la thèse (Figure 17, page 92), la durée plus courte de l'entrainement en endurance au début du programme permet de réaliser des poses régulières entre les différentes activités proposées dans la séance ; l'augmentation de la durée de l'endurance s'accompagne d'une densification de la séance, avec une durée en activité plus longue.

Dans le cadre de la préhabilitation, il est possible d'envisager cette notion de densité à l'échelle de l'ensemble du programme. Dans les programmes de réhabilitation respiratoires ambulatoires des patients atteints de pathologies respiratoires chroniques, une fréquence de 2 à 3 séances par semaine sur une durée de 8 à 12 semaines est actuellement recommandée (191). En préhabilitation, les délais préopératoires étant potentiellement contraints, la stratégie pour atteindre une charge d'entrainement prédéfinie sera de moduler la fréquence d'entrainement et donc l'alternance effort/repos à l'échelle de la semaine pour tenir les délais impartis.

4.3. Etude n°5 : Effet relatif de deux densités d'entraînement préopératoire chez les patients atteints d'un CBNPC (Preo-Dens) : un essai randomisé d'équivalence.

4.3.1. Présentation et rationnel de l'étude.

La préhabilitation des patients à risque modéré à élevé de complications postopératoires est à présent fortement développée localement grâce à la filière précédemment décrite dans la partie 2 (Figure 16 page 90). Dans ce cadre, nous avons concentré nos efforts de recherche sur l'optimisation de ce programme.

Tout d'abord, nous avons tenté d'identifier une charge totale d'entrainement efficace pour améliorer la capacité cardio-respiratoire préopératoire des patients en attente de résection pour CBNPC, à travers une analyse exploratoire de notre cohorte rétrospective des patients ayant bénéficié d'une préhabilitation dans notre centre de 2014 à fin 2017 (171). Cette analyse exploratoire nous a orienté vers la prescription d'environ 15 séances de réentrainement.

La difficulté du contexte oncologique est de trouver le compromis entre la nécessité de la planification rapide du projet thérapeutique, et le délai nécessaire à l'obtention des bénéfices de la réhabilitation préopératoire. Une équipe rapporte la difficulté de mettre en place un programme d'entrainement sur quatre semaines, perçu comme pouvant retarder la chirurgie (192). Afin de prévenir tout risque d'allongement du délai de prise en charge chirurgicale, les équipes de préhabilitation proposent couramment des programmes courts avec des fréquences d'entrainement élevées allant jusqu'à cinq à six séances par semaine (160, 166, 174, 188, 193), cependant seule l'étude de Licker et al. (166) se place dans un contexte ambulatoire.

Il semble important de préciser que la réhabilitation préopératoire est envisagée de chez des patients pour lesquels il existe un risque de complications postopératoires modéré à élevé, selon les niveaux de risques définis par les algorithmes d'évaluation préopératoires

européens, américains et britanniques (56-58). La haute densité de l'entrainement, à défaut d'engendrer une stimulation physiologique importante, peut augmenter la fatigue ou limiter l'adhérence à l'entrainement, notamment si celui-ci requiert des déplacements, et se surajoute à un planning thérapeutique incluant de nombreuses consultations et examens complémentaires (194). Aucune étude n'avait encore évalué l'impact de la densité de l'entrainement préopératoire sur les bénéfices obtenus.

L'objectif de l'essai randomisé contrôlé présenté ci-dessous était de comparer la variation de $\dot{V}O_2$pic obtenue à la suite d'une même charge totale d'entrainement (15 séances) selon deux densités différentes, à savoir cinq fois par semaine pendant trois semaines, ou trois fois par semaine pendant cinq semaines. Nous avions émis l'hypothèse que les résultats obtenus seraient équivalents.

Les résultats de ce travail ont été rapportés sous la forme d'un article original soumis le 08/09/2021 dans la revue CHEST , dont l'impact factor était de 9,410 en 2020 (Rang A) (195)

Ma contribution dans ce travail a été :

- Identification de la question de recherche ;

- Rédaction du projet et obtention d'une bourse de recherche auprès du conseil scientifique de l'association ADIR ;

- Déclaration de l'essai clinique (RIPH de catégorie 2) auprès de l'agence nationale de sécurité du médicament et des produits de santé (ID-RCB : 2018-A03301-54) ;

- Dépôt du dossier pour le CPP sur la plateforme CNRIPH (https://cnriph.sante.gouv.fr/) et gestion des modifications nécessaires pointées par le CPP (accord le 09/04/2019 par le CPP Sud-Est IV). Gestion des amendements en cours de programme ;

- Préenregistrement du protocole de l'étude sur la plateforme Clinicaltrial.gov (NCT03936764) et mise à jour annuelle ;

- Recherche et soumission du devis d'assurance de l'étude au promoteur ;

- Inclusion, suivi et acquisition des données de l'étude ;

- Participation à l'élaboration du plan statistique et à la réalisation des analyses ;

- Rédaction et soumission du manuscrit.

La version du manuscrit de l'article présenté ci-dessous correspond au contenu de la soumission auprès de la revue scientifique.

Type: Original research

Relative effects of two preoperative exercise training densities in patients with non-small-cell lung cancer (Preo-Dens): a randomised equivalence trial.

Short title: Comparison of two preoperative training densities before NSCLC resection.

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Author contributions:

1.has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2.has drafted the submitted article or revised it critically for important intellectual content;

3.has provided final approval of the version to be published;

4.has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

FEG: 1,2,3,4; PS: 1,2,3,4; FB: 1,2,3,4; GP: 2,3,4; CM: 2,3,4; YC: 2,3,4; JFM: 2,3,4; JMB: 2,3,4; AC: 2,3,4; DD: 1,2,3,4; TB: 1,2,3,4.

Abstract (246 words)

Background: Preoperative exercise training in patients scheduled for lung resection for non-small cell lung cancer (NSCLC) is increasingly supported by research, however programs are very heterogeneous. Optimal training parameters need to be determined. This study aimed to assess the equivalence of two training densities.

Methods: 36 patients with diagnosed or suspected NSCLC with a moderate to high risk of postoperative complications were enrolled in a 15-sessions supervised outpatient prehabilitation program and randomised to a non-dense training group (NDTG: 3 sessions/week for 5 weeks) or a dense training group (DTG: 5 sessions/week for 3 weeks). The primary outcome was the change in preoperative cardiorespiratory fitness ($\Delta\dot{V}O_2$peak).

Results: A difference in the $\Delta\dot{V}O_2$peak of -1.3 ml/kg/min was found between NDTG and DTG and the 2-sided 95% confidence interval (95% CI -2.7 to 0.1) exceeded the pre-set margin of equivalence of 1.75 ml/kg/min in favour of dense training. There were no significant between-group differences for any of the secondary outcomes. CPET variables, the functional domain of the quality-of-life questionnaire and quadriceps strength improved significantly in both groups. There were no changes in lung function or nutritional status.

Conclusions: A preoperative exercise training program of 15 sessions performed over 3 weeks at a rate of 5 sessions per week, or over 5 weeks at the rate of 3 sessions per week, did not produce an equivalent $\dot{V}O_2$peak response. Although the confidence interval was in favour of dense training, further work is needed to confirm the superiority of this training modality.

Study Registration: https://clinicaltrials.gov/ct2/show/NCT03936764

Keywords: Non-small cell lung cancer; Lung resection; Preoperative care; Exercise training; Prehabilitation.

List of abbreviations:

BMI: body mass index

CPET: cardiopulmonary exercise testing

DTG: dense training group

DLCO: diffusing capacity of the lung for carbon monoxide

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity

LOCF: last observation carried forward

MIP: maximal inspiratory pressure

NDTG: non-dense training group

NSCLC: non-small cell lung cancer

QMVIC: quadriceps maximal voluntary isometric contractions

QoL: quality of life

$\dot{V}CO_2$: expired carbon dioxide flow

$\dot{V}E/\dot{V}CO_2$ slope: linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$)

$\dot{V}O_2$peak: peak oxygen uptake

VT: ventilatory threshold

Wpeak: peak work rate

Introduction

Lung cancer is the most common type of cancer and the leading cause of cancer death worldwide (1). Lung resection is currently the recommended curative treatment for early-stage non-small cell lung cancer (NSCLC) (2). Measurement of peak oxygen consumption ($\dot{V}O_2$peak) by cardiopulmonary exercise testing (CPET) is recommended to assess perioperative risk in frail patients (3, 4). Physical preparation for surgery, termed prehabilitation, which involves exercise training, support with smoking cessation, nutritional advice, respiratory physiotherapy and postoperative education, has become increasingly dispensed over the past ten years.

Prehabilitation programs have been shown to improve preoperative cardiorespiratory conditioning and reduce the occurrence and severity of postoperative complications in patients with NSCLC (5). However, the training parameters (duration, frequencies, intensity) used in the different studies are very heterogeneous. In a preliminary study, we found a significantly greater improvement in physiological variables in patients who performed 15 or more preoperative training sessions as part of a multimodal outpatient program (6). We therefore designed our programs with a prescription of 15 sessions.

The organisation of prehabilitation must consider both the need for rapid surgery and the need to provide a sufficient training load to obtain physiological benefits. Programs involving daily training could provide considerable physiological stimulation in a short timeframe, however such intense training could cause significant fatigue or limit adherence. Patients scheduled for lung resection undergo many preoperative consultations and examinations and may struggle to also participate in prehabilitation. To date, no study has

evaluated the relative impact of different densities of outpatient prehabilitation on the physiological benefits.

The aim of this study was to compare the effects of two densities of a 15-session program: 3 times a week over 5 weeks and 5 times a week over 3 weeks, on the $\dot{V}O_2$peak response. We hypothesized that the training densities would yield equivalent results.

Methods

Study Design and participants

This prospective, assessor-blind (primary outcome), equivalence, randomised trial was approved by the French ethics committee Sud-Est IV (ethical approval n°19.01.29.69434), registered at the National Institutes of Health ClinicalTrials.gov website (NCT03936764) and conducted by ADIR Association (Rouen, France) in partnership with Rouen University Hospital. Written informed consent was obtained from all participants. Consecutive adult patients with suspected or confirmed stage I–III NSCLC and a moderate to high perioperative risk ($\dot{V}O_2$peak < 20 ml/kg/min) were screened for eligibility. Exclusion criteria were cardiological contraindications to training, neoadjuvant radio-chemotherapy, refusal to carry out a training program, a comorbidity that limited cycling (e.g. orthopaedic, vascular, neurologic limitations), exacerbation or medical recommendation of early cessation of the prehabilitation program. The results of the study are reported according the Consolidated Standards of Reporting Trials (CONSORT) statement for noninferiority and equivalence randomized trials (7).

Prehabilitation program

Each prehabilitation session lasted approximately 90 minutes. The first session was individual, and the following sessions were performed in groups of around 6 patients. The program included the following components:

1/ Aerobic endurance training on a cycle ergometer at the ventilatory threshold (VT) determined during the initial CPET. The first session lasted for 15 to 20 minutes. The duration increased by 5 minutes each session to reach 45 minutes (including a 5-minute warmup and a 5-minute active recovery). The intensity was then increased by 5 or 10 watts, as tolerated (8).

2/ Peripheral muscle strengthening on weight machines performed at 60% to 70% of the 1-repetition maximum (1-RM) (3 exercises: whole-leg extension, whole-arm pull down and whole-arm extension). Three sets of 12 movements were carried out for each exercise and the load was increased regularly as tolerated (9).

3/ Inspiratory muscle training using an inspiratory threshold valve calibrated to at least 30% of the maximal inspiratory pressure (MIP). Patients were encouraged to carry out 15 minutes of independent training daily and to increase the resistance regularly (10).

4/ Smoking cessation support (11) and education regarding mucus clearance techniques, deep-breathing, directed and protected coughing, and postoperative mobilisation (12).

Components 3 and 4 were mainly delivered during the first individual session, and reminders and advice were provided during the following 14 group sessions.

Outcomes

A comprehensive medical history was collected for each patient, cardiorespiratory fitness and pulmonary function were assessed by a physician who was blind to patient allocation before and after the 15 planned prehabilitation sessions. The same physiotherapist, who was

not blind to patient allocation, assessed peripheral strength and non-invasive nutritional variables, at the first and last session. The self-report quality of life questionnaire was completed during the first and last sessions.

Primary outcome was the post-training change (Δ) in cardiorespiratory fitness measured by the $\dot{V}O_2$peak in ml/kg/min. Secondary outcomes were the Δ of the other physiological variables measured during CPET, pulmonary function, non-invasive nutritional markers, quadriceps maximal voluntary isometric contractions (QMVIC), and quality of life (QoL). Postoperative outcomes were collected from the medical records at 30 days.

CPET

CPET was performed on an electromagnetic ergometer (Ergoline 900, GmbH, Bitz, Germany). A face mask, pneumotach and gas analyser (Vyntus CPX, Vyaire Medical, Mettawa, IL) were used to assess oxygen uptake (V̇O2) and carbon dioxide production (V̇CO2), breath by breath. Heart rate was continuously monitored using a 12-lead electrocardiogram and perceived exertion was assessed using the Borg scale. After a 3-minute warm-up period, incremental ramp exercise (aimed to last for about 10 minutes using steps from 5 to 15 W/min depending on the physician's evaluation, the patient's history and usual physical activity levels) was applied to exhaustion (13). V̇O2 measured during the last fully sustained ramp was defined as the V̇O2peak and was expressed as a percentage of the predicted value according to age, weight and sex (13, 14). Patients were considered as responders to training if their V̇O2peak increased by at least 10% (15).

Pulmonary Function

Pulmonary function tests were carried out according to the American Thoracic Society and the European Respiratory Society guidelines (Masterscreen, Jaeger, Wittsburg, Germany). Only spirometry with forced expiratory volume in one second (FEV1), and forced vital capacity (FVC), were retested after prehabilitation (not plethysmography or lung diffusion). Values were expressed as percentages of established predicted values for European populations (16).

MIP was measured before and after prehabilitation using an electronic manometer (POWERbreatheKH1, HaB International Ltd, Southam, UK).

QoL

QoL was estimated by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire and modular supplement for Lung Cancer patients (EORTC QLQ-C30 / LC13), a 30-question questionnaire with a 13-question modular specific supplement for patients with lung cancer (17). Score range from 0 to 100, and a higher score reflects either better function or less symptomatic effect.

Nutrition

Nutritional status was estimated non-invasively by bioimpedance analysis of fat mass, total body water and lean body mass (Bodystat® 1500MDD, (5/50 kHz), Bodystat, Douglas, Isle of Man, UK) calculated as a % of total body weight. The measurement was carried out before exercise, in a standardized supine position, after urination and 10 min of rest (18). Since the patient then performed the exercise training session, fasting was not required. The pre and post prehabilitation measurements were taken at the same time of day.

QMVIC

Bilateral QMVIC were evaluated with hand held dynamometry (MicroFET2®, Hogan Health Industries, Inc., UT, USA) according to a standardized methodology (19). The results obtained were expressed in absolute values and as a percentage of the corresponding theoretical normal values for each lower limb (20).

Adherence and adverse event

Adherence to the prehabilitation program was defined as the ratio of the number of sessions attended to the 15 sessions prescribed. Any adverse event during or related to exercise training was recorded.

Postoperative outcomes

Postoperative outcomes included hospital length of stay (LoS) and postoperative complications, which were recorded and graded according to the Clavien–Dindo classification (21).

Sample size

We wished to determine the equivalence of a dense and a non-dense supervised prehabilitation program on improvements in cardiorespiratory fitness measured by the $\Delta\dot{V}O_2$peak. Equivalence is represented by the alternative, rather than the null hypothesis: $H0: |\mu A - \mu B| \geq \delta$ $H1: |\mu A - \mu B| < \delta$.

Taking into account an expected between group difference ($\mu A - \mu B$) of zero, a risk α of 0.05 and a risk β of 0.20, a two-sided 95% CI, an equivalence margin (δ) of 1.75 ml/kg/min, and a standard deviation (σ) of 1.62 ml/kg/min in $\Delta\dot{V}O_2$peak (6), the following equation: $nA =$

κnB and $nB = (1 + \frac{1}{\kappa})(\sigma \frac{z1-\alpha+z1-\beta/2}{|\mu A-\mu B|-\delta})^2$ (22); determined that a total of 30 participants was required, divided into two groups. Assuming a 20% dropout risk, we set the sample size to 36 participants.

Randomisation

Consenting patients were randomly assigned after baseline assessment to the non-dense training group (NDTG) or dense training group (DTG) with a ratio of 1:1. The randomization sequence was developed before initiation of the trial using a computer-generated sequence (www.randomizer.org) and concealed until enrolment in the first prehabilitation session.

Statistical analysis

Categorial data were expressed as numbers (percentages). Continuous data were expressed as means ± standard deviation or medians (25th–75th percentile) according to the data distribution. Normality was assessed using the D'Agostino & Pearson omnibus normality test. Categorial data were compared using a Fisher's exact test or Chi-square test and continuous data were compared using an unpaired or paired t-test, or a Mann-Whitney or Wilcoxon test as appropriate.

As intention to treat (ITT) analysis may increase the risk of falsely claiming noninferiority or equivalence, per protocol (PP) analysis was chosen for the primary analysis (23). ITT analysis, using the last observation carried forward (LOCF) method (24), was reported as a secondary sensitivity analysis, as recommended (7).

A p-value <0.05 was considered statistically significant. GraphPad Prism 5.03 software was used for all analyses.

Results

Patients

The 36 participants were recruited between May 2019 and April 2021. The flow-chart and baseline characteristics are reported in Figure 1 and Table 1.

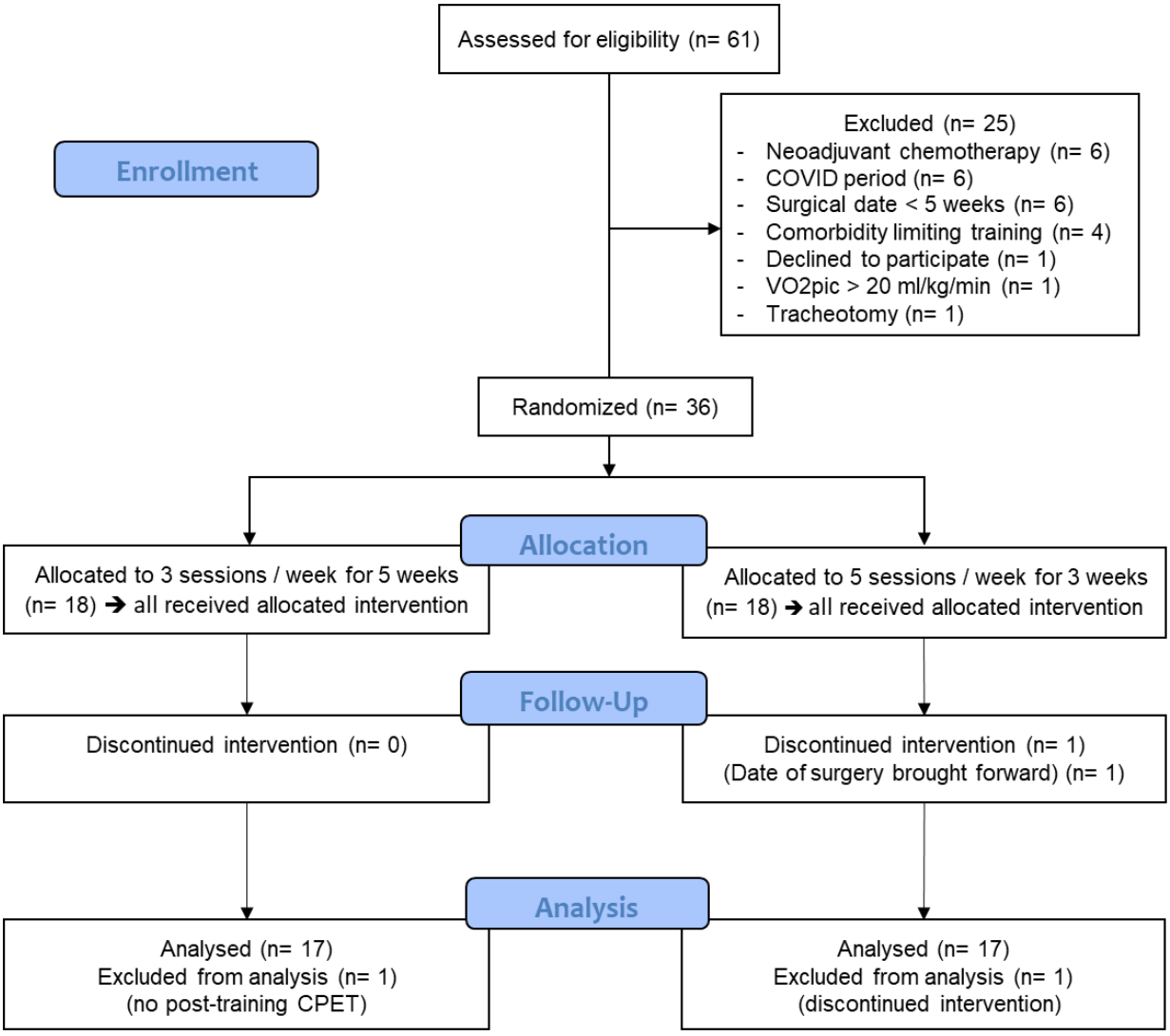

Figure 1: Study flow-chart.

Table 1: Patient characteristics.

Variable (units)		All (n=36)	NDTG (n=18)	DTG (n=18)	p
Male		23 (63.9)	9 (50.0)	14 (77.8)	0.16
Age (years)		66.3 ± 8.1	64.8 ± 7.8	67.8 ± 8.3	0.26
BMI (kg/m^2)		29.0 ± 5.9	28.8 ± 5.0	29.2 ± 6.8	0.82
$\dot{V}O_2$peak (% pred.)		63.6 ± 15.3	66.6 ± 15.4	60.7 ± 15.1	0.26
$\dot{V}O_2$peak (mL/kg/min)		13.5 ± 3.3	14.1 ± 3.2	12.9 ± 3.3	0.26
$\dot{V}E/\dot{V}CO_2$ slope		37.3 (32.0-44.0)	37.3 (31.5-44.9)	35.7 (31.1-43.2)	0.86
FEV1 (L)		1.9 ± 0.7	1.9 ± 0.7	1.9 ± 0.7	0.94
FEV1 (% pred.)		74.0 ± 27.9	75.4 ± 25.9	72.6 ± 30.6	0.78
FVC (mL)		3.0 ± 0.8	2.9 ± 0.8	3.2 ± 0.9	0.35
FVC (% pred.)		89.6 ± 22.1	89.6 ± 18.6	89.5 ± 25.7	0.98
DLCO (% pred.)		56.0 (45.3-69.5)	54.5 (44.5-68.8)	58.0 (45.8-70.0)	0.75
MIP (cmH_2O)		60.7 ± 18.3	60.5 ± 20.6	60.9 ± 16.3	0.95
COPD		22 (61.1)	8 (44.4)	14 (77.8)	0.09
Hypertension		19 (52.8)	10 (55.6)	9 (50.0)	1.0
Hypercholesterolemia		14 (38.9)	8 (44.4)	6 (33.3)	0.73
Cardiovascular disease		13 (36.1)	5 (27.8)	8 (44.4)	0.49
Diabetes		10 (27.8)	4 (22.2)	6 (33.3)	0.71
Anxiety-depression syndrome		5 (13.9)	3 (16.7)	2 (11.1)	1.0
Ortho/rheumatology disease		8 (22.2)	4 (22.2)	4 (22.2)	1.0
Medications (n/patient)		6 (3-7)	5 (3-8)	6 (4-7)	0.55
Tobacco	Non-Smoker	2 (5.5)	1 (5.5)	1 (5.5)	1.0
	Smoker	11 (30.6)	5 (27.8)	6 (33.3)	1.0
	Former	23 (63.9)	12 (66.7)	11 (61.1)	1.0
	Exposure (PY)	42.0 (35.5-60.0)	40.0 (34.0-53.8)	47.5 (35.0-60.0)	0.57

Data are presented as numbers (%) or means ± SD or medians (25th to 75th percentile); NDTG: non-dense-training group (3 sessions/week over 5 weeks); DTG: dense-training group (5 sessions/week over 3 weeks); BMI: body-mass index; $\dot{V}O_2$peak: peak of oxygen uptake; $\dot{V}E/\dot{V}CO_2$ slope: linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$); FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; MIP: maximal inspiratory pressure; COPD: chronic obstructive pulmonary disease.

Primary outcome: equivalence of $\Delta\dot{V}O_2$peak

Mean difference in $\Delta\dot{V}O_2$peak between the NDTG and the DTG was -1.3 ml/kg/min (95% CI -2.7 to 0.1). This difference did not lie between the pre-set margins of equivalence (δ) of 1,75 ml/kg/min and was thus in favour of dense training (Figure 2).

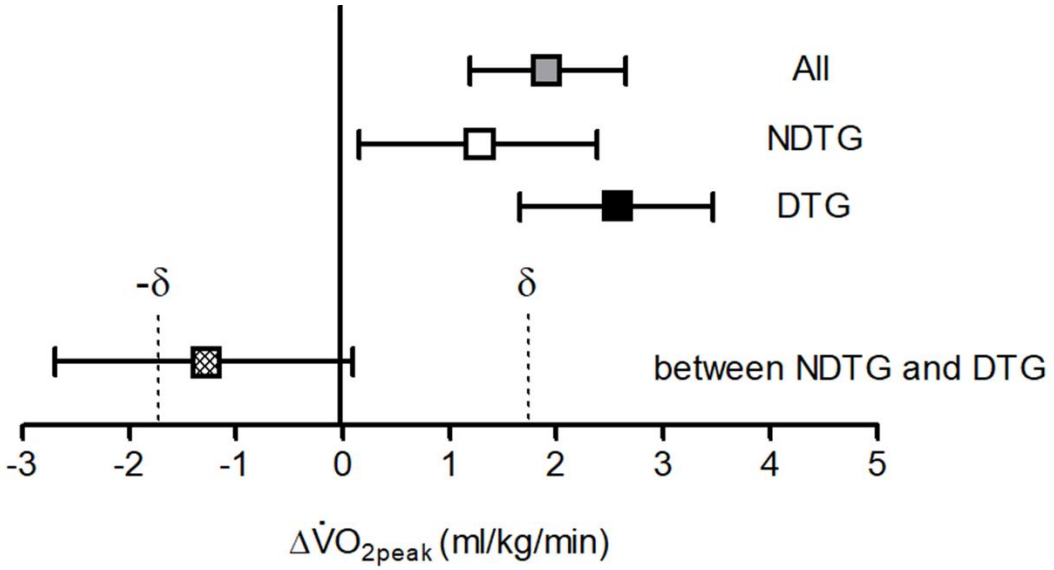

Figure 2: change (Δ) in peak oxygen uptake (V̇O2peak) after prehabilitation for all patients, non-dense-training group (NDTG: 3 sessions/week during 5 weeks), dense-training group (DTG: 5 sessions/week during 3 weeks), and difference between groups. The 2-sided 95% Confidence Interval (95% CI -2.7 to 0.1) exceeded the pre-set margin of equivalence (δ) of 1.75 ml/kg/min in favour of dense training.

Secondary outcomes

Preoperative Outcomes

Changes in preoperative outcomes pre/post prehabilitation for all patients and comparison between NDTG and DTG are reported in Table 2. There was no significant between group difference in the change in CPET outcomes, pulmonary function, QoL, nutritional markers, or QMVIC.

Table 2: prehabilitation program response (Δ pre/post) for all patients, both groups, and between group p-value. (Intention to treat analysis is reported in Appendix 1).

Variable (units)	Δ All	Δ NDTG	Δ DTG	p-value
CPET	*n=34*	*n=17*	*n=17*	
$\dot{V}O_2$peak (mL/kg/min)	1.9 ± 2.1	1.3 ± 2.2	2.6 ± 1.8	0.07
$\dot{V}O_2$peak (% pred.)	8.9 ± 8.0	6.8 ± 9.0	11.1 ± 6.5	0.12
$\dot{V}O_2$VT (mL/kg/min)	1.1 ± 1.6	1.0 ± 1.5	1.1 ± 1.6	0.78
$\dot{V}E/\dot{V}CO_2$ slope	0.1 (-5.3 to 2.0)	1.0 (-6.8 to 3.3)	-1.0 (-4.3 to 1.0)	0.36
WRpeak (Watts)	12.5 (0.0 to 15.0)	15.0 (0.0 to 15.0)	10.0 (0.0 to 15.0)	0.87
WRpeak (% pred.)	9.5 (0.8 to 18.0)	10.0 (2.5 to 18.0)	9.0 (0.0 to 16.5)	0.73
Pulmonary Function	*n=34*	*n=17*	*n=17*	
FEV1 (L)	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.2	0.91
FEV1 (% pred.)	2.0 ± 10.5	3.6 ± 12.4	0.2 ± 7.8	0.35
FVC (L)	-0.1 ± 0.4	-0.1 ± 0.5	-0.2 ± 0.2	0.59
FVC (% pred.)	-0.7 ± 14.5	1.1 ± 17.8	-2.8 ± 9.7	0.44
Pimax (cmH_2O)	10.4 ± 13.1	10.6 ± 16.2	10.2 ± 9.2	0.92
Nutrition	*n=35*	*n=18*	*n=17*	
Weight (kg)	0.3 ± 1.4	0.6 ± 1.4	0.0 ± 1.5	0.27
Fat mass (%)	0.2 ± 2.3	0.1 ± 2.8	0.3 ± 1.6	0.77
Total body water (%)	-0.4 ± 2.2	-0.2 ± 2.6	-0.5 ± 1.8	0.74
Lean body mass (%)	0.1 ± 0.5	0.1 ± 0.7	0.2 ± 0.3	0.74
QoL (EORTC)	*n=35*	*n=18*	*n=17*	
Functional score	6.7 (2.2 to 15.6)	5.6 (0.0 to 17.7)	6.7 (3.3 to 14.4)	0.89
Symptom score	2.5 (-5.1 to 5.1)	2.5 (-3.2 to 5.1)	2.6 (-5.2 to 10.3)	0.99
Global score	8.3 (0.0 to 16.7)	8.3 (-2.1 to 16.7)	8.3 (0.0 to 16.7)	0.69
LC13 score	2.6 (-2.6 to 5.2)	1.3 (-5.1 to 5.1)	2.6 (-2.6 to 7.7)	0.53
Quadriceps strength*	*n=33*	*n=18*	*n=15*	
QMVIC right (Nm)	8.3 ± 14.6	5.7 ± 13.8	11.3 ± 15.4	0.28
QMVIC right (% pred.)	6.7 ± 12.4	5.9 ± 12.2	7.6 ± 12.9	0.69
QMVIC left (Nm)	8.6 ± 15.8	8.2 ± 18.3	9.1 ± 12.7	0.88
QMVIC left (% pred.)	7.4 ± 12.6	7.9 ± 15.4	6.8 ± 8.6	0.81

Data are presented as means ± SD or medians (25th to 75th percentile); NDTG: non-dense-training group (3 sessions/week over 5 weeks); DTG: dense-training group (5 sessions/week over 3 weeks); $\dot{V}O_2$peak: peak of oxygen uptake; $\dot{V}O_2$VT: oxygen uptake at ventilatory threshold; $\dot{V}E/\dot{V}CO_2$ slope: linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO2$); WRpeak: peak power on cycle-ergometer; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; MIP: maximal inspiratory pressure; QoL: quality of life; QMVIC: quadriceps maximal voluntary isometric contractions. *QMVIC was not measured at baseline in two patients with a history of skin ulcers on the anterior side of the tibia, no pre/post data was therefore imputed.

Adherence and adverse event

The mean adherence rate for scheduled sessions (%) was 87.4 ± 11.2 and 86.3 ± 11.3 (p=0.77) for the NDTG and the DTG respectively. No adverse events occurred.

Postoperative outcomes

Only 26 patients (72.2%) finally underwent surgery at the end of their prehabilitation program. Ten surgical interventions were not carried out for the following reasons: 3 patients with stable nodules under surveillance, 3 discoveries of metastases, 2 unfavourable onco-geriatric opinions, 1 benign biopsy result and 1 refusal of surgery. Postoperative outcomes for all patients and between group comparisons are reported in Table 3.

Table 3: postoperative outcomes for all patients and between groups comparison

Variable (units)	**All (n=26)**	**NDTG (n=13)**	**DTG (n=13)**	**p**
Intervention modality				
VATS-RATS (n)	20 (76.9)	8 (61.5)	12 (92.3)	0.16
Thoracotomy (n)	6 (23.1)	5 (38.5)	1 (7.7)	
Type of surgery				
Pneumonectomy/bilobectomy (n)	3 (11.5)	3 (23.1)	0 (0.0)	
Lobectomy (n)	12 (46.2)	7 (53.8)	5 (38.5)	0.06
Wedge/Segmentectomy (n)	11 (42.3)	3 (23.1)	8 (61.5)	
Postoperative outcomes				
Postoperative complications (CDC ≥ 2) (n)	6 (23.1)	4 (30.8)	2 (15.4)	0.65
Chest tube drainage (days)	3.0 (3.0-4.0)	3.0 (3.0-4.3)	3.0 (2.0-4.0)	0.13
Postoperative LoS (days)	4.0 (3.0-5.3)	4.0 (4.0-7.0)	3.0 (2.5-5.0)	0.05
Total LoS (days)	5.0 (4.0-6.3)	5.0 (5.0-8.0)	4.0 (3.5-6.0)	0.03

Data are presented as numbers (%), or medians (25th–75th percentile); NDTG: non-dense-training group (3 sessions/week over 5 weeks); DTG: dense-training group (5 sessions/week over 3 weeks); VATS: video-assisted thoracoscopic surgery; RATS: robot-assisted thoracoscopic surgery; CDC: Clavien-Dindo classification; LoS: length of stay.

Sensitivity analysis

There were no deviations in the training modality received from the initial allocation. The ITT analysis (Appendix 1) of primary and other preoperative outcomes did not alter the results of the PP analysis; the clinical implications were similar.

The comparison of the proportion of responders ($\Delta\dot{V}O_2peak \geq 10\%$ from baseline) and non-responders ($\Delta\dot{V}O_2peak < 10\%$ from baseline) for each training density is reported in a supplemental figure (Appendix 2).

The intra-group change in preoperative outcomes pre/post prehabilitation is reported in a supplemental table (Appendix 3).

Discussion

Main result

The main finding of this study was that the effect of non-dense training (3 sessions / 5 weeks) and dense training (5 sessions / 3 weeks) on the $\Delta\dot{V}O_2peak$ was not equivalent since the 95% CI crossed the margin of equivalence in favour of dense training (Figure 2). However, the difference in the delta values was only a trend therefore we cannot conclude as to the superiority of dense training (Table 2). The results for the secondary outcomes were neither significant nor clinically notable and therefore do not explain the trend in favour of dense training (Table 2).

Both groups underwent an identical total prescribed training load with a comparable rate of adhesion. For both training modalities, the duration can be considered as short with regards to the magnitude of physiological modifications mostly observed in longer periods of rehabilitation in patients with COPD (25). Improvements in muscle strength are due to a combination of neurological and morphological factors, with a predominance of neurological

factors during the first weeks of training (26, 27). It is likely that the grouping of training sessions over a short period (densified training) leads to greater neuro-physiological stimulation, however we have no electromyographical or biological data to support this assumption. It is also possible that the almost daily supervision facilitated patient motivation. We were concerned that a dense outpatient training program would lead to a reduced quality of life or lack of adherence, however this was not the case.

Regarding the postoperative results (Table 3), the complication rate in the patients with a moderate to high risk was close to the overall complication rate of 18.5% reported by the European Society of Thoracic Surgeons from their database (28). Likewise, the median postoperative LoS was 5 days (range 4-6) which is slightly lower, than the median duration reported in patients operated with VATS (median 6 days (4-8)) (28) and could potentially be due to the prehabilitation performed. LoS was significantly shorter in the dense training group, however, this was certainly due to the difference in the distribution in terms of surgical procedures performed between the two groups rather than the training modalities.

Sensitivity analysis

The comparison of the proportion of responders in each group was inconclusive due to a lack of statistical power since the study was not designed specifically for such an analysis (Appendix 2).

The intra-group analysis showed a significant improvement in CPET outcomes in both groups except for ventilation efficiency, in accordance with previous studies (15, 29) (Appendix 3). It is interesting to note that for both training modalities, the average $\Delta\dot{V}O_2$peak of the whole cohort (1.9 ± 2.1 ml/kg/min) was similar to that which we reported in our previous work (1.9 ± 1.9 ml/kg/min) (29). This supports the consistency of the mean results obtained by this 15-

session program. Conversely, there was no change in lung function (measured by FEV1 and FVC), however the impact of prehabilitation on lung function in NSCLC patients is limited and contrasted in the literature (30-34). The nutritional markers evaluated did not change after prehabilitation. These measures have not been previously reported in lung cancer patients but the results are consistent with the effect of prehabilitation in colorectal patients prior surgery (35). Regarding the effects of the prehabilitation program on QoL measured by the EORTC-QLQ-C30-LC13, the two modalities produced similar results: the sub-scores most sensitive to training were the symptom and global-QoL domains, with an improvement above the MID of +3 points (36), as previously reported (32, 37). Finally, although the change in QMVIC was not significantly different between the two groups (Table 2), the intra-group analysis showed a more homogeneous and systematic improvement in the dense training group (Appendix 3). Although there are no data in the literature for NSCLC patients, a meta-analysis reported that healthy untrained subjects benefit more from higher training frequencies with moderate loads (196). It is possible that the higher frequency of resistance training in the DTG produced slightly greater improvements in strength, although the difference with NDTG is non significant and clinically questionable.

Clinical implications

The positive effects of preoperative exercise training in patients scheduled for lung resection for NSCLC are increasingly scientifically supported, however these programs are very heterogeneous (5). One-week programs with twice daily training and multimodal management have recently been described, but they involve hospitalization (33, 37). The durations of supervised outpatient programs described in prospective trials are at least 3-weeks, and training frequencies range from 3 to 5 times per week (5). The preoperative delay remains the limiting

factor for the optimization of cardio-respiratory fitness. This has led to suggestions that dense training should be offered to frail patients with impaired cardio-respiratory function or major postoperative risk factors. One of our concerns relating to dense training was that it would increase fatigue or introduce overtraining in patients who were undergoing diagnostic and therapeutic assessments for NSCLC. However, our results confirm that it is possible to obtain worthwhile physiological benefits in a short period of time with a condensed programme of 5-weekly sessions over 3 weeks with no negative effect on adherence or QoL. This could increase the number of patients who can be enrolled in prehabilitation, despite short presurgical delays. All though less dense programs are not equivalent, they can still improve $\dot{V}O_2$peak and should be considered for patients who refuse or are unable to participate in daily training sessions (for social or family reasons, for example).

Strength and limitations

This study has several strengths, including compliance with the CONSORT methodology, and with the pre-registered protocol. We reported both the PP and ITT analysis, the results of which are consistent. Complementary sensitivity analyses (inter-group and responder rate) were performed to help interpret the clinical implications.

The pre-set margin of equivalence (δ) of $\Delta\dot{V}O_2$peak at 1.75 ml/kg/min could be considered as wide. This value corresponded to the mean difference previously observed between patients who completed 15 training sessions or more and those who received a lower training load (29). We therefore wanted to evaluate whether the density at which the training load (15 sessions of 90 minutes) was dispensed impacted on the clinical benefit. Furthermore, this value of 1.75 was equivalent to a half metabolic equivalent of task (1MET = 3.5 ml/kg/min), a value that can distinguish different levels of functional activity (39). Although we can

conclude that the two densities were non-equivalent, in favour of a denser training modality, it was not possible to conclude with regards to the superiority of this modality.

Regarding the secondary outcomes and sensitivity analyses, the sample size was not calibrated for these exploratory analyses. These results should be considered with caution due to a lack of power and no correction for multiple testing. Regarding postoperative outcomes, the distribution of the types of surgery and interventional modalities was not balanced despite randomization, which limits the interpretation of results.

Finally, in terms of external validity, our results can be transposed to outpatient prehabilitation programs, however their validity with regard to inpatient or home-based programs is limited.

Conclusion

A preoperative exercise training program of 15 sessions over 5 weeks at a rate of 3 sessions per week, or over 3 weeks at a rate of 5 times per week, did not produce an equivalent $\Delta\dot{V}O_2$peak response. Although the confidence interval was in favour of the denser modality, further work is needed to confirm the superiority of dense preoperative exercise training in people with scheduled lung resection surgery for NSCLC.

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4.3.2. Discussion de l'étude n°5

Résultats Principaux

Cette étude randomisée prospective menée sur 36 patients en attente de résection pulmonaire pour CBNPC nous a montré que la charge globale d'entrainement proposée n'est pas le seul facteur entrant en compte dans l'optimisation de la capacité aérobie en préhabilitation. Le même programme de 15 séances de réentrainement proposé ici selon deux densités ne rapporte pas des résultats équivalents, avec une différence de $\Delta\dot{V}O_2$pic de -1,3 ml/kg/min [IC 95% -2,7 à 0,1] en faveur du groupe ayant bénéficié d'un entrainement plus dense.

Bien que nous observions une tendance en faveur d'un mode d'entrainement condensé, ceci ne signifie pas pour autant une stricte supériorité de cette modalité d'entrainement. De futurs travaux sont nécessaires pour répondre sur ce point. Ces résultats nous permettent cependant d'apporter des réponses éclairées et positives sur les bénéfices des programmes de préhabilitation accélérés, tant auprès des patients que des prescripteurs, pour en diffuser l'utilisation en pratique clinique.

Concernant les résultats secondaires, nos résultats ne semblent pas rapporter de différence cliniquement pertinente au terme des deux modalités d'entrainement, tant sur le plan de la qualité de vie, que de la force musculaire périphérique mesurée de manière isométrique au niveau du quadriceps.

Il est intéressant de noter que les résultats de cette étude prospective sont concordants avec les résultats rapportés dans notre précédent travail rétrospectif (171). Tout d'abord, nous retrouvons une variation de $\Delta\dot{V}O_2$pic de 1,9 ± 2,1 ml/kg/min dans la présente étude contre et 1,9 ± 1,9 ml/kg/min chez les patients ayant réalisé au moins 15 séances d'entrainement, tout comme le gain d'environ un palier incrémental (de 10 à 15 watts) lors de la seconde EFX. Parallèlement, nous n'avons pas noté de modification de l'efficience ventilatoire mesurée via la pente $\dot{V}E/\dot{V}CO_2$, tout comme dans nos précédents résultats (171).

Enfin, nous n'avons pas relevé de modification significative, tant de la masse corporelle que de sa répartition mesurée par impédancemétrie, ni de la fonction respiratoire mesurée

par spirométrie (Tableau 2 de l'étude ci-dessus). Comme nous l'avons évoqué précédemment, seuls les résultats relatifs à la force musculaire, ainsi que la puissance développée et son expression métabolique via la $\dot{V}O_2$pic ont été significativement modifiés. Cette amélioration physique semble perçue dans le quotidien des patients puisque l'on note une amélioration cliniquement pertinente, de plus de 3 points (197), de la médiane de chaque domaine du questionnaire EORTC-QLQ-C30 LC13.

La comparaison des résultats postopératoires entre les deux groupes n'est malheureusement pas valide. En effet, l'effectif limité de notre étude sur ces critères, associé à une répartition déséquilibrée entre les types de chirurgie et approches chirurgicales malgré la randomisation (Tableau 3 de l'étude ci-dessus), ne nous permet pas de réaliser une analyse interprétable. A l'échelle de l'ensemble des 36 patients, nous notons cependant un taux de complications proche des résultats globaux rapportés dans la littérature à 18,5% (4), et ce malgré une population très à risque au regard des comorbidités, du nombre de traitements par patient, et de la $\dot{V}O_2$pic moyenne à 13.5 ± 3.3 ml/kg/min. De même, l'analyse de la durée d'hospitalisation totale rapporte une médiane de 5 (4 - 6) jours, ce qui est légèrement inférieur, potentiellement grâce à la préhabilitation, à la durée médiane rapportée chez les patients opérés par VATS dans la base de données de l'ESTS avec une médiane de 6 (4 – 8) jours (4).

Comment expliquer l'absence d'équivalence ?

Les données de la littérature relatives aux modifications bioénergétiques expliquant le gain de $\dot{V}O_2$pic retrouvée en physiologie intégrative chez les patients atteints de BPCO sont les suivants (198) : amélioration du métabolisme oxydatif grâce à l'augmentation de la micro vascularisation musculaire (rapport capillaire/fibre) et de l'activité des enzymes oxydatives, qui s'accompagne d'une diminution de l'acidose lactique induite par l'exercice, et l'atténuation de la baisse du rapport phosphocréatine/phosphore inorganique au cours de l'exercice. Il est conventionnellement admis que ces modifications de la physiologie musculaire nécessitent des durées d'entrainement d'au moins 8 semaines (198). La non-équivalence de nos résultats quant au gain de $\dot{V}O_2$pic étant en faveur du groupe ayant

bénéficié d'un entrainement plus court, l'adaptation bioénergétique n'est probablement pas le facteur explicatif de notre résultat principal.

Parallèlement, il est reconnu que les gains de force sont dus à une combinaison de facteurs neurologiques et morphologiques, avec une prépondérance de l'adaptation des facteurs neurologiques au cours des premières semaines d'entraînement (199). Grâce à la récente mise au point de techniques de suivi électromyographique à haute densité, des données objectives sur les mécanismes d'adaptation neuromotrice ont pu être observé. Martinez-Valdes et al. ont ainsi rapporté que seulement six séances d'entrainement sur cyclo-ergomètre, réparties sur 2 semaines, étaient associées à une modification de la vitesse de conduction des unités motrices des muscles vastes médial et latéral (200). L'étude de Del Vecchio et al. a pu confirmer qu'une courte période de renforcement musculaire (4 semaines) améliore la force maximale volontaire en association avec une diminution des seuils d'excitabilité des unités motrices (201). Ces auteurs concluent que le gain de force précoce est attribuable à une augmentation des afférences synaptiques excitatrices ou à des adaptations des propriétés des motoneurones. Nous pouvons donc supposer que le fait de regrouper les séances d'entraînement sur une courte période, soit un entrainement de forte densité, a potentiellement stimulé de manière plus répétée et continue la plasticité neuromotrice. En l'absence de mesure électromyographique, il ne nous est pas possible de répondre à cette supposition.

Enfin, la supervision quotidienne peut avoir une influence sur la motivation des patients. Contrairement à nos appréhensions, proposer un entrainement ambulatoire dense ne s'est pas accompagné d'une dégradation de la qualité de vie ou d'une moindre adhésion aux séances. Une évaluation qualitative complémentaire sur la perception du programme, tant vis-à-vis des contraintes que de l'aspect motivationnel serait pertinente. Ces données ne sont pas présentes dans la littérature à ce jour.

4.4. A la recherche du programme d'entrainement préopératoire optimal

4.4.1. Durée, fréquence et densité

La durée des protocoles évalués dans la littérature s'étend globalement de 1 à 5 semaines, avec des fréquences d'entrainement comprises entre 3 et 5 fois par semaine (183).

Dans le cadre de notre revue-systématique et méta-analyse nous avons procédé à une sous-analyse en séparant les résultats obtenus selon la durée des programmes de préhabilitation (Annexe 3.10). L'analyse en sous-groupes des sept études proposant un entraînement préopératoire densifié de courte durée (≤ 2 semaines) a rapporté une réduction significative des complications postopératoires avec un RR à 0,47 [IC à 95 % 0,31 à 0,69]. Paradoxalement, le niveau de certitude concernant les programmes de plus longue durée (≥ 3 semaines) est non significatif avec un intervalle de confiance élargi, allant jusqu'à un effet marginal avec un RR à 0,63 [IC 95% 0,38 à 1,04]. On retrouve cette même observation concernant la durée moyenne d'hospitalisation avec une réduction de -2,7 jours [IC à 95 % -3,9 à 0,-1,5] pour les programmes densifiés de courte durée (≤ 2 semaines) et de-1,1 jours [IC à 95 % -4,2 à 1,9] concernant les programmes de plus longue durée (≥ 3 semaines). Les deux types de programmes rapportent cependant des bénéfices significatifs concernant la distance de marche au TDM6 avec une amélioration de 25,9 m [IC à 95 % 14,6 à 37,2] et 95,9 m [IC à 95 % 27,2 à 164,6] pour les programmes densifiés de courte durée (≤ 2 semaines) ou de plus longue durée (≥ 3 semaines) respectivement. Notons que la pertinence clinique semble plus marquée en faveur de programmes plus longs (183) (Annexe 3.10).

Parallèlement, la dernière étude que nous avons exposé dans cette thèse vient étayer l'hypothèse d'une stimulation physiologique non-équivalente entre les programmes condensés ou étalés dans le temps. En effet, nous avons retrouvé une absence d'équivalence, avec une amélioration moyenne plus importante de la $\dot{V}O_2$pic chez les patients ayant bénéficié d'un entrainement condensé (195).

Ces éléments ne nous permettent pas aujourd'hui de conclure à la supériorité d'une modalité d'entrainement, notamment si nous prenons en compte le facteur confondant du

lieu de réentrainement (hospitalisation ou ambulatoire). Cependant, un faisceau de preuves scientifiques nous permet d'affirmer que des programmes denses de courte durée sont à la fois faisables et efficaces pour améliorer la condition cardio-respiratoire préopératoire, et contribuer à prévenir les complications postopératoires. Une stratégie d'entrainement de courte durée permettant d'élargir le nombre de patients bénéficiaires de ces programmes est certainement à considérer.

La réalisation de programmes intégrant à la fois une fréquence de séances élevée (≥ 5 fois par semaine) sur une période prolongée (5 à 6 semaines) pourrait potentiellement apporter des bénéfices d'autant plus importants, grâce à une charge d'entrainement totale majorée. Nous n'avons pas d'éléments permettant de répondre à cette hypothèse, cependant la faisabilité, le rapport coût/efficacité, et enfin l'acceptabilité de tels programmes seraient à évaluer.

4.4.2. Intensité de l'effort

Dans le cadre de nos travaux, nous avons abordé les effets d'un programme d'entrainement continu à charge modérée, celle-ci étant initialement proposée au SV1 correspondant à environ 50 à 60% de la $\dot{V}O_2$pic atteinte à l'EFX (78).

L'intensité d'entrainement est un facteur influençant la réponse physiologique qui interviendra au moment de la compensation à la suite de la séance d'entrainement. Plus l'intensité de l'entrainement est importante, soit proche de la capacité maximale du sujet, plus les bénéfices escomptés sont importants. Ceci a été démontré chez les patients atteints de syndrome respiratoire obstructif à travers les travaux de Casaburi et al. rapportant une diminution significativement plus importante de la lactatémie, des paramètres ventilatoires et de la fréquence cardiaque à l'EFX en faveur du groupe ayant bénéficié d'un entrainement à haute intensité (80% Pmax) versus intensité modérée (50% Pmax) (202). Bien que ceci soit applicable sur le plan théorique, les études menées auprès des patients atteints de pathologies respiratoires chroniques tendent à montrer qu'une faible proportion des patients traités sont capables de tolérer des intensités d'entrainement élevées. Ainsi, Maltais et al.

rapportent que seulement 5 patients sur 42 ont toléré un entrainement à une puissance supérieure à 70% de leur Pmax au cours d'un programme de réhabilitation respiratoire (203).

Afin d'exposer le patient à des stimuli intenses, tout en maintenant une acceptabilité de l'entrainement, certaines équipes proposent des programmes d'entrainement à haute intensité entrecoupés d'intervalles de récupération (« *High intensity interval training* » HIIT). Ainsi, l'équipe de Licker et al. proposaient dans leur étude une alternance de cycles de 10 minutes composés de 15 secondes d'exercice à 80-100% de la Pmax, entrecoupées de 45 secondes de récupération à intensité modérée (166). Bathia et al. ont réanalysé les données de cette étude et confirmé la faisabilité et la tolérance hémodynamique de cette technique d'entrainement chez les sujets atteints de CBNPC en attente de chirurgie (204). Cependant, il s'agit de la seule cohorte randomisée contrôlée évaluant ce type d'entrainement dans notre population d'intérêt. De plus, cette étude compare l'HIIT aux soins courants ne présente pas de troisième groupe entrainé à intensité modérée. Nous manquons de données pour évaluer la supériorité ou non de l'utilisation du HIIT par rapport aux entrainements décrits à intensité modérée.

Minnella et al. ont réalisé une étude contrôlée randomisée comparant spécifiquement un entrainement préopératoire par HIIT versus intensité modérée continue (MICT) en oncologique digestive (205) (Figure 22). Les protocoles d'entrainements réalisés à raison de 3 fois par semaine pendant 4 semaines, étaient inclus dans un programme multimodal identique proposant une éducation périopératoire, une prise en charge nutritionnelle, et une gestion de l'anxiété. Leurs résultats ne font remonter aucune différence entre MICT et HIIT sur le gain préopératoire de $\dot{V}O_2$pic 1,97 ml/kg/min [IC 95% 0,75 à 3,19] pour le groupe HIIT versus 1,71 [IC 95% 0,56 to 2,85] pour le groupe MICT (p=0,753).

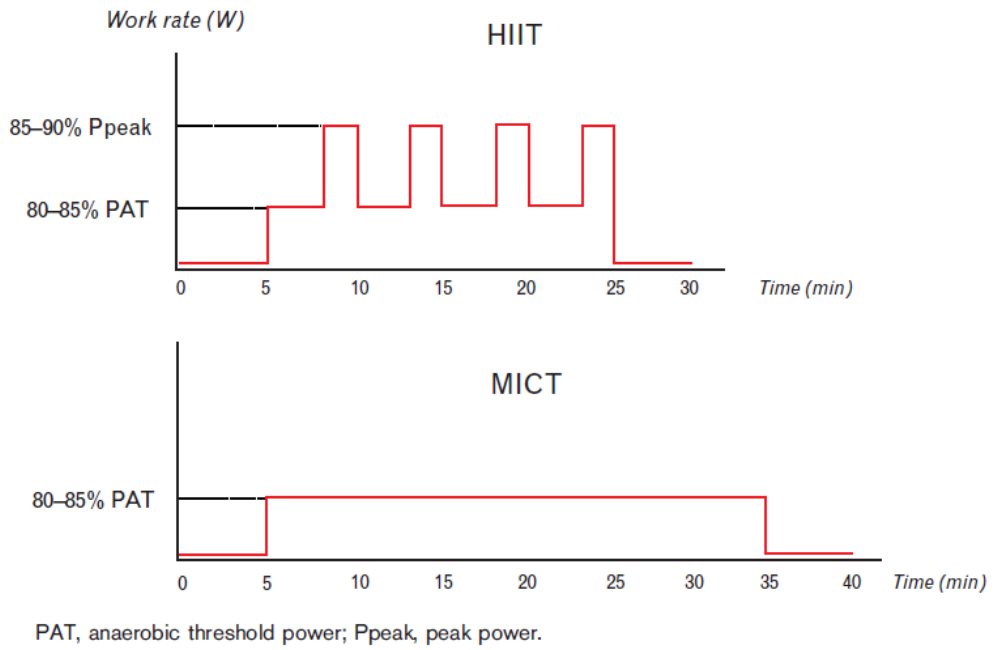

Figure 22 : Représentation graphique de l'entraînement à l'exercice dans les groupes d'entraînement par intervalles à haute intensité (HIIT) et d'entraînement continu à intensité modérée (MICT) d'après Minnella et al. (205) ; Ppeak : puissance au pic ; PAT : puissance au seuil anaérobie.

Smyth et al. ont récemment publié une méta-analyse évaluant les effets de l'HIIT auprès des patients en attente de résections oncologiques thoraciques et digestives confondues (206). Les auteurs ont pris le parti de comparer l'effet des programmes de HIIT aux patients recevant des soins courants ou un entrainement à intensité modérée (intégrés en tant que même contrôle dans l'analyse) . Leurs résultats ne rapportent pas d'effet significatif d'un entrainement par HIIT sur la $\dot{V}O_2$pic préopératoire avec une différence moyenne de 0,83 kg/ml/min [IC 95% -0,51 à 2,17] (206). Notons que l'effet du HIIT versus soins courants seul est certainement masqué par l'association avec des participants ayant bénéficié d'un entrainement à intensité modérée.

Ainsi comme le suggèrent Minnella et al. (205) dans leur conclusion, l'HIIT et le MICT ne présentent pas de supériorité l'un par rapport à l'autre mais peuvent permettre de varier les entrainements ou de s'adapter aux préférences du patient pour maximiser l'adhérence.

4.4.3. Entrainement combiné

Le réentrainement basé sur des exercices en endurance sur cyclo-ergomètre ou à la marche est l'outil le plus décrit pour la réadaptation physique des insuffisants respiratoires chroniques. Cette intervention qualifiée de « pierre angulaire » de la réhabilitation respiratoire (207), a montré aujourd'hui ses bénéfices pour prévenir les complications postopératoires (183). Tout comme en réhabilitation conventionnelle des interventions physiques complémentaires peuvent aussi être considérée. Proposer des entrainements combinés permet sur le plan pratique de multiplier les activités physiques au cours des sessions d'entrainement sur des modes de sollicitations plus ou moins intenses. Cette stratégie vise à augmenter le volume des séances et par conséquent la charge totale d'entrainement grâce à la variation des activités qui rendent la séance moins monotone, mais aussi à diversifier des stimuli neuromoteurs.

Exercice en résistance

L'association de l'entrainement en endurance et en résistance est systématiquement recommandée depuis plusieurs années chez les patients respiratoires chroniques (133). Il est donc naturel de constater que l'entrainement en résistance est considéré dans la majorité des études évaluant les programmes d'entrainement préopératoire chez les patients atteints de CBNPC, comme nous l'avons relevé dans les caractéristiques des études inclues dans notre revue systématique (183).

Variation des tâches : entrainement non linéaire

Bien que ceci n'ait pas été évalué chez les personnes en attente de résection pulmonaire, la mise en place d'un entrainement dit « non-linéaire », c'est-à-dire basé sur des types d'exercices ainsi que des intensités/durées variables à chaque séance, a montré des bénéfices supérieurs à un entrainement conventionnel linéaire chez les patients atteints de

BPCO (208). L'intégrations d'activités physiques adaptées et d'exercices fonctionnels peut être un moyen de tendre vers ces bénéfices de la variation des stimuli.

Entrainement des muscles inspirateurs (EMI)

Suite à la dernière méta-analyse de Ge et al. (146), la réalisation d'un programme d'EMI avant chirurgie majeure bénéficie d'un niveau de preuve suffisant pour être conseillé en pratique clinique. Il a été montré que l'adjonction de l'EMI à un programme multimodal de réhabilitation respiratoire conventionnel n'était pas associée à un bénéfice clinique supérieur, hormis concernant la Pimax (209, 210). Ainsi, la question du cumul entre l'EMI et l'entrainement à l'effort global peut se poser sur le plan de la plus-value.

La majorité des études randomisées disponibles dans le domaine de l'oncologie thoracique évaluent cette pratique combinée au réentrainement physique (173, 192, 211). Son utilisation en tant que technique isolée comparée aux soins courants, ou un entrainement combiné (EMI + entrainement à l'exercice), a uniquement été évaluée par Huang et al. dans une étude randomisée de trois groupes de 30 patients (212). Leurs résultats tendent à montrer qu'un programme combiné (EMI + entrainement à l'exercice) serait supérieur à un programme isolé d'EMI seul, le programme combiné étant le seul à présenter une réduction significative des complications postopératoires par rapport au groupe contrôle bénéficiant de soins courants. Leur analyse n'inclue malheureusement pas de comparaison directe entre le groupe entrainement combiné ou EMI seul.

Laurent et al. ont récemment décrit un entrainement plus global de la musculature respiratoire en endurance grâce à un dispositif d'hyperpnée isocapnique (213). Cet entrainement, réalisé dans les 4 semaines avant résection pour CBNPC, permet une augmentation de l'endurance ventilatoire avant chirurgie et pourrait expliquer la diminution des complications post-opératoires pulmonaires obtenue après l'entraînement. Bien que cette technique soit plus complexe que l'entraînement en force des muscles respiratoires car elle nécessite la mesure préalable de la Capacité Vitale Lente (CVL) et de le Ventilation Maximale Minute (VMM) et que son coût soit plus élevé, l'adhésion des patients est très satisfaisante (213). De par la stimulation continue du système cardio-respiratoire au travers

de cette technique de réentrainement, son utilisation auprès de patients ne pouvant pas réaliser un entrainement aérobie global en raison de comorbidités orthopédiques ou rhumatismales est potentiellement à retenir.

4.4.4. Mode de supervision

La question de l'accessibilité à la préhabilitation est intrinsèquement liée à la disponibilité de l'offre de soins dans le domaine de la réhabilitation. Quelque soient les zones géographiques, le taux de patients bénéficiant de l'accès à une structure de réhabilitation est dérisoire au regard du nombre de patient justifiant de cette prise en soins (214). Dans ce contexte, les différents modes de supervision de la réhabilitation méritent d'être étudiés.

Hospitalisation

La mise en place de programmes très rapides d'une semaine en hospitalisation complète est une stratégie proposée par Pehlivan et al. (215) ainsi que Benzo et al. (192) en 2011, puis reprise par l'équipe chinoise de Lai et al. qui ont publié une série de travaux issus d'une première étude en 2016-2017 (186-188), et une nouvelle étude en 2019 (174). Ces programmes ont le grand avantage de permette une supervision complète à la fois sur le plan nutritionnel, sevrage tabagique, prise en charge psychologique éventuelle… mais aussi la réalisation de multiples séances d'exercices physiques et respiratoire quotidiennes. Bien que les résultats rapportés par ces études randomisées contrôlées soient cliniquement pertinents concernant la diminution des complications et la durée de séjour postopératoires, ils nécessitent l'accueil en structure hospitalière ou centre spécialisé. L'évaluation des coûts et du taux de patient acceptant une hospitalisation préalable sont de potentiels freins à la généralisation de ce mode de préhabilitation. Ceci n'a pas été évalué à notre connaissance.

Séances ambulatoires

Un programme de réentrainement préopératoire ambulatoire peut permettre de concilier une supervision auprès d'une équipe spécialisée en réhabilitation sans engendrer une hospitalisation complète. C'est la stratégie que nous avons tenté de développer à travers la création de la filière de soins présentée en Figure 16 (page 90). Nous retrouvons ce mode de supervision dans les études publiées par Stefanelli et al. (164), Sebio-Garcia et al. (216) et Liker et al. (166). Ces trois études décrivent des protocoles d'entrainement de 3 à 5 séances par semaine sur des périodes allant de 3 à 8 semaines, ce qui les rapproche de notre pratique clinique (171). Un autre point commun est la supervision par une équipe de réhabilitation de l'ensemble des séances.

Certains projets de recherche en cours évaluent des programmes hybrides basés sur des séances supervisées par une équipe spécialisée, combinées à des séances autonomes à domicile. Ainsi, dans son protocole, l'équipe italienne de Fogazzaro et al. propose une répartition pour moitié de séances en centre, l'autre moitié étant réalisée à domicile sur la base des objectifs établis lors des séances supervisées (211). En ce qui concerne l'expérience française de Laurent et al., le programme de réentrainement proposé est réalisé en totalité au domicile du patient avec l'intervention hebdomadaire d'un professionnel pour s'assurer du bon déroulement du programme et ajuster les paramètres d'entrainement en fonction des progrès physiques du patient (217). Ces deux projets, encore en phase d'inclusion ou d'analyse, permettront d'évaluer l'efficacité de ces modalités d'entrainement.

Autonomisation

Certains auteurs ont décrit des programmes autonomes ou faiblement supervisés au domicile des patients. Tout d'abord, Liu et al. ont proposé un programme de réentrainement à domicile d'environ 2 semaines (175). Suite à une consultation dédiée incluant un ensemble d'évaluation et de conseil éducatif, le patient rentrait à domicile avec un livret d'exercices et de conseils globaux incluant des objectifs. Un suivi hebdomadaire téléphonique avec des questions standardisées était proposé pour évaluer l'adhérence, les progrès et proposer des objectifs complémentaires. Bien que les auteurs rapportent une amélioration moyenne au

TDM6 de 60 m [IC 95% 32.4 à 89.5] par rapport au groupe contrôle, l'ensemble des critères secondaires (complications postopératoires, qualité de vie…) ne présentait pas de différence significative (175). Sur un modèle d'autonomisation proche, Kim et al. ont proposé un programme autonome de marche progressive guidé à l'aide d'un podomètre et d'objectifs prédéfinis au cours d'une consultation individuelle (218). Ce mode de stimulation physique, à moindre coût et encadrement médical réduit, rapporte des résultats bénéfiques sur la capacité physique préopératoire ainsi que les complications postopératoires et la durée moyenne de séjour.

Il a été démontré dans le domaine de la réhabilitation respiratoire chronique que les programmes les plus encadrés (ambulatoires ou en hospitalisation) produisent des bénéfices cliniques supérieurs aux programmes à domicile ou autonome (219). A notre connaissance, cette comparaison n'a pas encore été évaluée dans le contexte préopératoire. Pour autant, les trois grands modes de supervisions précédemment évoqués sont certainement complémentaires afin d'augmenter l'offre de soins tout en la personnalisant aux besoins des patients. L'essor des technologies de suivi médicalisé évaluée dans le cadre de la réhabilitation conventionnelle est actuellement encore en phase d'évaluation de faisabilité auprès des patients préopératoires. La diffusion de la télé-réhabilitation impactera certainement les options de supervision de la préhabilitation dans un avenir proche.

4.4.5. Adapter la préparation physique à l'évaluation du risque ?

Au regard de l'ensemble des paramètres pouvant être pris en compte dans la programmation de l'optimisation physique du futur opéré thoracique pulmonaire, la définition de différents parcours de soins, personnalisés aux besoins du patient nécessitent d'être définis. La faisabilité en termes d'adhésion et de sûreté de ces programmes n'est plus à démontrer. Proposer des parcours réellement applicables en pratique clinique, ces derniers étant encore trop limités à de la recherche clinique, nécessitera de les proportionner au niveau de risque pour deux éléments majeurs :

- **L'accessibilité aux structures de soins** : proposer une autonomisation complète ou partielle aux patients les moins à risque permettra de réserver aux patients les plus fragiles des soins multimodaux en centre spécialisé, tout en maintenant des délais de prise en soins raisonnables. Ceci est d'autant plus important que le délai de prise en charge en préhabilitation est un facteur prédictif d'adhésion ou non à la préhabilitation (220).
- **L'efficacité médico-économique :** le financement de ces programmes à grande échelle dépendra de dépenses de soins proportionnées aux besoins des patients selon leur profil de. A titre d'exemple Boden et al. ont rapporté qu'une simple consultation de kinésithérapie préopératoire de 30 min (incluant initiation à la kinésithérapie postopératoire et incitation à la pratique d'une activité physique régulière avant la chirurgie), était à la fois associée à une réduction non seulement des complications postopératoires (144), mais aussi des coûts hospitaliers (221). L'impact coût-efficacité des programmes multimodaux plus complets nécessite d'être démontré dans les études à venir.

Sur la base de l'analyse de la littérature et des algorithmes relatifs à l'évaluation avant chirurgie thoracique nous proposons une perspective à la fois dans l'évaluation du risque du patient et dans la proportionnalité du programme de préhabilitation correspondant. En accord avec les recommandations anglo-saxonnes (57, 58), une consultation de kinésithérapie précoce dans le parcours préopératoire permettrait de filtrer les patients les moins à risque de morbi-mortalité à l'aide d'un test simplifié de la capacité à l'exercice, ainsi que d'évaluer la force inspiratoire et l'efficacité de la toux du patient. Chez les patients d'emblée présumés à risque élevé lors des premières évaluations médicales, ou présentant une capacité à l'exercice amoindrie au cours des tests de terrain réalisés en consultation kinésithérapique, l'EFX permettrait d'affiner l'évaluation tout en fournissant un niveau d'entrainement spécifique.

Enfin, en s'inspirant des niveaux de risque définis actuellement (57), nous proposons 4 types de programmes allant d'une simple éducation préopératoire poursuivie de manière autonome à un programme multimodal en hospitalisation.

Cette stratégie d'évaluation et de préhabilitation aurait, sur le plan théorique, le triple intérêt de réserver les créneaux d'EFX aux patients les plus à risques, d'éduquer à la kinésithérapie postopératoire, et d'accélérer l'orientation vers un parcours de préhabilitation allégé pour les patients les moins à risque. Cet algorithme, proposé par Laurent et Gravier (222) (Figure 23), reste à évaluer en pratique courante, tant sur le plan de l'adhésion des patients à leur prise en charge dans ce contexte lourd, que des résultats post-opératoires et que l'impact économique.

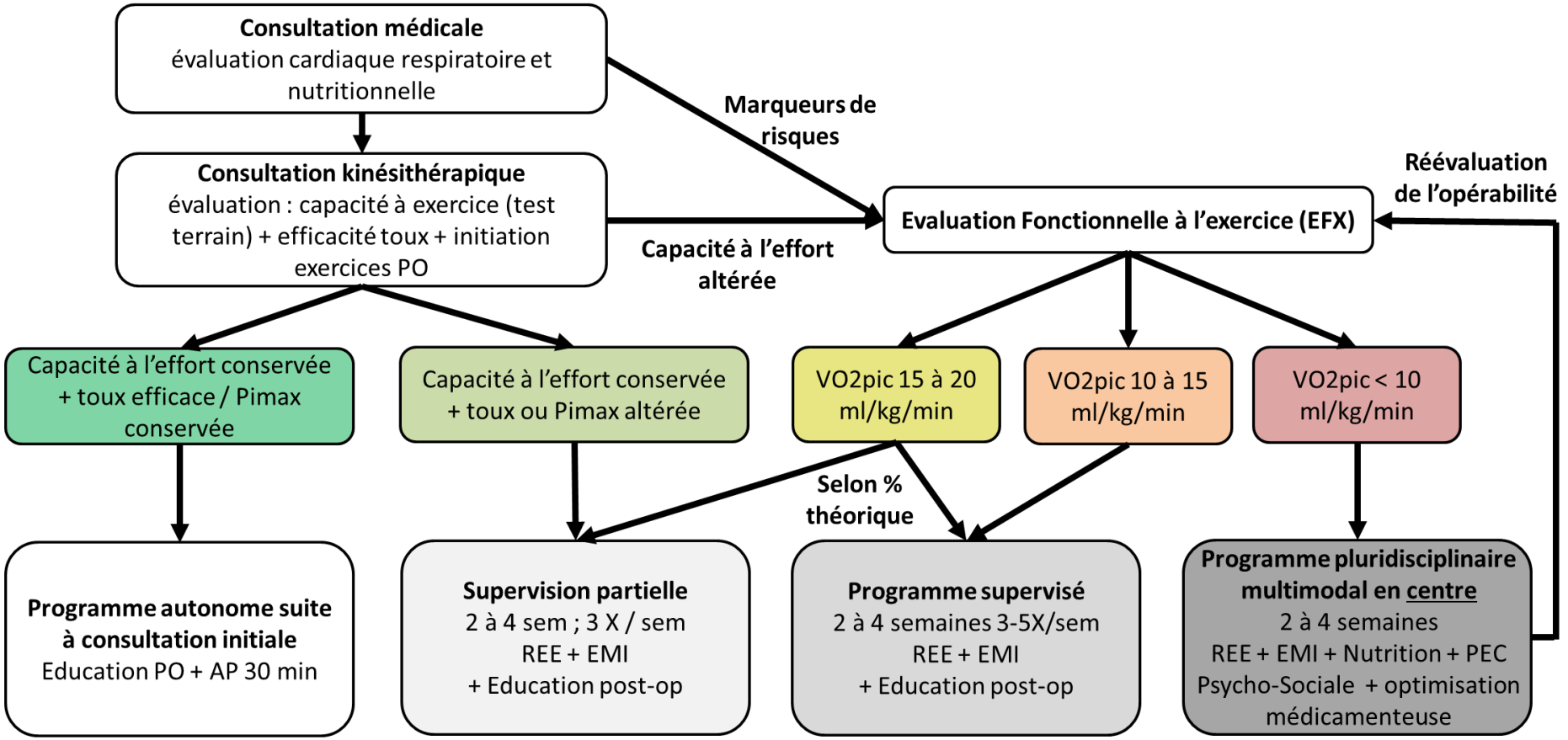

Figure 23 : proposition d'algorithme d'adaptation de la préhabilitation au niveau de risque avant chirurgie thoracique pulmonaire proposé par Laurent H. et Gravier FE. (222). AP : activité physique ; EMI : entrainement des muscles inspirateurs ; PEC : prise en charge ; Pimax : pression inspiratoire maximale ; PO : postopératoire ; REE : réentrainement à l'effort ; VO2pic : consommation pic en oxygène.

4.5. Conclusion de la Troisième partie

Dans cette troisième et dernière partie nous avons traité les axes d'optimisation de l'entrainement préopératoire et une part des composantes qui forment plus largement la préhabilitation.

L'article original que nous avons inclus dans cette partie traite de l'effet de la densité de l'entrainement préopératoire. Nous savons à présent que la quantité de stimuli totale n'est pas le seul facteur de la réponse à l'entrainement, et que les modalités de programmation de cette charge totale d'entrainement ne produisent pas des résultats équivalents. Ainsi, dans notre pratique clinique basée sur un programme ambulatoire supervisé, nous inciterons dans la mesure de la faisabilité concrète (impératifs médicaux et familiaux), à une programmation plus dense de l'entrainement.

Suite à ce travail et grâce aux données à notre disposition dans la littérature, nous avons discuté de l'influence d'autres paramètres, dont la modulation pourrait influencer l'efficacité du programme. Nous avons traité de l'intensité du réentrainement, des exercices associés, ainsi que de leur mode de supervision. Au total, les données disponibles actuellement pour répondre aux meilleurs paramètres et modalités d'entrainement restent rare et peu discriminantes.

Une réponse générique pour chaque paramètre semble difficilement possible si la diversité des profils de patients adressés en préhabilitation n'est pas prise en compte. Ainsi, en s'inspirant des algorithmes d'évaluation en chirurgie thoracique (développés en partie 1), nous avons terminé cette dernière partie sur une proposition d'adaptation de l'entrainement au niveau de risque de chaque patient.

5. Conclusion Générale

Quelques soient les progrès scientifiques sur le plan chirurgical et anesthésiologique, les facteurs propres au patient conditionnent les résultats postopératoires. Parmi ces facteurs, certains sont modifiables, dont la capacité à l'exercice qui a été le fil conducteur de nos travaux de recherche. Tout au long de ce manuscrit de thèse, nous avons successivement abordé les grandes étapes permettant d'aboutir à une modification préopératoire significative du conditionnement cardio-respiratoire du patient.

Tout d'abord, l'évaluation de la capacité à l'exercice est un préambule indispensable. Elle permet non seulement de stratifier le niveau de risque, mais aussi de proposer une prise en charge préventive adaptée grâce à l'entrainement préopératoire. Dans ce cadre, nous avons exposé deux travaux originaux, centrés sur l'évaluation préopératoire. Le premier nous a permis d'identifier qu'environ 30% des patients reçus en EFX préopératoire fournissaient des efforts sous-maximaux, et le second nous a permis de mettre en évidence qu'une performance de plus de 49 levers de chaises en 3 minutes permettait d'identifier les patients avec une $\dot{V}O_2pic$ supérieure à 15 ml/kg/min. Ces deux travaux complémentaires, nous encouragent à réduire les paliers d'incrément, voire répéter l'EFX de certains patients, pour maximiser la validité de la capacité à l'exercice mesurée. Ceci peut allonger la durée de l'évaluation de la capacité à l'exercice et impacter le volume de patients qui accèdent à l'EFX dans un contexte déjà limité. C'est pourquoi l'identification de tests de terrain validés aisément réalisables en pratique clinique auprès des patients atteints de CBNPC tient une importance capitale.

En second lieu, l'évaluation permet de mettre en place des mesures préventives, dont un réentrainement préopératoire, chez les patients à risque postopératoire. A travers une analyse rétrospective de notre pratique clinique, nous avons mesuré concrètement les bénéfices physiologiques du programme de réentrainement préopératoire entrepris depuis 2014. Ces résultats, déjà présumés par de nombreux cliniciens, sont aujourd'hui étayés par des études contrôlées randomisées réalisées dans toutes les régions du monde. Les résultats

de notre revue systématique et méta-analyse confirment les bénéfices significatifs sur le taux de complications postopératoires. De futures études complémentaires permettront d'améliorer le niveau de preuve quant à la qualité de vie et la capacité fonctionnelle à plus long terme.

Enfin, au regard du niveau de preuve grandissant de l'efficacité de l'entrainement préopératoire, nous avons choisi de concentrer nos efforts de recherches prospectives sur les modalités d'optimisation. L'étude prospective que nous avons entrepris de mai 2019 à mai 2021 a évalué l'effet de la densité de l'entrainement préopératoire. Nous avons mis en évidence que la densité de programmation des séances d'entrainement peut produire des résultats non équivalents. De nombreux paramètres peuvent influencer les bénéfices du réentrainement : intensité, association de différents exercices, supervision... Les données disponibles actuellement pour répondre aux meilleurs paramètres et modalités d'entrainement restent rare et peu discriminantes. L'adaptation au cas par cas de ces paramètres au niveau de risque et aux facteurs personnels du patient est à envisager.

Au total, les cinq articles originaux inclus dans ce manuscrit de thèse nous ont permis de valider ou invalider scientifiquement nos hypothèses autour de l'évaluation et de l'entrainement préopératoires des patients de chirurgie pulmonaire oncologique. Ces résultats nous aident à optimiser notre pratique clinique et à préparer de futurs projets autour de l'entrainement préopératoire de résection pulmonaire oncologique.

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Annexes

Annexe 1 : 8eme édition de la classification TNM des tumeurs du poumon (A), et correspondance des stades d'après la 8e édition de la classification TNM (B).

Annexe 2 : données en ligne complémentaires de l'article : *Cardiopulmonary exercise testing in patients with non-small cell lung cancer : trust the $\dot{V}O_2$peak ?*

Annexe 3 : données en ligne complémentaires de l'article : *Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis.*

Annexe 4 : Réponse lettre à l'éditeur : *Prehabilitation versus standard care-What impact on complications ?*

Annexe 5 : données en ligne complémentaires étude Preo-Dens

Annexe 1.1. : 8eme édition de la classification TNM des tumeurs du poumon (14)

TNM	Description
Tumeur	
TX	Tumeur primitive ne pouvant être évaluée ou démontrée par la présence de cellules malignes dans les expectorations ou un LBA sans visualisation de la tumeur par des examens endoscopiques ou d'imagerie.
T0	Pas de signe de tumeur primitive
Tis	Carcinome in situ
T1	Tumeur de 3 cm ou moins dans sa plus grande dimension, entourée par le poumon ou la plèvre viscérale, sans signe bronchoscopique d'invasion plus proximale que la bronche lobaire (cad. N'atteignant pas la bronche souche)
	T1a(mi) Adénocarcinome miniinvasif
	T1a ≤ 1 cm ou moins dans sa plus grande dimension
	T1b Tumeur de plus de 1 cm sans dépasser 2 cm dans sa plus grande dimension
	T1c Tumeur de plus de 2 cm sans dépasser 3 cm dans sa plus grande dimension
T2	Tumeur de plus de 3 cm sans dépasser 5cm dans sa plus grande dimension ou présentant une des caractéristiques suivantes : • Atteinte de la bronche souche quelle que soit sa localisation par rapport à la carène sans l'envahir • Invasion de la plèvre viscérale • Présence d'une atélectasie ou d'une pneumopathie obstructive s'étendant jusqu'au hile, touchant tout ou une partie du poumon
	T2a Tumeur **de plus de 3 cm sans dépasser 4 cm dans sa plus grande dimension**
	T2b Tumeur **de plus de 4 cm sans dépasser 5 cm dans sa plus grande dimension**
	Tumeur de toute taille avec envahissement d'une structure adjacente (paroi thoracique, diaphragme, plèvre médiastinale, péricarde pariétale) Ou tumeur à moins de 2cm de la carène sans envahissement ou atélectasie Ou nodules tumoraux séparés dans le même lobe
T3	Tumeur **de plus de 5 cm sans dépasser 7 cm dans sa plus grande dimension** ou tumeur associée à un ou plusieurs nodules séparés dans le même lobe que la tumeur primitive, ou envahissant directement une des structures suivantes : paroi thoracique (y compris la plèvre pariétale et les tumeurs de l'apex), le nerf phrénique ou le péricarde pariétal
T4	Tumeur **de plus 7 cm dans sa plus grande dimension** ou tumeur de toute taille associée à un ou plusieurs nodules dans un lobe ipsilatéral différent de la tumeur primitive ou envahissant directement une des structures suivantes : diaphragme, médiastin, cœur, gros vaisseaux, trachée, nerf laryngé récurrent, œsophage, corps vertébral et carène
Ganglions (Nodes)	
NX	Ganglions lymphatiques régionaux ne pouvant être explorés
N0	Pas de métastase ganglionnaire lymphatique régionale
N1	Métastase dans les ganglions lymphatiques intrapulmonaires, péri-bronchique et/ou hilaires ipsilatéraux, y compris par envahissement direct

N2	Métastase dans les ganglions lymphatiques médiastinaux ipsilatéraux et/ou sous-carinaires
N3	Métastase dans les ganglions lymphatiques médiastinaux controlatéraux, hilaires controlatéraux, scalènes ou sus-claviculaires ipsilatéraux ou controlatéraux
Métastases	
MX	Les métastase à distance n'ont pas pu être évaluées
M0	Absence de métastase à distance
M1	Présence de métastase à distance
	M1a Nodule(s) tumoral(aux) distinct(s) dans un lobe controlatéral, tumeur avec nodules pleuraux ou péricardiques ou épanchement pleural (ou péricardique) malin
	M1b Métastase à distance unique
	M1c Multiples métastases dans un ou plusieurs organes

Les modifications apportées par rapport à la 7e édition de la classification TNM des tumeurs du poumon (12) sont mises en évidence en gras comme modélisé par Westell & Jacoulet (10)

Annexe 1.2. : Correspondance des stades d'après la 8e édition de la classification TNM (14)

		N catégorie			
		Stade			
Description 7e éd. TNM	Proposition T et M	N0	N1	N2	N3
T1 jusqu'à 1cm	T1a	IA1 (IA)	IIB (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	IA2 (IA)	IIB (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	IA3 (IA)	IIB (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	IIB (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	IIA (IB)	IIB (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	IIB (IIA)	IIIA (IIB)	IIIB (IIIA)	IIIC (IIIB)
T3 structures	T3	IIB	IIIA	IIIB (IIIA)	IIIC (IIIB)
T3 > 7cm	T4	IIIA (IIB)	IIIA	IIIB (IIIA)	IIIC (IIIB)
T3 diaphragme	T4	IIIA (IIB)	IIIA	IIIB (IIIA)	IIIC (IIIB)
T3 endobronche : localisation/ atélectasie 3-4 cm	T2a	IB (IIB)	IIB (IIIA)	IIIA	IIIB
T3 endobronche : localisation/ atélectasie 4-5 cm	T2b	IIA (IIB)	IIB (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	IIIC (IIIB)
M1a	M1a	IVA (IV)	IVA (IV)	IVA (IV)	IVA (IV)
M1b unique	M1b	IVA (IV)	IVA (IV)	IVA (IV)	IVA (IV)
M1b multiple	M1c	IVB (IV)	IVB (IV)	IVB (IV)	IVB (IV)

L'évolution des stades par rapport à la 7e édition de la classification TNM des tumeurs du poumon (12) sont précisées avec rappel de l'ancien stade entre parenthèse comme modélisé par Westell & Jacoulet (10)

Annexe 2 : données complémentaires de l'article : Cardiopulmonary exercise testing in patients with non-small cell lung cancer: trust the $\dot{V}O_2$peak? Journal of thoracic disease. 2020 Oct;12(10):5313-23

Annexe 2.1. Supplemental Table 1: Comorbidities and medications.

Diagnosed / treated comorbidities	n (%)	Medications	n (%)
Cardiovascular		Antihypertensive	96 (47.3)
Arterial hypertension	97 (47.8)	Long-acting bronchodilators	94 (46.3)
Arteriopathy	42 (20.7)	Antiplatelet agent	86 (42.4)
Cardiopathies	25 (12.3)	Lipid-lowering	70 (34.5)
Atrial fibrillation	12 (5.9)	Antiarrhythmic of which beta-blocker	40 (19.7) 32 (15.8)
Stroke	9 (4.4)	Inhaled corticosteroids	38 (18.7)
Vein thrombosis	6 (3.0)	Anxiolytic	35 (17.2)
Pulmonary embolism	4 (2.0)	Gastric antisecretory	34 (16.7)
Respiratory		Short-acting bronchodilators	30 (14.8)
Chronic Obstructive Pulmonary disease / Emphysema	109 (53.7)	Opioid analgesic	25 (12.3)
Apnoea	14 (6.9)	Oral anti-diabetic	24 (11.8)
Asbestosis	6 (3.0)	Paracetamol	23 (11.3)
Tuberculosis	4 (2.0)	Antidepressant	21 (10.3)
Asthma	3 (1.5)	Anticoagulant	18 (8.9)
Aspergillosis	3 (1.5)	Vitamins	16 (2.5)
Digestive / Metabolic / Endocrine		Thyroid hormone	15 (7.4)
Dyslipidaemia	63 (31.0)	Insulin	14 (6.9)
Diabetes	35 (17.3)	Diuretic	14 (6.9)
Alcoholism	22 (10.8)	Hypnotics	13 (6.4)
Hypothyroidy	14 (6.9)	Anti-gout	7 (3.4)

Peptic ulcer	11 (5.4)	Nicotine substitutes	6 (3.0)
Chronic pancreatitis	4 (2.0)	Alpha blockers	6 (3.0)
Renal failure	3 (1.5)	Nocturnal oxygen therapy and/or ventilation	5 (2.5)
Orthopaedic and Rheumatology		Antifungal	5 (2.5)
Hip / knee prosthesis	14 (6.9)	Oral corticosteroids	5 (2.5)
Osteoarthritis	11 (5.4)	Anti-epileptic	4 (2.0)
Chronic low back pain	10 (4.9)	Immunosuppressant	4 (2.0)
Spinal hernia	8 (3.9)	Antihistamine	3 (1.5)
Gouty arthritis	6 (3.0)		
Rheumatoid arthritis	4 (2.0)		
Osteoporosis	3 (1.5)		
Oncologic			
Pulmonary	12 (5.9)		
Prostate	12 (5.9)		
Gynaecological	3 (1.5)		
Colorectal	3 (1.5)		
Otorhinolaryngologic	2 (1.0)		
Psychological			
Anxio-depressive syndrome	19 (9.4)		
Per patient *median (IQR)*	3 (2 – 4)	**Per patient** *median (IQR)*	4 (2 – 6)

Annexe 2.2. Analyse de la population, protocole d'incrément, et utilisation d'une $\dot{V}O_2$max ou pic, des références inclues dans la méta-analyse de Benzo et al. 2007 (80).

Etude	Population	Protocole Incrémental	$\dot{V}O_2$pic ou $\dot{V}O_2$max ?	$\dot{V}O_2$max/pic moyenne
Bechard (1987)	50 Vétérans	12.5 watts/min	"*Maximal O2 consumption (…) defined as the highest VO2 obtained during the exercise study*"	$\dot{V}O_2$max, 17.01 ± 0.77 vs 9.95 ± 1.52 ml/kg/min, p<0.001 sans complication vs avec complication respectivement
Bolliger (1995) (90)	80	échauffement départ 20 watts, rampe 20 watts/min	"*most patients reached a plateau in their oxygen consumption curve or developed a metabolic acidosis at peak exercise*"	$\dot{V}O_2$max, 19.7 ± 5 vs 14.7 ± 3 ml/kg/min, p=0.0002 sans complication vs avec complication respectivement
Boysen (1990)	17 Vétérans	Tapis de course : départ 2 mph pente nulle. Rampe 1 mph/min	Seulement notion de « $\dot{V}O_2$*max* »	$\dot{V}O_2$max 20.63 ± 5.53 vs 17.00 ± 4.30 ml/kg/min sans complication vs avec complication respectivement
Brunelli (2002) (92)	160	Test de montée d'escalier (SCT)	Seulement notion de « $\dot{V}O_2$*max* » (pas de réelle mesure de $\dot{V}O_2$ => estimation)	$\dot{V}O_2$max 25.85 (4.4) vs 23.61 (4.0) ml/min/kg p=0.03
Brutsche (2000) (77)	125	échauffement départ 20 W, rampe 20 W/min	Seulement notion de « $\dot{V}O_2$*max* »	$\dot{V}O_2$max 22.1±5.4 vs 17.9±5.4 ml/min/kg, p=0.0003 sans complication vs avec complication respectivement
Epstein (1993) (93)	42	"*work rate determined using the method of Wasserman et al*."	"$\dot{V}O_2$*peak averaged during the last 30 s of exercise* »	$\dot{V}O_2$pic 16.7±0.8 vs 16.4± 1.4 ml/min/kg, p= NS

Larsen (1997) (94)	97	10 ou 15 watts/min	Seulement notion de « $\dot{V}O_2max$ »	$\dot{V}O_2$max 1540±422 vs 1271±369 ml/min (soit env 18 vs 22 ml/kg/min) sans complication vs avec complication respectivement
Markos (1989) (95)	53	100 kilopond-meters/min (***soit environ 16,3 watts/min***)	Seulement notion de « $\dot{V}O_2max$ »	$\dot{V}O_2$max (ml/min/kg) Non calculé pour l'ensemble des patients : 22.1 ± 2.9 pré-lobectomie
Morice (1992) (96)	8	10 watts/min	"*peak oxygen uptake*"	$\dot{V}O_2$pic (ml/min/kg) 16.7 ± 1.9 Les patients avec une $\dot{V}O_2$pic <15 ml/kg/min ont été exclu et adressé vers un traitement non chirurgical.
Smith (1984) (97)	22 Vétérans	10 watts/min	Seulement notion de « $\dot{V}O_2max$ » Mais ambiguïté $\dot{V}O_2$pic	$\dot{V}O_2$max 22.4 ± 1.4 vs 14.9 ± 0.9 ml/min/kg, p<0.001 sans complication vs avec complication respectivement
Torchio (1998) (98)	56	Abstract	Utilisation de $\dot{V}O_2$pic et max	Non disponible
Villani (2004) (99)	150	Abstract	Seulement notion de « $\dot{V}O_2max$ »	Non disponible
Wang (1999) (100)	40	12.5 watts/min	Seulement notion de « $\dot{V}O_2max$ » Mais ambiguïté $\dot{V}O_2$pic	$\dot{V}O_2$max 17.8 ± 0.9 vs 16.3 ± 1.2 ml/min/kg, p=0.27 sans complication vs avec complication respectivement
Wang (2000) (101)	57	échauffement départ 20 W, rampe 20 W/min	Seulement notion de « $\dot{V}O_2max$ » Mais ambiguïté $\dot{V}O_2$pic	$\dot{V}O_2$max 19.2 ± 4.3 vs 15.0 ± 2.4 ml/min/kg, p<0.001

Annexe 3 : données en ligne complémentaires de l'article : Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis.

Annexe 3.1. Stratégie de recherche

Appendix 1. Example search strategy.

The search strategy for PubMed, shown below, used a sensitivity-maximising searching method. It was adapted for the other databases.

#1 (((((lung cancer[MeSH Terms]) OR (lung cancer[Title/Abstract])) OR (lung neoplasms[MeSH Terms])) OR (lung neoplasms[Title/Abstract])) OR (non small cell lung cancer[MeSH Terms])) OR (non small cell lung cancer[Title/Abstract])

#2 ((((((thoracic surgery[MeSH Terms]) OR (thoracic surgery[Title/Abstract])) OR (lung resection[Title/Abstract])) OR (pneumonectomy[Title/Abstract])) OR (lobectomy[Title/Abstract])) OR (segmentectomy[Title/Abstract])) OR (pulmonary resection[Title/Abstract])

#3 (((((Rehabilitation[MeSH Terms]) OR (Rehabilitation[Title/Abstract])) OR (Exercise [MeSH Terms])) OR (Exercise [Title/Abstract])) OR (prehabilitation[Title/Abstract])) OR (physical therapy[Title/Abstract])

#4 (((perioperative care[MeSH Terms]) OR (preoperative care[MeSH Terms])) OR (perioperative[Title/Abstract])) OR (preoperative[Title/Abstract])

#5 ((((((randomized controlled trial[Publication Type]) OR (randomized controlled trial[MeSH Terms])) OR (controlled clinical trial[Publication Type])) OR (controlled clinical trial[Title/Abstract])) OR (randomized[Publication Type])) OR (randomized[Title/Abstract])) OR (random[Title/Abstract])

#6 #1 AND #2 AND #3
#7 #6 AND #4
#8 #6 OR #7 AND #5

Appendix 2. Characteristics of included studies about preoperative exercise before lung resection in non-small cell lung cancer patients

First author (date)	Participants	Intervention	Duration / Frequency / Modality	Outcomes	Notes
Pehlivan et al. (2011)	60 people with operable (stage IA to IIIB) lung cancer without major cardiac morbidity, referred for surgery Ratio ♂/♀: unreported Age: 54 ± 8.5 years FEV1 (%): 71.2±18.2	Intensive physical therapy (IPT): - chest physiotherapy: diaphragmatic, pursed lip, segmental breathing exercise, usage of incentive spirometry, coughing exercise. - walking exercise: treadmill (according to the patient's tolerance to exercise speed and time, working heart rate at 0.65-0.8 HRmax) Control: no intervention/usual care	1-week Walking exercise: 3 sessions/day (*only two supervised*) inpatient preoperative program	Primary outcome: hospital length of stay Secondary outcomes: Pulmonary function test, arterial blood gas, ventilation-perfusion scintigraphy, postoperative complications	Lung cancer resection probably performed only by thoracotomy

Benzo et al. (2011) a	9 people with lung cancer and moderate to severe COPD referred for surgery Ratio ♂/♀: unreported Age: unreported FEV1 (%): unreported	Preoperative pulmonary rehabilitation performed according to the American Thoracic Society/ European Respiratory Society guidelines on exercise prescription Control: no intervention/usual care	4-weeks No information about frequency No information about in/outpatient modality	Hospital Length of stay, postoperative pulmonary complications No primary outcome defined	Lung cancer resection by thoracotomy or video assisted thoracoscopy No detailed results provided for study a (withdrawn) Study a included in the same publication of Benzo (2011) study b
Benzo et al. (2011) b	19 people with lung cancer and moderate to severe COPD referred for surgery Ratio ♂/♀: 9/10	Preoperative pulmonary rehabilitation: - endurance training: 20min of the lower extremity (on a treadmill or a semi-seated ergometer), and 20min of the upper extremity (arm-R-size exercises, arm ergometer or semi-seated ergometer). The intensity was adjusted according to both self-efficacy (“very confident”) and perceived exertion (2/10 on the BORG scale);	1-week 2 sessions/day	Hospital Length of stay, postoperative pulmonary complications, exercise capacity	

	Age: 71.1±7.6 FEV1 (%): 47.5±12.3	- muscle strengthening: upper and lower extremities using elastic bands, 2 sets of 10-12 repetitions; - inspiratory muscle training: threshold IMT or P-flex valve, 15-20min per day a level of perceived exertion of "somewhat hard"; - incentive spirometry and deep breathing exercises (included pursed lips breathing exercises), - self-walking and education Control: no intervention/usual care	inpatient preoperative program	No primary outcome defined	
Fang et al. (2013)	44 people with lung cancer and severe COPD referred for surgery Ratio ♂/♀: 34/10 Age: 59.7.1±10.0 FEV1 (%): 52.0±7.9	Preoperative exercise training: - endurance training: 40min of seating pedal power car or treadmill set to 60-80% of initial VO2peak, adjusted every two days, with oxygen provision as needed to maintain SpO2 ≥ 90%; - education to diaphragmatic and pursed-lips breathing techniques Control: no intervention/usual care	2-weeks 5 sessions/week No information about in/outpatient modality	Pulmonary function test, exercise capacity (CPET), quality of life, postoperative pulmonary complications, oxygen therapy, mechanical ventilation time, hospital length of stay	Lung cancer resection probably by thoracotomy Three-arm study. Only people from group A1 and A2 were included in the meta-analysis.

				No primary outcome defined	
Morano et al. (2013)	24 people with lung cancer and impaired respiratory function (COPD or other chronic respiratory diseases) referred for surgery Ratio ♂/♀: 9/15 Age: 66.8.1±7.7 FEV1 (%): 48.6±12.7	Preoperative pulmonary rehabilitation: - aerobic training: 10-30min of walking on a treadmill at 80% of Wpeak; - upper limb strengthening: proprioceptive neuromuscular facilitation method; - inspiratory muscle training: 10 to 30min at 10 to 60% of MIP; - flexibility, stretching and balance exercise; - education classes: pre- and post-operative care, knowledge of the surgical process, energy conservation techniques, relaxation and stress management techniques, nutrition, need to seek health services when necessary. Control: - breathing exercise: lung expansion exercises, sustained maximal inspirations, diaphragmatic and pursed-lips breathing, incentive spirometry (without inspiratory muscle training); - educational classes (same as intervention group)	4-weeks 5 sessions/week No information about in/outpatient modality	Pulmonary function test, arterial blood gas, exercise capacity (6MWT), length of stay in the hospital, postoperative pulmonary complications No primary outcome defined	Lung cancer resection by thoracotomy (only 1 video assisted thoracoscopy)

Stefanelli et al. (2013)	40 people with lung cancer and COPD (without chronic respiratory insufficiency) referred for surgery Ratio ♂/♀: 23/17 Age: 65.1±7 FEV1 (%): 57.5±17.6	Preoperative pulmonary rehabilitation: 15 sessions of 3 hours including - endurance training: high-intensity training of upper- (rowing ergometer) and lower-limb muscles (treadmill and ergometric bicycle), intensity: 70% Wpeak, increased by 10W when tolerate during 30min; - breathing exercise Control: no intervention/usual care	3-weeks 5 sessions/week outpatient preoperative exercise training	Pulmonary function test, dyspnoea, exercise capacity (CPET) No primary outcome defined	Lung cancer resection by thoracotomy N in each group non defined in full-text (considered as 20/20)
Sommer et al. (2016)	40 people with lung cancer referred for surgery Ratio ♂/♀: 16/24 Age: 69.2±34.5 FEV1 (%): 94.6±24.7	Preoperative exercise training (group 1 and 2): - endurance training: 30 min cardiorespiratory exercise with heart-rate monitoring and diary logbook Control (group 3 and 4): no intervention/usual care until surgery.	2-weeks *variable according to time before surgery* 7 session/week	Pulmonary function test, exercise capacity (6MWT), functional assessment (Functional Assessment of Cancer Therapy-Lung), adverse event, adherence, postoperative	Lung cancer resection by thoracotomy or video assisted thoracoscopy Four-arm study, adherence to the preoperative program is the only exploitable

			daily exercise until surgery home-based preoperative exercise training	pulmonary complications No primary outcome defined	outcome with regard to the study design
Tenconi et al. (2017) and Fugazzaro et al. (2016)	50 people with lung cancer, without neoadjuvant therapy, referred for surgery Ratio ♂/♀: unreported Age: unreported FEV1 (%): unreported	Preoperative pulmonary rehabilitation: Outpatient supervised 2-hours sessions include - aerobic exercise: 30-40min lower limb training on a cycloergometer, intensity based to reach 60-80% of the estimated Wpeak - muscle strengthening: 2-3 sets of 10 repetitions at the 10-RM for upper and lower limbs; - respiratory muscle training including breathing pattern training, PEP training and IMT ≥30% MIP; - therapeutic education Homebased 1-hour sessions include : - respiratory muscle training (twice a day), lower limb aerobic exercise training (60-	2 to 3 weeks 6 outpatient sessions: 2 or 3 times/week plus 8 home-based sessions: 3 to 4 times/week	Primary outcome: exercise capacity (6MWT) Secondary outcomes: Pulmonary function test, postoperative pulmonary complications, length of stay in the hospital, quality of life (SF-12), psychometric evaluation (HADs),	Results are provided as a congress abstract (Tenconi et al. 2017) but the trial protocol has been published (Fugazzaro et al. 2017)

		80% HRmax) monitored using a pedometer and a heart-rate monitor Control: no intervention/usual care		pain (NRS), compliance, adverse event	
Lai et al. (2017)	101 people with lung cancer and high postoperative complication risk factors, referred for surgery Ratio ♂/♀: 56/45 Age: 64.2±7.4 FEV1 (%): unreported *ppoFEV1 (%): 66.1±17.4*	Preoperative pulmonary rehabilitation: - endurance training: 30min of a semi-seated ergometer, intensity adjusted according to tolerance and regularly adjusted; - breathing exercise: 15-30 of abdominal breathing and 20 breaths (3 times/day) of breath holding and expiratory incentive spirometry; Control: no intervention/usual care	1-week 2 sessions/day inpatient preoperative exercise training	Primary outcome: postoperative pulmonary complications Secondary outcomes: exercise capacity (6MWT), quality of life (EORTC-QLQ-C30 & LC13_NC), costs	Lung cancer resection by thoracotomy or video assisted thoracoscopy

Sebio Garcia et al. (2017)	40 people (*analyzed 22*) with lung cancer and high postoperative complication risk factors, without neoadjuvant therapy, referred for surgery Ratio ♂/♀: 20/2 Age: 70.2±7.6 FEV1 (%): 77.6±22.3	Preoperative exercise training: - lower limb aerobic training: 30min of interval training with 1min at 80% Wpeak and 4min at 50% Wpeak, intensity was regularly adjusted; - peripheral muscle strengthening: 6 exercises consisting in 3 sets of 15 repetitions using elastic band or body weight exercise; - breathing exercises: incentive spirometry with an end-inspiratory hold (twice daily) Control: no intervention/usual care	Duration not fixed *4 to 8-weeks* 3 to 5 sessions /week *median [IQR] number of sessions 16 [8-25]* outpatient (*likely*) preoperative exercise training	Primary outcome: exercise capacity (CWET at 80% Wpeak) Secondary outcomes: exercise capacity (6MWT), muscle strength, quality of life (SF-36v2), hospital length of stay, postoperative pulmonary complications	Lung cancer resection by video assisted thoracoscopy Only the prehabilitation group was evaluated a second time before surgery.

Huang et al. (2017)	60 people with lung cancer and high postoperative complication risk factors referred for surgery Ratio ♂/♀: 41/19 Age: 63.3±7.6 FEV1 (%): unreported *ppoFEV1 (%): 69.6±16.5*	Preoperative pulmonary rehabilitation: - aerobic training: 20min of lower limb semi-seated ergometer, intensity set as tolerated; - breathing exercises: abdominal, thoracic, pursed lips breathing and incentive spirometry (4-time/day); - psychological-educational guidance about anxiety, depression and perioperative activities Control: no intervention/usual care	1-week 2 sessions/day inpatient preoperative exercise training	Primary outcome: postoperative pulmonary complications Secondary outcomes: pulmonary function test, exercise capacity (6MWT), quality of life (EORTC-QLQ-C30 & LC13_NC), hospital length of stay, fatigue and dyspnea index	Lung cancer resection by thoracotomy or video assisted thoracoscopy Three arm study: exercise training plus IMT group (n=30), only IMT group (n=30) and usual care group (n=30). Only the exercise training plus IMT and usual care groups were considered
Licker et al. (2017)	151 people with lung cancer, without neoadjuvant therapy, referred for surgery	Preoperative pulmonary rehabilitation: - aerobic training: 30min on cyclo-ergometer consisting in 5min of warm-up at 50% Wpeak followed by two 10-min series of interval training (15s at 80-100% Wpeak and 15s of rest, adjusted according to the highest intensity tolerated, and 5min of cool	Duration not fixed *3 to 5-weeks*	Primary outcome: 30-day postoperative morbidity (modified version of the thoracic	Lung cancer resection by thoracotomy or video assisted thoracoscopy

	Ratio ♂/♀: 91/60 Age: 64.0±11.5 FEV1 (%): 87.0±20.5	down), with 4-min rest between the two series; - peripheral muscle strengthening: leg press, leg extension, back extension, seat row, biceps curl, chest and shoulder press (individual basis); - advices about perioperative management (mobilization, risk factors) Control: no intervention/usual care	2 to 3 sessions /week *median [IQR] number of sessions 8 [7-10]* outpatient preoperative exercise training	mortality and morbidity classification ≥2) Secondary outcomes: Pulmonary function test, exercise capacity (CPET, 6MWT), physical activity, mortality, length of stay in the post anesthesia care unit and in the hospital, rate of admission to the intensive care unit	
Lai et al. (2019)	68 people with lung cancer and high postoperative complication risk factors referred for surgery	Preoperative pulmonary rehabilitation: - aerobic exercise: 30-min supervised by physiotherapist with a cross-trainer (Nu-step) including upper and lower limbs exercises; - breathing exercises: incentive spirometry supervised by nurse, 20 breaths/session	1-week	Primary outcome: exercise capacity (6MWT)	Lung cancer resection by video assisted thoracoscopy

	Ratio ♂/♀: 35/33 Age: 63.8±7.5 FEV1 (%): unreported *ppoFEV1 (%): 51.9±4.5*	- preoperative education Control: no intervention/usual care	Aerobic exercise: 1 sessions/day Incentive spirometry: 3 sessions/day inpatient preoperative exercise training	Secondary outcomes: pulmonary function test, arterial blood gas, quality of life (EORTC-QLQ-C30), postoperative pulmonary complications, hospital length of stay	
Liu et al. (2020)	85 people (*analyzed 73*) with lung cancer referred for surgery Ratio ♂/♀: 23/40 Age: 56.2±9.5	Prehabilitation program: - aerobic exercise (jogging, walking or cycling) at target HR = (220 - age – resting HR) x70% + resting HR) and adjustment with Borg scale score 13 – 16; - resistance exercise: upper and lower-limbs, chest and core muscles, start with initial	2-weeks 5 sessions/week home-based preoperative	Primary outcome: exercise capacity (6MWT) Secondary outcomes: pulmonary function test, disability, psychometric	Lung cancer resection by video assisted thoracoscopy

	FEV1 (%): 91.1±15.5	baseline strength and adjustment with Borg scale 13-16; - breathing exercises: incentive spirometry, cough and breath holding; - nutritional support; - psychological guidance and relaxation	exercise training instruction booklet with details and standard diaries to note the activities performed + weekly telephone calls	evaluation (HADs), length of stay in the hospital, postoperative pulmonary complications, mortality	
		Control: no intervention/usual care			

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second.; ppo: predictive postoperative.

Annexe 3.3. Evaluation détaillée du risque de biais à l'aide de l'outils RoB2 pour le critère de jugement des complications postopératoires (et déclinaison Clavien-Dindo ≥2)

Unique ID	liu2020	**Study ID**	Liu et al. 2020	**Assessor**	FEG (PS/TB)
Ref or Label	Anesthesia and analgesia. 2020;131(3):840-9	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications (and CDC >2)	**Results**	RR = 0.78 [95%CI 0.23 to 2.67]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The patients were then assigned randomly to the prehabilitation or control group according to computer-generated random numbers concealed in sealed envelopes"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Table 1. Baseline assessments and surgery Characteristics of the study population. The statistical comparison is not reported for the characteristics, no significant difference a priori. The authors planned to adjust the analysis of the primary outcome for evident baseline imbalances
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"This single-blind, randomized controlled" ; Participant and personnel were not blinded.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	Only patients receiving VATS surgery were included in the study
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	No drop-out or exclusion in the intervention group related to the proposed intervention (see flow-chart)
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	"Finally, no participant was excluded due to low compliance."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	

	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Not a real intention to treat but relatively low attrition (14%) and no significant difference in baseline characteristic between those people who excluded or not “A total of 37(/43) patients in the prehabilitation group and 36(/42) patients in the control group were included in the modified intention-to-treat dataset and finally analyzed” “There were no significant differences between the analyzed population and the patients who were randomized but excluded in terms of demographic and physiological characteristics”
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
	4.1 Was the method of measuring the outcome inappropriate?	N	"Surgical outcomes included short-term recovery quality, length of stay (LOS), chest tube duration, postoperative complications, and mortality, which were recorded and graded according to the Clavien–Dindo classification"
Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	"Perioperative care was applied with a standardized clinical pathway by a multidisciplinary team for patients undergoing VATS lobectomy with the same anesthesia and postoperative analgesia strategy."
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"The assessors were blinded to the patient allocation"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	NCT03068507 : "The primary end point is functional walking capacity as measured by the 6 minutes walking distance (6MWD) 4 weeks postoperatively. The secondary end points include lung function improvement (baseline vs. preoperative) , self-reported

			physical activity, health-related quality of life scales and prognosis information (postoperative complications, length of hospital stay, ICU stay time, hospitalization expenses, etc.)." => Nos history of change in these outcomes The use of the Clavien-Dindo classification was not pre-specified in the registration ; quality of life was prespecified but is not reported within the manuscript
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	only occurrence of complications within 30 days of surgery, use of the Clavien-Dindo scale not pre-specified but used in clinical practice and not susceptible to change the analysis.
	5.3 ... multiple eligible analyses of the data?	PN	Complications are reported transparently, cannot be analyzed in multiple ways. "Four patients in the prehabilitation group had postoperative complications with grade II Clavien–Dindo classification (2 atrial fibrillation, 1 sinus tachycardia, and 1 wound infection). In the control group, 2 patients had complications with grade II (1 atrial fibrillation and 1 sinus tachycardia), and 3 patients had complications with grade III (1 active hemorrhage needing operation, 1 pneumonia and atelectasis of the lower right lung needing operation, and 1 acute kidney injury needing dialysis therapy)"
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	lai2019	**Study ID**	Lai et al. 2019	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Translational Medicine. 2019 Oct;7(20):544	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications (and CDC >2)	**Results**	RR = 0.33 [95% CI 0.12, 0.93]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
	1.1 Was the allocation sequence random?	Y	

Bias arising from the randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	“The patients were randomly assigned into one of two treatment types using a random number table" assignment "after baseline assessments were completed”
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see Table 2 baseline characteristics between the two groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"Due to the nature of this research, we could not keep the participants blind to group assignment."
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	The operative and postoperative process is identical apart from the intervention. Only VATS lobectomy.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	In the study, all but 2 patients could endure the training intensity, which attests to the feasibility and safety of this training mode
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	According to the intention of the treatment principle, all the randomized patients were included in the analysis. The study flow can be seen in supporting Figure 1.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Meanwhile, according to the rule of ClavienDindo complication classification (15), PPCs were classified and divided into 5 grades, which are detailed in supporting Table 1.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The study staff and statistical analyses were all blind to patient allocation during data collection.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	ChiCTR1800014512 : Postoperative pulmonary complications initially positioned as the main outcome with an inclusion objective of 100 patients in each group. Change of the main outcome for 6MWD and revision of the count for 34 patients in each group in the published version.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	only occurrence of complications within 30 days of surgery, use of the Clavien-Dindo scale not pre-specified but used in clinical practice and not susceptible to change the analysis.
	5.3 ... multiple eligible analyses of the data?	N	Complications are reported transparently, cannot be analyzed in multiple ways. see table 4
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	licker2017	**Study ID**	Licker et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic oncology. 2017;12(2):323-33	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications	**Results**	RR = 0.72 [95% CI 0.50, 1.05]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Consenting patients were randomized on a 1:1 basis into a rehabilitation (Rehab) arm and UC arm by using a permuted block of four patients. The randomization sequence was developed before initiation of the trial and concealed until after enrollment"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Table 1. Demographic and Clinical Characteristics of the Study Population
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"The Lung Cancer Rehabilitation Study was a prospective randomized, open, blinded end point controlled trial using assessor blinding"
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	

	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	Same perioperative management : "Lung resections were performed by open thoracotomy or video-assisted thoracic surgery and, standardized perioperative interventions included antibiotic prophylaxis, restrictive fluid management, thoracic epidural analgesia, and protective lung ventilation. After surgery, patients were managed in a postanesthesia care unit (PACU) and were transferred to the surgical ward when the discharge criteria were met. Routine postoperative physiotherapy consisted of deep breathing using an incentive spirometer, coughing exercise, and assistance with ambulation."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	"In the Rehab group, the rate of adherence to the prescribed training sessions was 87 ± 18% (a median of eight sessions [IQR25%–75% ¼ 7–10]), and no SAE was reported during the HIIT sessions."
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Not actually "intention-to-treat analysis" but low attrition rate (8%), evenly distributed between groups "Between October 2011 and October 2014, 189 patients were screened, 164 provided consent, and 13 were excluded (Fig. 1). Therefore, 151 patients were analyzed"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"Surgical and anesthetic data were extracted from the electronic patient data management system. Postoperatively, patients were followed until hospital discharge to report any adverse events according to a modified version of the thoracic mortality and morbidity (TMM) classification system"

	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"blinded end point controlled trial using assessor blinding"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	postoperative Pulmonary Complications are pre-specified as pripary outcome in trial registry record (NCT01258478) Stopped early due to some data-dependent process (formal stopping rule) => possible overestimation of the real effect
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	"The primary outcome was a composite end point of postoperative morbidity (30-day mortality or any complications with TMM grades of 2)."
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	lai2017	**Study ID**	Lai et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Interactive cardiovascular and thoracic surgery. 2017;25(3):476-83	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications (and CDC >2)	**Results**	RR = 0.35 [95% CI 0.14, 0.90]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	“eligible patients were allocated to a treatment or a control group, based on a randomization table generated by a computer by an independent person, with group allocation placed in sequential opaques envelopes. Group allocation was revealed by a research assistant”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see Table 1: Baseline and clinical characteristics between the intervention and control groups
	Risk of bias judgement	**Low**	
Bias due to deviations	2.1 Were participants aware of their assigned intervention during the trial?	Y	Participant and personnel were not blinded “It is impossible for the

from intended interventions	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	patients to be blinded to their treatment group allocation”
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	The operative and postoperative process is identical apart from the intervention.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	"In our study, 6 patients did not finish the 7-day regimen. Two of them required an operation before completing the 7-day regimen; 2 requested withdrawal from the study because of a perceived lack of benefit; and 2 requested withdrawal because they felt they could not endure the regimen." => only (4/51) 8% failures in the implementation of the intervention
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	6 people stopped exercise training but were included in the analysis
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Definition of PPC and "PPCs were ultimately defined as Clavien-Dindo grade II to grade V" in lai 2016 (Journal of Surgical Research)
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	“all study personnel collecting data and conducting statistical analyses were blinded to patient allocation”
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	Retrospective registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	

Overall bias	Risk of bias judgement	High	

Unique ID	huang2017	Study ID	Huang2017	Assessor	FEG (PS/TB)
Ref or Label	Journal of thoracic disease. 2017;9(7):1919-29	Aim	adhering to intervention (the 'per-protocol' effect)	The effect of adhering to intervention…	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	Comparator	Usual Care	Source	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications (and CDC >2)	Results	RR = 0.42 [95% CI 0.17, 1.04]	Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Participants were divided into three groups and randomization was performed by the coordinating investigator with a computerbased 1:1:1 ratio"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers), we consider that the blindness was probably not achieved.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	Same perioperative process (see "Postoperative management" paragraph)
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	Only 2 drop-out (6.5%) linked to the intervention: "1 patient had acute COPD exacerbation 2 had new worsening of knee pain"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"During the rehabilitation, 5 patients dropped out because of loss of motivation (n=2), acute COPD exacerbation (n=1), and a new worsening of knee pain (n=2) (Figure 1). In consideration of the intention to treat (ITT) principle, we included these patients in the final analysis." (the 2 patients who stoped due to lack of motivation are part of a 3rd IMT

			group not included in our systematic review / meta-analysis)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"PPCs were redefined and classified into five grades according to the Clavien-Dindo Complication Classification System"
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	All participants were assessed and recorded by a statistician who was blind to the study design.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	Retrospective registration of the protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	sebiogarcia2017	**Study ID**	Sebio Garcia et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Clinical rehabilitation. 2017;31(8):1057-67	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications	**Results**	RR = 0.75 [95% CI 0.36, 1.57]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
	1.1 Was the allocation sequence random?	Y	

Bias arising from the randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	"Randomization was undertaken using a randombased computer programme […] with an allocation ratio of 1:1 [...] Individual allocations were placed in consecutively numbered and sealed opaque envelopes by a third person not involved in the study"
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y	"Despite the randomization, patients in the prehabilitation group tended to have a higher body mass index, lower pulmonary function and lower peak exercise capacity"
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	Participant and personnel were not blinded (only assessor)
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	All patients underwent video-assisted thoracic surgery through one or two ports performed by highly experienced surgeons. The operation report was checked after the surgery to ensure that the surgery was performed with the same technique. There was only one reconversion to thoracotomy (control group) and the patient was excluded from the analysis.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PY	see 3.1
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PY	see 3. 1
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y	"Of the 20 patients randomized to the prehabilitation group, only 50% completed the study, which lead us to perform a per-protocol analysis instead of an intention-to-treat analysis owing to the large percentage of patients with relevant missing data."
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	High attrition "Of the 20 patients randomized to the prehabilitation group, only 50% completed the study, which lead us to perform a per-protocol analysis instead of an intentionto-treat analysis owing to the large percentage of patients with relevant missing data."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"Postoperative pulmonary complications were classified according to the Melbourne Group Scale, which was specifically designed to identify those complications that were more likely to be prevented with a physiotherapy intervention"
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"assessor-blind controlled trial"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	Outcomes are described in NCT registration but the timeframe is not the same (no evaluation post-intervention preoperatively in NCT registration) Functional capacity (secondary outcome) is not reported post-intervention preoperatively. Some important secondary outcomes are reported but were not specified in the initial registration (length of stay in the hospital, postoperative pulmonary complications).
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	fang2013	**Study ID**	Fang et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	Chinese Journal of Rehabilitation Medicine. 2013;28(7):619-23	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Postoperative Complications	**Results**	RR = 0.67 [95% CI 0.29, 1.56]	**Weight**	1
Domain	**Signalling question**			**Response**	**Comments**

Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"The group A (22 cases) was randomly divided into the exercise subsection A1 and the control group A2 (22 cases)"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	See "Table 1. Comparison indice in the exercise subsection A1 and the control A2 before operation"
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers), we consider that the blindness was probably not achieved.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	"There was no obvious difference in these two groups in respect to preoperative and intraoperative operations."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	"The present investigation demonstrated that all the 39 patients completed the exercise training for 2 weeks"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	No attrition
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	"Postoperative cardiopulmonary complications, Oxygen therapy, mechanical ventilation time and hospital days were all observed"
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	The occurrence of an event qualified as a complication would have deserved a precise definition (learned society recommendation or validated classification)
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"the experiment was conducted blindly and thus physicians did not know grouping of patients"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	

	Risk of bias judgement			**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			N	No registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			PY	
	5.3 ... multiple eligible analyses of the data?			PY	
	Risk of bias judgement			**High**	
Overall bias	**Risk of bias judgement**			**High**	
Unique ID	morano2013	**Study ID**	Morano et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	Archives of physical medicine and rehabilitation. 2013;94(1):53-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Chest Physio Therapy	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications	**Results**	RR = 0.21 [95% CI 0.06, 0.80]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The randomization was done in “blocks” of 4, and individual allocations were placed in sealed envelopes. An external investigator blinded to the allocation sequence picked the envelopes."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	see "Table 2 Baseline characteristics of the 24 patients before 4 weeks of PR vs CPT" "The baseline characteristics observed between the 2 treatment arms (PR vs CPT) were comparable for demographic, clinical, surgical, and functional parameters except for the measures of MIP and MEP"
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"Randomized single-blinded study" => only assessor
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NI	Not enough information to know if the types of surgery were the same in the two groups
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	No attrition in the intervention group.
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?	N	"All the patients from the PR group and the CPT group successfully completed the 5 sessions per week during 1 month."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y	"Results analyzed both by intention to treat and per protocol showed that the CPT group had more

			postoperative complications than the PR group"
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"An intention-to-treat analysis was done including the 3 patients in the CPT group who did not have surgery and assuming no change for the PPCs. Results analyzed both by intention to treat and per protocol showed that the CPT group had more postoperative complications than the PR group."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Postoperative outcomes are listed in table 4, and correspond to the main postoperative outcomes measured in clinical practice. A more precise definition of the qualification of each event would have been relevant.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"Postoperative outcomes were obtained from the medical records by a physical therapist blinded to the treatment assignment."
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	Retrospective registration (record date: 07/06/2011) “This randomized trial study recruited 31 patients between the period of March 2008 and March 2011”
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	"The randomization was done in “blocks” of 4, and individual allocations were placed in sealed envelopes. An external investigator

Unique ID	benzo2011	**Study ID**	Benzo et al. 2011	**Assessor**	FEG (PS/TB)
Ref or Label	Lung cancer. 2011;74(3):441-5	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Postoperative Complications	**Results**	RR = 0.53 [95% CI 0.18, 1.55]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Only statement that the study is randomized : "Nine patients were randomized to the control arm and 10 patients to the pulmonary rehabilitation arm."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"Baseline characteristics were evenly distributed between the two arms." See Table 1 "Baseline characteristics"
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	Randomized single blinded design (only assessor)
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PN	"Patients had to have lung cancer resection by open thoracotomy (segment, lobe or pneumonectomy) or by Video Assisted Thoracoscopy (at least lobe) and moderate to severe COPD" => No information on the distribution of the type of surgery in each group in the results
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	"Two patients (one on each arm) were missing length of stay data; because they were considered inoperable once they were in the operating room and were excluded from the outcome analysis (final analyses were based on data from 17 patients)." => no other drop-out
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NI	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Law attrition, evenly distributed between groups, unrelated to the proposed intervention (patient deemed inoperable)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	"End points of these two studies were hospital length of stay and post operative pulmonary complications (pneumonia (new infiltrate + either fever (>38.5 ◦C) and white cell count >11,000 or fever and purulent secretions), severe atelectasis (requiring bronchoscopy), prolonged chest tubes (>7 days), and prolonged mechanical ventilation (>24 h)."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"Outcomes were obtained using chart review by a nurse trained in the abstraction of the desired outcomes from the medical records and blinded to the treatment"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	No Registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	pehlivan2011	**Study ID**	Pehlivan et al. 2011	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Thoracic and Cardiovascular Surgery. 2011;17(5):461-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Postoperative Complications	**Results**	RR = 0.20 [95% CI 0.02, 1.61]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the	1.1 Was the allocation sequence random?	Y	"Patients, […] were randomly allocated (according to hospital

randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	record number) to control or study group. […] Randomization was performed according to an internetbasedrandom number generator." No information about allocation concealment.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"There was no statistically significant difference between groups according to age, weight, height, body mass index (BMI) and cigarette smoking and performed operations. The distribution of parameters was balanced as shown in Table 1."
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	Participant and personnel were not blinded
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	Same perioperative management; no significant difference in the type of surgery in each arm. ; "In addition, both groups had postoperative routine physical therapy"
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	No drop-out in the group benefiting from the intervention
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	Although adherence in number of sessions is not reported, the authors do not report difficulty in following the exercise program.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	No attrition
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Postoperative complication reported ar :Atelectasis, Fever ,Dyspnea, Hemorrhagic drainage, Pneumonia, Pulmonary embolism. A more precise definition of the qualification of each event would have been relevant.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"the experiment was conducted blindly and thus physicians did not know grouping of patients"

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	No Registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Liu et al. 2020	Preoperative Exercise Training	Usual Care	Postoperative Complications (and CDC >2)	+	+	+	+	!	!
Lai et al. 2019	Preoperative Exercise Training	Usual Care	Postoperative Complications (and CDC >2)	+	+	+	+	!	!
Licker et al. 2017	Preoperative Exercise Training	Usual Care	Postoperative Complications	+	+	+	+	!	!
Lai et al. 2017	Preoperative Exercise Training	Usual Care	Postoperative Complications (and CDC >2)	+	+	+	+	-	-
Huang2017	Preoperative Exercise Training	Usual Care	Postoperative Complications (and CDC >2)	+	+	+	+	-	-
Sebio Garcia et al. 2017	Preoperative Exercise Training	Usual Care	Postoperative Complications	!	!	-	+	-	-
Fang et al. 2013	Preoperative Exercise Training	Usual Care	Postoperative Complications	!	+	+	!	-	-
Morano et al. 2013	Preoperative Exercise Training	Chest Physio Therapy	Postoperative Complications	+	!	+	!	-	-
Benzo et al. 2011	Preoperative Exercise Training	Usual Care	Postoperative Complications	!	-	+	+	-	-
Pehlivan et al. 2011	Preoperative Exercise Training	Usual Care	Postoperative Complications	!	+	+	!	-	-

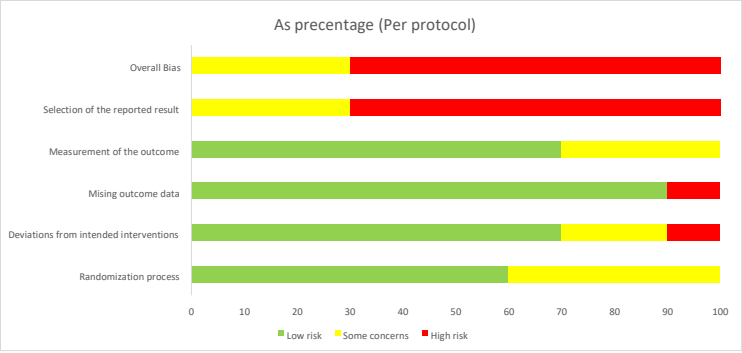
D1 Randomisation process

D2Deviations from the intended interventions

D3Missing outcome data

D4Measurement of the outcome

D5Selection of the reported result



Annexe 3.4 Evaluation détaillée du risque de biais à l'aide de l'outils RoB2 pour le critère de jugement mortalité

Unique ID	Liu2020	**Study ID**	Liu et al. 2020	**Assessor**	FEG (PS/TB)
Ref or Label	Anesthesia and analgesia. 2020;131(3):840-9	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Mortality	**Results**	RR = 0.97 [95% CI 0.02, 47.80]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The patients were then assigned randomly to the prehabilitation or control group according to computer-generated random numbers concealed in sealed envelopes"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Table 1. Baseline assessments and surgery Characteristics of the study population. The statistical comparison is not reported for the characteristics, no significant difference a priori. The authors planned to adjust the analysis of the primary outcome for evident baseline imbalances
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"This single-blind, randomized controlled" ; Participant and personnel were not blinded.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	Only patients receiving VATS surgery were included in the study
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	No drop-out or exclusion in the intervention group related to the proposed intervention (see flow-chart)
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	"Finally, no participant was excluded due to low compliance."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Not a real intention to treat but relatively low attrition (14%) and no significant difference in baseline characteristic between those people who excluded or not "A total of 37(/43) patients in the prehabilitation

			group a nts in the control ded in the modified intention-to-treat dataset and finally analyzed" "There were no significant differences between the analyzed population and the patients who were randomized but excluded in terms of demographic and physiological characteristics"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	no measurement ambiguity regarding mortality
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"The assessors were blinded to the patient allocation"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	NCT03068507 : "The primary end point is functional walking capacity as measured by the 6 minutes walking distance (6MWD) 4 weeks postoperatively. The secondary end points include lung function improvement (baseline vs. preoperative) , self-reported physical activity, health-related quality of life scales and prognosis information (postoperative complications, length of hospital stay, ICU stay time, hospitalization expenses, etc.)." => mortality not pre-specified in the registration process
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	mortality is an outcome that does not allow several measurement tools or multiple eligible analyses
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	lai2019	**Study ID**	Lai et al. 2019	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Translational Medicine. 2019 Oct;7(20):544	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Mortality	**Results**	RR= 1.00 [95% CI 0.02, 49.00]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The patients were randomly assigned into one of two treatment types using a random number table" assignment "after baseline assessments were completed"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see Table 2 baseline characteristics between the two groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"Due to the nature of this research, we could not keep the participants blind to group assignment."
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	The operative and postoperative process is identical apart from the intervention. Only VATS lobectomy.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	In the study, all but 2 patients could endure the training intensity, which attests to the feasibility and safety of this training mode
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	According to the intention of the treatment principle, all the randomized patients were included in the analysis. The study flow can be seen in supporting Figure 1.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	No measurement ambiguity regarding mortality
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	

	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The study staff and statistical analyses were all blind to patient allocation during data collection.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	ChiCTR1800014512 : Postoperative pulmonary complications initially positioned as the main outcome with an inclusion objective
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	mortality is an outcome that does not allow several measurement tools or multiple eligible analyses
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	licker2017	**Study ID**	Licker et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic oncology. 2017;12(2):323-33	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Mortality	**Results**	RR = 1.04 [95% CI 0.15, 7.20]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Consenting patients were randomized on a 1:1 basis into a rehabilitation (Rehab) arm and UC arm by using a permuted block of four patients. The randomization sequence was developed before initiation of the trial and concealed until after enrollment"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Table 1. Demographic and Clinical Characteristics of the Study Population
	Risk of bias judgement	**Low**	
	2.1 Were participants aware of their assigned intervention during the trial?	Y	"The Lung Cancer Rehabilitation Study was a prospective randomized, open, blinded end point controlled trial using assessor blinding"
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	

Bias due to deviations from intended interventions	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	Same perioperative management : "Lung resections were performed by open thoracotomy or video-assisted thoracic surgery and, standardized perioperative interventions included antibiotic prophylaxis, restrictive fluid management, thoracic epidural analgesia, and protective lung ventilation. After surgery, patients were managed in a postanesthesia care unit (PACU) and were transferred to the surgical ward when the discharge criteria were met. Routine postoperative physiotherapy consisted of deep breathing using an incentive spirometer, coughing exercise, and assistance with ambulation."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	"In the Rehab group, the rate of adherence to the prescribed training sessions was 87 ± 18% (a median of eight sessions [IQR25%–75% ¼ 7–10]), and no SAE was reported during the HIIT sessions."
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Not actually "intention-to-treat analysis" but low attrition rate (8%), evenly distributed between groups "Between October 2011 and October 2014, 189 patients were screened, 164 provided consent, and 13 were excluded (Fig. 1). Therefore, 151 patients were analyzed"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	No measurement ambiguity regarding mortality
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"blinded end point controlled trial using assessor blinding"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	postoperative Pulmonary Complications are pre-specified as pripary outcome in trial registry record (NCT01258478) ; mortality is one of the postoperative complications Stopped early due to some data-dependent process (formal stopping rule) => possible overestimation of the real effect
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	mortality is an outcome that does not allow several measurement tools or multiple eligible analyses
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	huang2017	**Study ID**	Huang2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic disease. 2017;9(7):1919-29	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Mortality	**Results**	RR = 0.33 [95% CI 0.01, 7.87]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Participants were divided into three groups and randomization was performed by the coordinating investigator with a computerbased 1:1:1 ratio"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers), we consider that the blindness was probably not achieved.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	Same perioperative process (see "Postoperative management" paragraph)
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	Only 2 drop-out (6.5%) linked to the intervention: "1 patient had acute

			COPD exacerbation 2 had new worsening of knee pain"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"During the rehabilitation, 5 patients dropped out because of loss of motivation (n=2), acute COPD exacerbation (n=1), and a new worsening of knee pain (n=2) (Figure 1). In consideration of the intention to treat (ITT) principle, we included these patients in the final analysis." (the 2 patients who stoped due to lack of motivation are part of a 3rd IMT group not included in our systematic review / meta-analysis)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	No measurement ambiguity regarding mortality
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	All participants were assessed and recorded by a statistician who was blind to the study design.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	Retrospective registration of the protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	mortality is an outcome that does not allow several measurement tools or multiple eligible analyses
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	fang2013	**Study ID**	Fang et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	Chinese Journal of Rehabilitation Medicine. 2013;28(7):619-23	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Postoperative Mortality	**Results**	RR = 0.20 [95% CI 0.01, 3.94]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"The group A (22 cases) was randomly divided into the exercise subsection A1 and the control group A2 (22 cases)"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	See "Table 1. Comparison indice in the exercise subsection A1 and the control A2 before operation"
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers), we consider that the blindness was probably not achieved.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	"There was no obvious difference in these two groups in respect to preoperative and intraoperative operations."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	"The present investigation demonstrated that all the 39 patients completed the exercise training for 2 weeks"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	No attrition
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	No measurement ambiguity regarding mortality
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	

	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"the experiment was conducted blindly and thus physicians did not know grouping of patients"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	mortality
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	No registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	mortality is an outcome that does not allow several measurement tools or multiple eligible analyses
	5.3 ... multiple eligible analyses of the data?	PN	No measurement ambiguity regarding
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	pehlivan2011	**Study ID**	Pehlivan et al. 2011	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Thoracic and Cardiovascular Surgery. 2011;17(5):461-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Postoperative Mortality	**Results**	RR = 1.00 [95% CI 0.02, 48.82]	**Weight**	1

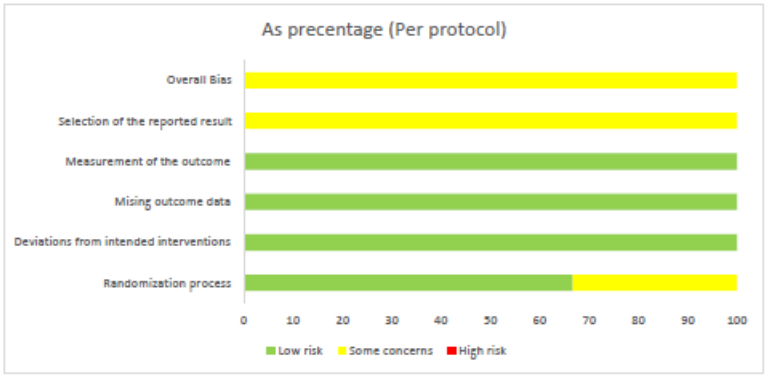
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Patients, […] were randomly allocated (according to hospital record number) to control or study group. […] Randomization was performed according to an internetbasedrandom number generator." No information about allocation concealment.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"There was no statistically significant difference between groups according to age, weight, height, body mass index (BMI) and cigarette smoking and performed operations. The distribution of parameters was balanced as shown in Table 1."
	Risk of bias judgement	**Some concerns**	

Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	Participant and personnel were not blinded
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	Same perioperative management; no significant difference in the type of surgery in each arm. ; "In addition, both groups had postoperative routine
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	No drop out in the group benefiting from the intervention
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	Although adherence in number of sessions is not reported, the authors do not report difficulty in following the exercise program.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	No attrition
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	No measurement ambiguity regarding mortality
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"the experiment was conducted blindly and thus physicians did not know grouping of patients"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	No Registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	mortality is an outcome that does not allow several measurement tools or multiple eligible analyses
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
liu2020	Liu et al. 2020	Preoperative Exercise Training	Usual Care	Postoperative Mortality	+	+	+	+	!	!
lai2019	Lai et al. 2019	Preoperative Exercise Training	Usual Care	Postoperative Mortality	+	+	+	+	!	!
licker2017	Licker et al. 2017	Preoperative Exercise Training	Usual Care	Postoperative Mortality	+	+	+	+	!	!
huang2017	Huang2017	Preoperative Exercise Training	Usual Care	Postoperative Mortality	+	+	+	+	!	!
fang2013	Fang et al. 2013	Preoperative Exercise Training	Usual Care	Postoperative Mortality	!	+	+	+	!	!
pehlivan2011	Pehlivan et al. 2011	Preoperative Exercise Training	Usual Care	Postoperative Mortality	!	+	+	+	!	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result



Annexe 3.5. : Evaluation détaillée du risque de biais à l'aide de l'outils RoB2 pour le critère de jugement durée de séjour hospitalier

Unique ID	PPC.liu2020	**Study ID**	Liu et al. 2020	**Assessor**	FEG (PS/TB)
Ref or Label	Anesthesia and analgesia. 2020;131(3):840-9	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Length of Stay	**Results**	MD = 0.00 days [95% CI -0.78, 0.78]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 "The patients were then assigned randomly to the prehabilitation or control group according to computer-generated random numbers concealed in sealed envelopes"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	1.3 Table 1. Baseline assessments and surgery Characteristics of the study population. The statistical comparison is not reported for the characteristics, no significant difference a priori. The authors planned to adjust the analysis of the primary outcome for evident baseline imbalances
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 "This single-blind, randomized controlled" ; Participant and personnel were not blinded.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	2.3 Only patients receiving VATS surgery were included in the study
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 No drop-out or exclusion in the intervention group related to the proposed intervention (see flow-chart)

	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	2.5 "Finally, no participant was excluded due to low compliance."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	2.1/2 "This single-blind, randomized controlled" ; Participant and personnel were not blinded. 2.3 Only patients receiving VATS surgery were included in the study 2.4 No drop-out or exclusion in the intervention group related to the proposed intervention (see flow-chart) 2.5 "Finally, no participant was excluded due to low compliance."
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	3.1 "There were no significant differences between the analyzed population and the patients who were randomized but excluded in terms of demographic and physiological characteristics"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	4.2 "Perioperative care was applied with a standardized clinical pathway by a multidisciplinary team for patients undergoing VATS lobectomy with the same anesthesia and postoperative analgesia strategy."
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "The assessors were blinded to the patient allocation"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	5.1 NCT03068507 : "The primary end point is functional walking capacity as measured by the 6 minutes walking distance (6MWD) 4 weeks postoperatively. The secondary end points include lung function improvement (baseline vs. preoperative) , self-reported physical activity, health-related quality of life scales and prognosis information (postoperative complications, length of hospital stay, ICU stay time, hospitalization expenses, etc.)." => length of hospital stay was pre-specified
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	PPC.lai2019	**Study ID**	Lai et al. 2019	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Translational Medicine. 2019 Oct;7(20):544	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Length of Stay	**Results**	MD = -3.00 days [95% CI -4.71, -1.29]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 “The patients were randomly assigned into one of two treatment types using a random number table" assignment "after baseline assessments were completed”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 see Table 2 baseline characteristics between the two groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 "Due to the nature of this research, we could not keep the participants blind to group assignment."
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	2.3 The operative and postoperative process is identical apart from the intervention. Only VATS lobectomy.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 In the study, all but 2 patients could endure the training intensity, which attests to the feasibility and safety of this training mode
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 According to the intention of the treatment principle, all the randomized patients were included in the analysis. The study flow can be seen in supporting Figure 1.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement	4.1 Was the method of measuring the outcome inappropriate?	N	4.1 Length of stay mesured in days

of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 The study staff and statistical analyses were all blind to patient allocation during data collection.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 length of stay not pre-specified in registration (ChiCTR1800014512)
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	PPC.licker2017	**Study ID**	Licker et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic oncology. 2017;12(2):323-33	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Length of Stay	**Results**	MD = 1.00 days [95% CI -0.61, 2.61]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the	1.1 Was the allocation sequence random?	Y	1.1/2 “Consenting patients were randomized on a 1:1

randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	basis into a rehabilitation (Rehab) arm and UC arm by using a permuted block of four patients. The randomization sequence was developed before initiation of the trial and concealed until after enrollment"
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 see Table 1. Demographic and Clinical Characteristics of the Study Population
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 "The Lung Cancer Rehabilitation Study was a prospective randomized, open, blinded end point controlled trial using assessor blinding"
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	2.3 Same perioperative management : "Lung resections were performed by open thoracotomy or video-assisted thoracic surgery and, standardized perioperative interventions included antibiotic prophylaxis, restrictive fluid management, thoracic epidural analgesia, and protective lung ventilation. After surgery, patients were managed in a postanesthesia care unit (PACU) and were transferred to the surgical ward when the discharge criteria were met. Routine postoperative physiotherapy consisted of deep breathing using an incentive spirometer, coughing exercise, and assistance with ambulation."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	2.4 "In the Rehab group, the rate of adherence to the prescribed training sessions was 87 ± 18% (a median of eight sessions [IQR25%–75% ¼ 7–10]), and no SAE was reported during the HIIT sessions."
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	

	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 Not actually “intention-to-treat analysis” but low attrition rate (8%), evenly distributed between groups “Between October 2011 and October 2014, 189 patients were screened, 164 provided consent, and 13 were excluded (Fig. 1). Therefore, 151 patients were analyzed"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "blinded end point controlled trial using assessor blinding"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	5.1 Hospital length of stay pre-specified in trial registry record (NCT01258478) Study stopped early due to some data-dependent process (formal stopping rule)
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	N	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	PPC.lai2017	**Study ID**	Lai et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Interactive cardiovascular and thoracic surgery. 2017;25(3):476-83	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Length of Stay	**Results**	MD = -2.10 days [95% CI -3.87, -0.33]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 “eligible patients were allocated to a treatment or a control group, based on a randomization table generated by a computer by an independent person, with group allocation placed in sequential opaques envelopes. Group allocation was revealed by a research assistant”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 see Table 1: Baseline and clinical characteristics between the intervention and control groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 Participant and personnel were not blinded “It is impossible for the patients to be blinded to their treatment group allocation”
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	2.3 The operative and postoperative process is identical apart from the intervention.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 "In our study, 6 patients did not finish the 7-day regimen. Two of them required an operation before completing the 7-day regimen; 2 requested withdrawal from the study because of a perceived lack of benefit; and 2 requested withdrawal because they felt

			they could not endure the regimen." => only (4/51) 8% failures in the implementation of the intervention.
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	2.5 see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 6 people stopped exercise training but were included in the analysis (data avaible)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "all study personnel collecting data and conducting statistical analyses were blinded to patient allocation"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 Retrospective registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	

Overall bias	Risk of bias judgement	Some concerns	

Unique ID	PPC.huang2017	Study ID	Huang2017	Assessor	FEG (PS/TB)
Ref or Label	Journal of thoracic disease. 2017;9(7):1919-29	Aim	adhering to intervention (the 'per-protocol' effect)	The effect of adhering to intervention…	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	Comparator	Usual Care	Source	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Postoperative Complications (and CDC >2)	Results	MD = -3.20 daus [95% CI -5.02, -1.38]	Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 “Participants were divided into three groups and randomization was performed by the coordinating investigator with a computer-based 1:1:1 ratio”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 see Table 2 Baseline characteristics of patients
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	2.1/2 No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers), we consider that the blindness was probably not achieved.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	2.3 Same perioperative process (see "Postoperative management" paragraph)
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 Only 2 drop-out (6.5%) linked to the intervention: "1 patient had acute COPD exacerbation 2 had new worsening of knee pain"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?	PN	2.5 see 2.4

	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 "During the rehabilitation, 5 patients dropped out because of loss of motivation (n=2), acute COPD exacerbation (n=1), and a new worsening of knee pain (n=2) (Figure 1). In consideration of the intention to treat (ITT) principle, we included these patients in the final analysis." (the 2 patients who stoped due to lack of motivation are part of a 3rd IMT group not included in our systematic review / meta-analysis)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 All participants were assessed and recorded by a statistician who was blind to the study design.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 Retrospective registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses

	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	PPC.sebiogarcia2017	**Study ID**	Sebio Garcia et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Clinical rehabilitation. 2017;31(8):1057-67	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Length of Stay	**Results**	MD = -1.00 days [95% CI -4.14, 2.14]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 “Randomization was undertaken using a randombased computer programme […] with an allocation ratio of 1:1 [...] Individual allocations were placed in consecutively numbered and sealed opaque envelopes by a third person not involved in the study”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y	1.3 “Despite the randomization, patients in the prehabilitation group tended to have a higher body mass index, lower pulmonary function and lower peak exercise capacity”
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 Participant and personnel were not blinded (only assessor)
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	2.3 All patients underwent video-assisted thoracic surgery through one or two ports performed by highly

			experienced surgeons. The operation report was checked after the surgery to ensure that the surgery was performed with the same technique. There was only one reconversion to thoracotomy (control group) and the patient was excluded from the analysis.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PY	2.4 50% drop-out or exclusion
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PY	2.5 see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y	2.6 "Of the 20 patients randomized to the prehabilitation group, only 50% completed the study, which lead us to perform a per-protocol analysis instead of an intention-to-treat analysis owing to the large percentage of patients with relevant missing data."
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	3.1 High attrition "Of the 20 patients randomized to the prehabilitation group, only 50% completed the study, which lead us to perform a per-protocol analysis instead of an intention-to-treat analysis owing to the large percentage of patients with relevant missing data."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "assessor-blind controlled trial"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	5.1 length of stay not pre-specified in registration (NCT01963923)
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	PPC.fang2013	**Study ID**	Fang et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	Chinese Journal of Rehabilitation Medicine. 2013;28(7):619-23	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Length of Stay	**Results**	MD = -3.10 days [-5.64, -0.56]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	1.1/2 “The group A (22 cases) was randomly divided into the exercise subsection A1 and the control group A2 (22 cases)”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	1.3 See "Table 1. Comparison indice in the exercise subsection A1 and the control A2 before operation"
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	2.1/2 No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers),
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	

			we consider that the blindness was probably not achieved.
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	2.3 "There was no obvious difference in these two groups in respect to preoperative and intraoperative operations."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 "The present investigation demonstrated that all the 39 patients completed the exercise training for 2 weeks"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	2.5 see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 No attrition
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "the experiment was conducted blindly and thus physicians did not know grouping of patients"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 No registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days

	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	PPC.morano2013	**Study ID**	Morano et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	Archives of physical medicine and rehabilitation. 2013;94(1):53-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Chest Physio Therapy	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Length of Stay	**Results**	MD = -4.40 days [-7.99, -0.81]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 "The randomization was done in “blocks” of 4, and individual allocations were placed in sealed envelopes. An external investigator blinded to the allocation sequence picked the envelopes."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	1.3 see "Table 2 Baseline characteristics of the 24 patients before 4 weeks of PR vs CPT" "The baseline characteristics observed between the 2 treatment arms (PR vs CPT) were comparable for demographic, clinical, surgical, and functional parameters except for the measures of MIP and MEP"
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 "Randomized single-blinded study" => only assessor
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	

	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NI	2.3 Not enough information to know if the types of surgery were the same in the two groups
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	2.4 No attrition in the intervention group.
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N	2.5 "All the patients from the PR group and the CPT group successfully compl Annexe 3.5 sions per we h."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y	2.6 "Results analyzed both by intention to treat and per protocol showed that the CPT group had more postoperative complications than the PR group"
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 "An intention-to-treat analysis was done including the 3 patients in the CPT group who did not have surgery and assuming no change for the PPCs. Results analyzed both by intention to treat and per protocol showed that the CPT group had more postoperative complications than the PR group."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "Postoperative outcomes were obtained from the medical records by a physical therapist blinded to the treatment assignment."
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	

	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	5.1 Retrospective registration (record date: 07/06/2011) "This randomized trial study recruited 31 patients between the period of March 2008 and March 2011"
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	PPC.benzo2011	**Study ID**	Benzo et al. 2011	**Assessor**	FEG (PS/TB)
Ref or Label	Lung cancer. 2011;74(3):441-5	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Length of Stay	**Results**	MD = -4.70 days [95% CI -9.19, -0.21]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	1.1/2 Only statement that the study is randomized : "Nine patients were randomized to the control arm and 10 patients to the pulmonary rehabilitation arm."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 "Baseline characteristics were evenly distributed between the two arms." See Table 1 "Baseline characteristics"
	Risk of bias judgement	**Some concerns**	

Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 Randomized single blinded design (only assessor)
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PN	2.3 "Patients had to have lung cancer resection by open thoracotomy (segment, lobe or pneumonectomy) or by Video Assisted Thoracoscopy (at least lobe) and moderate to severe COPD" => No information on the distribution of the type of surgery in each group in the results
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 "Two patients (one on each arm) were missing length of stay data; because they were considered inoperable once they were in the operating room and were excluded from the outcome analysis (final analyses were based on data from 17 patients)." => no other drop-out
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	2.5 see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	PN	2.6 NI but probably not
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 Low attrition, evenly distributed between groups, unrelated to the proposed intervention (patient deemed inoperable)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement	4.1 Was the method of measuring the outcome inappropriate?	PN	4.1 Length of stay mesured in days

of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "Outcomes were obtained using chart review by a nurse trained in the abstraction of the desired outcomes from the medical records and blinded to the treatment"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 No registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	PPC.pehlivan2011	**Study ID**	Pehlivan et al. 2011	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Thoracic and Cardiovascular Surgery. 2011;17(5):461-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Length of Stay	**Results**	MD = -4.26 days [95% CI -5.72, -2.80]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the	1.1 Was the allocation sequence random?	Y	1.1/2 "Patients, […] were randomly allocated

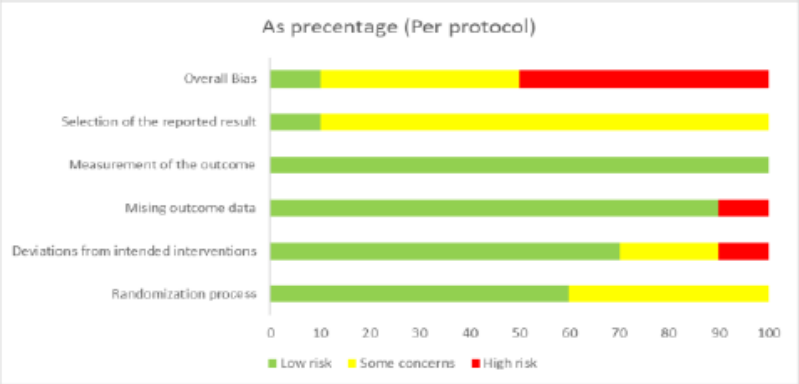
randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	(according to hospital record number) to control or study group. […] Randomization was performed according to an internetbased-random number generator." No information about allocation concealment.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 "There was no statistically significant difference between groups according to age, weight, height, body mass index (BMI) and cigarette smoking and performed operations. The distribution of parameters was balanced as shown in Table 1."
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 Participant and personnel were not blinded
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	2.3 Same perioperative management; no significant difference in the type of surgery in each arm. ; "In addition, both groups had postoperative routine physical therapy"
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	2.4 No drop-out in the group benefiting from the intervention
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	2.5 Although adherence in number of sessions is not reported, the authors do not report difficulty in following the exercise program.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 No attrition
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	

Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	4.1 Length of stay mesured in days
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	4.2 see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 “the experiment was conducted blindly and thus physicians did not know grouping of patients”
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 No registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	5.2 length of stay measured in days
	5.3 ... multiple eligible analyses of the data?	PN	5.3 no multiple eligible analyses
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Liu et al. 2020	Preoperative Exercise Training	Usual Care	Length of Stay	+	+	+	+	+	+
Lai et al. 2019	Preoperative Exercise Training	Usual Care	Length of Stay	+	+	+	+	!	!
Licker et al. 2017	Preoperative Exercise Training	Usual Care	Length of Stay	+	+	+	+	!	!
Lai et al. 2017	Preoperative Exercise Training	Usual Care	Length of Stay	+	+	+	+	!	!
Huang2017	Preoperative Exercise Training	Usual Care	Length of Stay	+	+	+	+	!	!
Sebio Garcia et al. 2017	Preoperative Exercise Training	Usual Care	Length of Stay	!	!	-	+	!	-
Fang et al. 2013	Preoperative Exercise Training	Usual Care	Length of Stay	!	+	+	+	!	-
Morano et al. 2013	Preoperative Exercise Training	Chest Physio Therapy	Length of Stay	+	!	+	+	!	-
Benzo et al. 2011	Preoperative Exercise Training	Usual Care	Length of Stay	!	-	+	+	!	-
Pehlivan et al. 2011	Preoperative Exercise Training	Usual Care	Length of Stay	!	+	+	+	!	-

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result



Annexe 3.6. Evaluation détaillée du risque de biais à l'aide de l'outils RoB2 pour le critère de jugement $\dot{V}O_2$pic

Unique ID	Licker2017	**Study ID**	Licker et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic oncology. 2017;12(2):323-33	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	CPET (VO2peak)	**Results**	MD = 4.40 ml/kg/min [95%CI 1.44, 7.36]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Consenting patients were randomized on a 1:1 basis into a rehabilitation (Rehab) arm and UC arm by using a permuted block of four patients. The randomization sequence was developed before initiation of the trial and concealed until after enrollment"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Table 1. Demographic and Clinical Characteristics of the Study Population
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"The Lung Cancer Rehabilitation Study was a prospective randomized, open, blinded end point controlled trial using assessor blinding"
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	Same perioperative management : Patients in the two groups were given advice regarding active mobilization (at least four 30minute walks per week) and risk factor management (e.g., healthy nutrition and smoking and alcohol cessation)
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	"In the Rehab group, the rate of adherence to the prescribed training sessions was 87 ± 18% (a median of eight sessions [IQR25%–75% ¼ 7–10]), and no SAE was reported during the HIIT sessions."

	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Not actually "intention-to-treat analysis" but low attrition rate (8%), evenly distributed between groups "Between October 2011 and October 2014, 189 patients were screened, 164 provided consent, and 13 were excluded (Fig. 1). Therefore, 151 patients were analyzed"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Symptom-limited CPET on cycloergometer according to American Thoracic Society. American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	CPET carried out according to current guidelines
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"blinded end point controlled trial using assessor blinding"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	"other physiological tests changes from baseline to week 3" (NCT01258478) ; the outcomes used among the physiological tests are not clearly pre-specified
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	

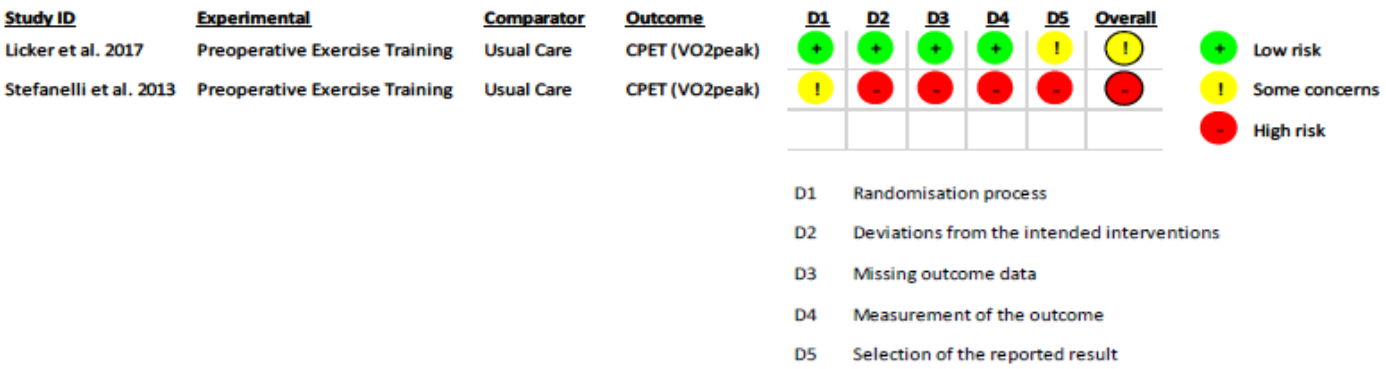
	5.3 ... multiple eligible analyses of the data?	PN	comparison of the mean difference of 6MWD and not of the final value, seems logical in front of the slight base difference (368 vs 398 meters p = 0.072)
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

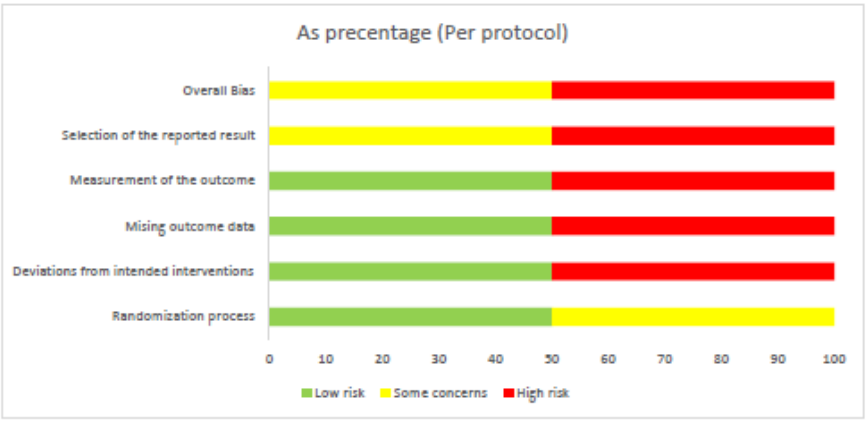
Unique ID	Stefanelli2013	**Study ID**	Stefanelli et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	European Journal of Cardio-thoracic	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	CPET (VO2peak)	**Results**	MD = 3.30 ml/kg/min [95% CI 2.24, 4.36]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"Patients were randomly assigned to two groups". No more information provided
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	"At T0, the two groups did not significantly differ in age (years ± SD, Group R vs S: 65.5 ± 7.4 vs 64.8 ± 7.3, P = NS), BMI (Group R vs S: 25.6 ± 4.5 vs 27.6 ± 3.5, P = NS), FEV1 and peakVO2"
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	No information
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PN	see "Study design" paragraph : "Patients were randomly assigned to two groups. The patients in the first group (rehabilitation, R) underwent a 3-week preoperative outpatient intensive PRP based on high-intensity training of both upper-

			and lower-limb muscles. Conversely, the patients in the second group (surgery, S) did not participate in the preoperative PRP and underwent only surgery according to the normal standard preoperative protocol."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NI	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NI	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NI	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	No flow chart
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	no evidence that the result was not biased by missing outcome data
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	see paragrah "Cardiopulmonary exercise test and evaluation of dyspnoea"
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI	see 4.4/5
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	cardiopulmonary exercise testing, is an examination that is carried out with encouragement to produce a maximum effort, apart from blindness of the assessors, partial encouragement is possible.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	No registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	VO2peak only measured with CPET
	5.3 ... multiple eligible analyses of the data?	PY	analysis intra and inter-group, in percentage and absolute value, final value and mean difference.

	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	





Annexe 3.7. Evaluation détaillée du risque de biais à l'aide de l'outils RoB2 pour le critère de jugement distance parcourue au test de marche de 6 minutes

Unique ID	liu2020	**Study ID**	Liu et al. 2020	**Assessor**	FEG (PS/TB)
Ref or Label	Anesthesia and analgesia. 2020;131(3):840-9	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	6MWD	**Results**	MD = 53.00 m [95% CI 24.02, 81.98]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The patients were then assigned randomly to the prehabilitation or control group according to computer-generated random numbers concealed in sealed envelopes"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Table 1. Baseline assessments and surgery Characteristics of the study population. The statistical comparison is not reported for the characteristics, no significant difference a priori. The authors planned to adjust the analysis of the primary outcome for evident baseline imbalances
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"This single-blind, randomized controlled" ; Participant and personnel were not blinded.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	"Patients in the control group received the usual clinical care, including comprehensive preoperative anesthesia assessment, perioperative drug recommendations for chronic diseases, smoking cessation, and abstinence."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	No drop-out or exclusion in the intervention group related to the proposed intervention (see flow-chart)
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	"Finally, no participant was excluded due to low compliance."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	

	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Not a real intention to treat but relatively low attrition (14%) and no significant difference in baseline characteristic between those people who excluded or not “A total of 37(/43) patients in the prehabilitation group and 36(/42) patients in the control group were included in the modified intention-to-treat dataset and finally analyzed” “There were no significant differences between the analyzed population and the patients who were randomized but excluded in terms of demographic and physiological characteristics”
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"The 6MWT was assessed according to the American Thoracic Society guidelines at baseline"
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	6MWT carried out according to current guidelines
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	" The 6MWT was assessed (...) by a doctor blinded to the patient allocation."
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	NCT03068507 : "The primary end point is functional walking capacity as measured by the 6 minutes walking distance (6MWD)"
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	No
	5.3 ... multiple eligible analyses of the data?	PN	significant difference in the evolution of 6MWD regardless of the analysis mode according to the results presented (final value or change from baseline)
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	lai2019	**Study ID**	Lai et al. 2019	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Translational Medicine. 2019 Oct;7(20):544	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to interventio n…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimenta l	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	6MWD	**Results**	MD = 19.90 m [95% CI 6.70, 33.10]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomizatio n process	1.1 Was the allocation sequence random?	Y	"The patients were randomly assigned into one of two treatment types using a random number table" assignment "after baseline assessments were completed"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see Table 2 baseline characteristics between the two groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"Due to the nature of this research, we could not keep the participants blind to group assignment."
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	The operative and postoperative process is identical apart from the intervention. Only VATS lobectomy.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	In the study, all but 2 patients could endure the training intensity, which attests to the feasibility and safety of this training mode
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	program carried out under supervision (inpatient modality) over a single week limiting the risk of non-adherence to the sessions.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	According to the intention of the treatment principle, all the randomized patients were included in the analysis. The study flow can be seen in supporting Figure 1.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	

	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"The 6-MWT was performed following the American Thoracic Society (ATS) Pulmonary Function Standards Committee recommendations."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	6MWT carried out according to current guidelines
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	"The study staff and statistical analyses were all blind to patient allocation during data collection."
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	ChiCTR1800014512 : Postoperative pulmonary complications initially positioned as the main outcome with an inclusion objective of 100 patients in each group. Change of the main outcome for 6MWD and revision of the count for 34 patients in each group in the published version.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	No
	5.3 ... multiple eligible analyses of the data?	PY	the comparison of the 6MWD can be analyzed with absolute values, the mean difference, or the mean change from baseline ... the analysis mode of the 6MWD was not pre-specified (in a context where the main outcome has already been changed)
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	licker2017	**Study ID**	Licker et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic oncology. 2017;12(2):323-33	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

Outcome	6MWD	Results	MD = 68.00 m [95% CI 28.29, 107.71]	Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Consenting patients were randomized on a 1:1 basis into a rehabilitation (Rehab) arm and UC arm by using a permuted block of four patients. The randomization sequence was developed before initiation of the trial and concealed until after enrollment"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Table 1. Demographic and Clinical Characteristics of the Study Population
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"The Lung Cancer Rehabilitation Study was a prospective randomized, open, blinded end point controlled trial using assessor blinding"
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	Same perioperative management : "Lung resections were performed by open thoracotomy or video-assisted thoracic surgery and, standardized perioperative interventions included antibiotic prophylaxis, restrictive fluid management, thoracic epidural analgesia, and protective lung ventilation. After surgery, patients were managed in a postanesthesia care unit (PACU) and were transferred to the surgical ward when the discharge criteria were met. Routine postoperative physiotherapy consisted of deep breathing using an incentive spirometer, coughing exercise, and assistance with ambulation."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	"In the Rehab group, the rate of adherence to the prescribed training sessions was 87 ± 18% (a median of eight sessions [IQR25%–75% ¼ 7–10]), and no SAE was reported during the HIIT sessions."
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Not actually "intention-to-treat analysis" but low attrition rate (8%), evenly distributed between groups

outcome data			"Between October 2011 and October 2014, 189 patients were screened, 164 provided consent, and 13 were excluded (Fig. 1). Therefore, 151 patients were analyzed"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"The 6-minute walk test (6MWT) was conducted by physiotherapists according to the ERS and American Thoracic Society
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	6MWT carried out according to current guidelines
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"blinded end point controlled trial using assessor blinding"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	6MWD non prespecified in trial registry record (NCT01258478)
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	no
	5.3 ... multiple eligible analyses of the data?	PN	comparison of the mean difference of 6MWD and not of the final value, seems logical in front of the slight base difference (368 vs 398 meters p = 0.072)
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	lai2017	**Study ID**	Lai et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Interactive cardiovascular and thoracic surgery. 2017;25(3):476-83	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to interventio n…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants

Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	6MWD	**Results**	MD = 18.70 m [95% CI 8.93, 28.47]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"eligible patients were allocated to a treatment or a control group, based on a randomization table generated by a computer by an independent person, with group allocation placed in sequential opaques envelopes. Group allocation was revealed by a research assistant"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see Table 1: Baseline and clinical characteristics between the intervention and control groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	Participant and personnel were not blinded "It is impossible for the patients to be blinded to their treatment group allocation"
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	The operative and postoperative process is identical apart from the intervention.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	"In our study, 6 patients did not finish the 7day regimen. Two of them required an operation before completing the 7-day regimen; 2 requested withdrawal from the study because of a perceived lack of benefit; and 2 requested withdrawal because they felt they could not endure the regimen." => only (4/51) 8% failures in the implementation of the intervention
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	program carried out under supervision (inpatient modality) over a single week limiting the risk of non-adherence to the sessions.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	6 people stopped exercise training but were included in the analysis
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	

Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	No definition of the methodology used for the 6MWT, but a research team experienced in the use of this type of measurement tool,
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"all study personnel collecting data and conducting statistical analyses were blinded to
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	patient allocation"
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	Retrospective registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	huang2017	**Study ID**	Huang2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic disease. 2017;9(7):1919-29	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to interventio n…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	6MWD	**Results**	MD = 32.67 m [95% CI 12.73, 52.61]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Participants were divided into three groups and randomization was performed by the coordinating investigator with a computerbased 1:1:1 ratio"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see Table 2
	Risk of bias judgement	**Low**	

Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers), we consider that the blindness was probably not achieved.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	Same perioperative management
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	Only 2 drop-out (6.5%) linked to the intervention: "1 patient had acute COPD exacerbation 2 had new worsening of knee pain"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	program carried out under supervision (inpatient modality) over a single week limiting the risk of non-adherence to the sessions.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"During the rehabilitation, 5 patients dropped out because of loss of motivation (n=2), acute COPD exacerbation (n=1), and a new worsening of knee pain (n=2) (Figure 1). In consideration of the intention to treat (ITT) principle, we included these patients in the final analysis." (the 2 patients who stoped due to lack of motivation are part of a 3rd IMT group not included in our systematic review / meta-analysis)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"The 6-MWT and PFTs were performed to assess the patients' initial cardiopulmonary function based on the American Thoracic
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"All participants were assessed and recorded by a statistician who was blind to the study design."
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	

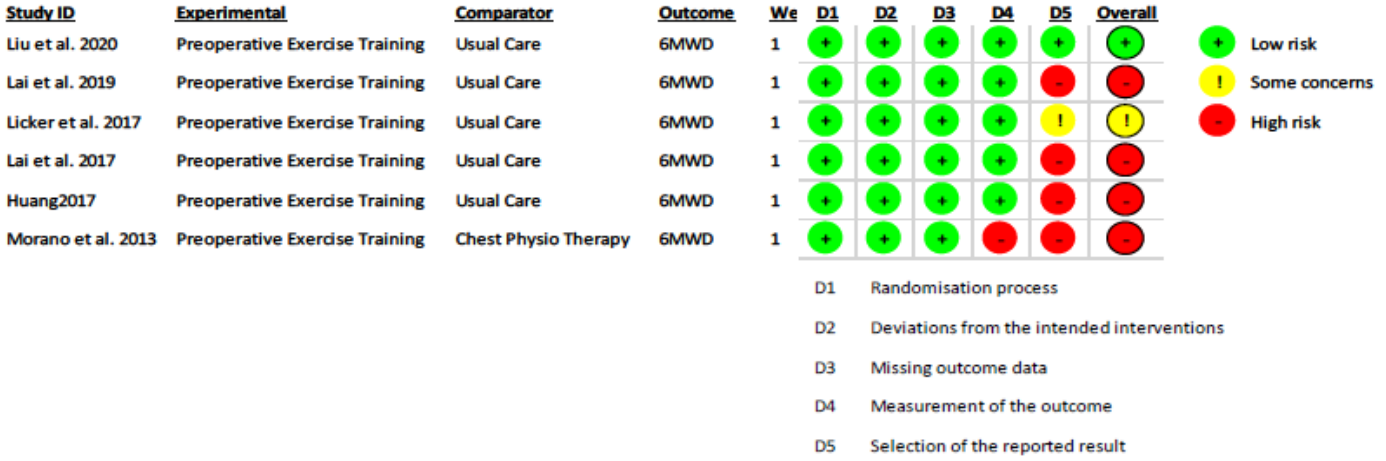
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	6MWD was not a pre-specified outcome. Retrospective registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

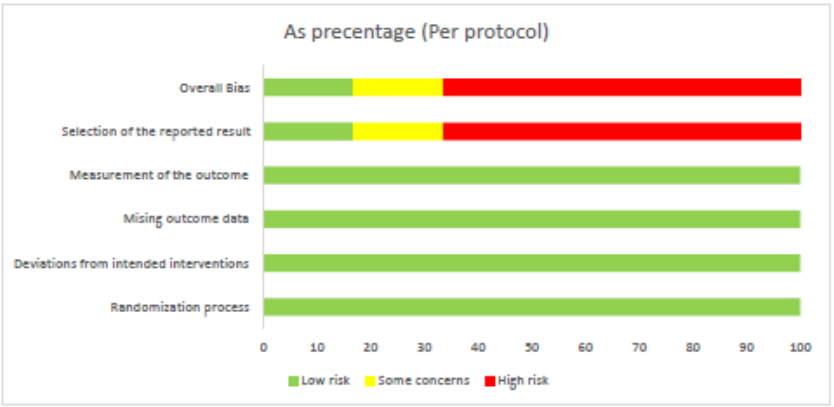
Unique ID	morano2013	**Study ID**	Morano et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	Archives of physical medicine and rehabilitation. 2013;94(1):53-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to interventio n…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimenta l	Preoperative Exercise Training	**Comparator**	Chest Physio Therapy	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	6MWD	**Results**	MD = 54.10 m [95% CI 43.93, 64.27]	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomizatio n process	1.1 Was the allocation sequence random?	Y	"The randomization was done in “blocks” of 4, and individual allocations were placed in sealed envelopes. An external investigator blinded to the allocation sequence picked the envelopes."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	see "Table 2 Baseline characteristics of the 24 patients before 4 weeks of PR vs CPT" "The baseline characteristics observed
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"Randomized single-blinded study" => only assessor
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	same preparation for surgery "All the patients participated in classes about the importance of preoperative and postoperative care and knowledge of the surgical process, energy conservation techniques, relaxation and stress management techniques, focus on nutrition, and the need to

			seek health services when necessary. There was no control group for the minimum education and preoperative IMT."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	No attrition in the intervention group.
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N	"All the patients from the PR group and the CPT group successfully completed the 5 sessions per week during 1 month."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"An intention-to-treat analysis was done including the 3 patients in the CPT group who did not have surgery and assuming no change for the PPCs. Results analyzed both by intention to treat and per protocol showed that the CPT group had more postoperative complications than the PR group."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	only specifies the use of the "6-minute walk test (6MWT)" without further clarification. Since this is a research team with experience in rehabilitation, the reference methodology of this test should probably be correctly applied.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	"Postoperative outcomes were obtained from the medical records by a physical therapist blinded to the treatment assignment." => no information about preoperative outcomes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	the patient can potentially be encouraged in a different way during the assessment.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PY	
	Risk of bias judgement	**High**	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	Retrospective registration (record date: 07/06/2011) "This randomized trial study recruited 31 patients between the period of March 2008 and March 2011"
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	





Annexe 3.8. Evaluation détaillée du risque de biais à l'aide de l'outils RoB2 pour le critère de jugement fonction pulmonaire (VEMS et CVF)

Unique ID	liu2020	**Study ID**	Liu et al. 2020	**Assessor**	FEG (PS/TB)
Ref or Label	Anesthesia and analgesia. 2020;131(3):840-9	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Pulmonary Function (FEV1 and FVC)	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2"The patients were then assigned randomly to the prehabilitation or control group according to computer-generated random numbers concealed in sealed envelopes"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Table 1. Baseline assessments and surgery Characteristics of the study population.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"This single-blind, randomized controlled" ; Participant and personnel were not blinded.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	"Perioperative care was applied with a standardized clinical pathway by a multidisciplinary team for patients undergoing VATS lobectomy with the same anesthesia and postoperative analgesia strategy."
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	No drop-out or exclusion in the intervention group related to the proposed intervention (see flow-chart)
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	"Finally, no participant was excluded due to low compliance."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	

	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Not a real intention to treat but relatively low attrition (14%) and no significant difference in baseline characteristic between those people who excluded or not "A total of 37(/43) patients in the prehabilitation group and 36(/42) patients in the control group were included in the modified intention-to-treat dataset and finally analyzed" "There were no significant differences between the analyzed population and the patients who were randomized but excluded in terms of demographic and physiological characteristics"
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"Lung function was measured using a portable spirometer (MIR Spirolab; Medical International Research Headquarters, Rome, Italy) with the patient in standing position. Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF) were measured, and FEV1/FVC was calculated. Respiratory measurements were conducted at the same time as the 6MWT and were repeated 3 times, with the best results recorded." "Reference ATS Committee on proficiency Standards for Clinical Pulmonary Function Laboratories."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	"Perioperative care was applied with a standardized clinical pathway by a multidisciplinary team for patients undergoing VATS lobectomy with the same anesthesia and postoperative analgesia strategy."
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"The assessors were blinded to the patient allocation"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	NCT03068507 : "The secondary end points include lung function improvement (baseline vs. preoperative)" => Nos history of change in this outcome
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	the definition of the lung function parameters are standardised, and the pre-defined measurement times have been respected
	5.3 ... multiple eligible analyses of the data?	PN	results expressed in mean difference, no significant results reported
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	lai2019	**Study ID**	Lai et al. 2019	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Translational Medicine. 2019 Oct;7(20):544	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Pulmonary Function (FEV1 and FVC)	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The patients were randomly assigned into one of two treatment types using a random number table" assignment "after baseline assessments were completed"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see Table 2 baseline characteristics between the two groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"Due to the nature of this research, we could not keep the participants blind to group assignment."
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	The operative and postoperative process is identical apart from the intervention. Only VATS lobectomy.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	In the study, all but 2 patients could endure the training intensity,

			which attests to the feasibility and safety of this training mode
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	According to the intention of the treatment principle, all the randomized 3.1 patients were included in the analysis. The study flow can be seen in supporting Figure 1.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	No information concerning the methodological references for pulmonary function tests, but use of the related guidelines concerning the 6MWT "American Thoracic Society (ATS) Pulmonary Function Standards Committee recommendations".
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	see 4.1 and 4.2
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The study staff and statistical analyses were all blind to patient allocation during data collection.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	pulmonary function pre-specified as secondary outcome (ChiCTR1800014512)
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	the definition of the lung function parameters are standardised, and the pre-defined measurement times have been respected
	5.3 ... multiple eligible analyses of the data?	PN	the inter-group difference is the only modality reported, no significant results.
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Bias due to deviations from intended interventions	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	caregivers), we consider that the blindness was probably not achieved.
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	Same perioperative process (see "Postoperative management" paragraph)
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	Only 2 drop-out (6.5%) linked to the intervention: "1 patient had acute COPD exacerbation 2 had new worsening of knee
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	see 2.4
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"During the rehabilitation, 5 patients dropped out because of loss of motivation (n=2), acute COPD exacerbation (n=1), and a new worsening of knee pain (n=2) (Figure 1). In consideration of the intention to treat (ITT) principle, we included these patients in the final analysis." (the 2 patients who stoped due to lack of motivation are part of a 3rd IMT group not included in our systematic review / meta-analysis)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	methodology for measuring respiratory function not detailed, but research team part of a university hospital center performing these tests in daily clinical practice
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	All participants were assessed and recorded by a statistician who was blind to the study design.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was	N	only "Peak Expiratory Flow" pre-specified; retrospective registration

the reported result	finalized before unblinded outcome data were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	huang2017	**Study ID**	Huang2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic disease. 2017;9(7):1919-29	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Pulmonary Function (FEV1 and FVC)	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Participants were divided into three groups and randomization was performed by the coordinating investigator with a computerbased 1:1:1 ratio"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	see "Table 2 Baseline characteristics of patients"
	Risk of bias judgement	**Low**	
	2.1 Were participants aware of their assigned intervention during the trial?	PY	No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of

Unique ID	morano2013	**Study ID**	Morano et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	Archives of physical medicine and rehabilitation. 2013;94(1):53-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Chest Physio Therapy	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Pulmonary Function (FEV1 and FVC)	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**

Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"The randomization was done in "blocks" of 4, and individual allocations were placed in sealed envelopes. An external investigator blinded to the allocation sequence picked the envelopes."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	see "Table 2 Baseline characteristics of the 24 patients before 4 weeks of PR vs CPT", "The baseline characteristics observed between the 2 treatment arms (PR vs CPT) were comparable for demographic, clinical, surgical, and functional parameters except for the measures of MIP and MEP"
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	"Randomized single-blinded study" => only assessor
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	the preoperative period probably does not make any difference except for the training
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	No attrition in the intervention group.
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N	"All the patients from the PR group and the CPT group successfully completed the 5 sessions per week during 1 month."
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"An intention-to-treat analysis was done including the 3 patients in the CPT group who did not have surgery and assuming no change for the PPCs. Results analyzed both by intention to treat and per protocol showed that the CPT group had more postoperative complications than the PR group."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	methodology for measuring respiratory function not detailed, but research team part of a university hospital center

			performing these tests in daily clinical practice
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	see 4.2 ; same time point
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	"Postoperative outcomes were obtained from the medical records by a physical therapist blinded to the treatment assignment." => no information about preoperative outcomes.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	spirometry, is an examination that is carried out with encouragement to produce a maximum effort, apart from blindness of the assessors, partial encouragement is possible.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PY	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	Retrospective registration (record date: 07/06/2011) "This randomized trial study recruited 31 patients between the period of March 2008 and March 2011"
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	pehlivan2011	**Study ID**	Pehlivan et al. 2011	**Assessor**	FEG (PS/TB)
Ref or Label	Annals of Thoracic and Cardiovascular Surgery. 2011;17(5):461-8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Pulmonary Function (FEV1 and FVC)	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Patients, […] were randomly allocated (according to hospital record number) to control or study group. […] Randomization was performed according to an internetbasedrandom number generator." No information about allocation concealment.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"There was no statistically significant difference between groups according to age, weight, height, body mass index (BMI) and

			cigarette smoking and performed operations. The distribution of parameters was balanced as shown in Table 1."
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	Participant and personnel were not blinded
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	Same perioperative management; no significant difference in the type of surgery in each arm. ; "In addition, both groups had
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	No drop-out in the group benefiting from the intervention
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	Although adherence in number of sessions is not reported, the authors do not report difficulty in following the exercise program.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	No attrition
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	methodology for measuring respiratory function not detailed, but research team part of a university hospital center performing these tests in daily clinical practice
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	see 4.1 and 4.3
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	"the experiment was conducted blindly and thus physicians did not know grouping of patients"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was	N	No Registration

the reported result	finalized before unblinded outcome data were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	stefanelli2013	**Study ID**	Stefanelli et al. 2013	**Assessor**	FEG (PS/TB)
Ref or Label	European Journal of Cardio-thoracic Surgery. 2013;44(4):e260-e5	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; nonadherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s)
Outcome	Pulmonary Function (FEV1 and FVC)	**Results**		**Weight**	1

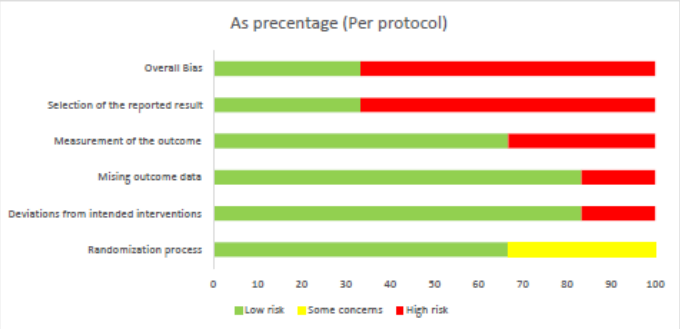
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	"Patients were randomly assigned to two groups". No more information provided
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	"At T0, the two groups did not significantly differ in age (years ± SD, Group R vs S: 65.5 ± 7.4 vs 64.8 ± 7.3, P = NS), BMI (Group R vs S: 25.6 ± 4.5 vs 27.6 ± 3.5, P = NS), FEV1 and peakVO2"
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	No information
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PN	see "Study design" paragraph : "Patients were randomly assigned to two groups. The patients in the first group (rehabilitation, R) underwent a 3-week preoperative outpatient intensive PRP based on high-intensity training of both upper- and lower-limb muscles. Conversely, the patients in the second group (surgery, S) did not participate in the preoperative PRP and underwent only surgery according to the normal standard preoperative protocol."

	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NI	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NI	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NI	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	No flow chart
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	no evidence that the result was not biased by missing outcome data
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	"All respiratory function tests and measurements were performed according to American Thoracic and European Respiratory Societies"
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	see 4.4/5
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	spirometry, is an examination that is carried out with encouragement to produce a maximum effort, apart from blindness of the assessors, partial encouragement is possible.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	No registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	the definition of the lung function parameters are standardised, and the pre-defined measurement times have been respected
	5.3 ... multiple eligible analyses of the data?	PY	analysis intra and inter-group, in percentage and absolute value, final value and mean difference.
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

Study ID	Experimental	Comparator	Outcome	We	D1	D2	D3	D4	D5	Overall
Liu et al. 2020	Preoperative Exercise Training	Usual Care	Pulmonary Function (FEV1 and FVC)	1	+	+	+	+	+	+
Lai et al. 2019	Preoperative Exercise Training	Usual Care	Pulmonary Function (FEV1 and FVC)	1	+	+	+	+	+	+
Huang2017	Preoperative Exercise Training	Usual Care	Pulmonary Function (FEV1 and FVC)	1	+	+	+	+	-	-
Morano et al. 2013	Preoperative Exercise Training	Chest Physio Therapy	Pulmonary Function (FEV1 and FVC)	1	+	+	+	-	-	-
Pehlivan et al. 2011	Preoperative Exercise Training	Usual Care	Pulmonary Function (FEV1 and FVC)	1	!	+	+	+	-	-
Stefanelli et al. 2013	Preoperative Exercise Training	Usual Care	Pulmonary Function (FEV1 and FVC)	1	!	-	-	-	-	-

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result



Annexe 3.9. Evaluation détaillée du risque de biais à l'aide de l'outils RoB2 pour le critère de jugement qualité de vie (score global de l'EORTC-QLQ-C30)

Unique ID	PPC.lai2017	**Study ID**	Lai et al. 2017	**Assessor**	FEG (PS/TB)
Ref or Label	Interactive cardiovascular and thoracic surgery. 2017;25(3):476-83	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	QoL (EORTC - global score)	**Results**	MD = 2.10 points [95% CI -2.86, 7.06]	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 "eligible patients were allocated to a treatment or a control group, based on a randomization table generated by a computer by an independent person, with group allocation placed in sequential opaques envelopes. Group allocation was revealed by a research assistant"
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 see Table 1: Baseline and clinical characteristics between the intervention and control groups
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	2.1/2 Participant and personnel were not blinded "It is impossible for the patients to be blinded to their treatment group allocation"
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	2.3 The operative and postoperative process is identical apart from the intervention.
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 "In our study, 6 patients did not finish the 7-day regimen. Two of them required an operation before

			completing the 7-day regimen; 2 requested withdrawal from the study because of a perceived lack of benefit; and 2 requested withdrawal because they felt they could not endure the regimen." => only (4/51) 8% failures in the implementation of the intervention
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	2.5 program carried out under supervision (inpatient modality) over a single week limiting the risk of non-adherence to the sessions.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 6 people stopped exercise training but were included in the analysis
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	4.1 "The EORTC-QLQ-C30 and EORTC-LC13 were used to assess patient symptoms and health-related quality of life." tool validated n patients with NSCLC
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	4.2 questionnaire completed by the patient himself at the same times
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "all study personnel collecting data and conducting statistical analyses were blinded to patient allocation"
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 Retrospective registration
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	

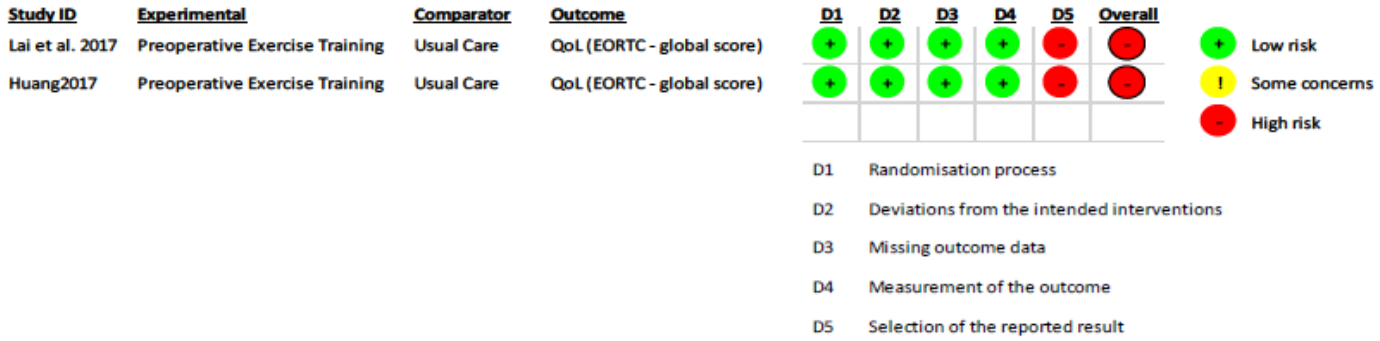
Unique ID	PPC.huang2017	**Study ID**	Huang2017	**Assessor**	FEG (PS/TB)
Ref or Label	Journal of thoracic disease. 2017;9(7):1919-29	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Preoperative Exercise Training	**Comparator**	Usual Care	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	QoL (EORTC - global score)	**Results**	MD = 6.70 points [95% CI 0.63, 12.77]	**Weight**	1

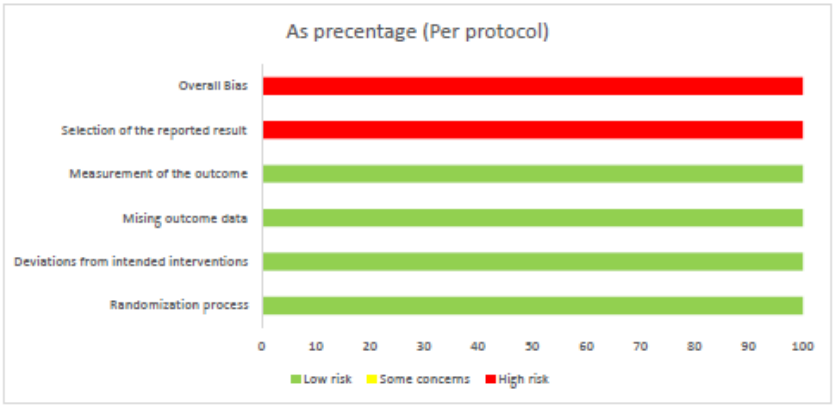
Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1/2 “Participants were divided into three groups and randomization was performed by the coordinating investigator with a computer-based 1:1:1 ratio”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	1.3 see Table 2
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PY	2.1/2 No specified, but due to the evaluated intervention (physical therapy requiring the participation and active supervision of caregivers), we consider that the blindness was probably not achieved.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	

Annexe 3.9

	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	2.3 Same perioperative management
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	2.4 Only 2 drop-out (6.5%) linked to the intervention: "1 patient had acute COPD exacerbation 2 had new worsening of knee pain"
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	2.5 program carried out under supervision (inpatient modality) over a single week limiting the risk of non-adherence to the sessions.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	3.1 "During the rehabilitation, 5 patients dropped out because of loss of motivation (n=2), acute COPD exacerbation (n=1), and a new worsening of knee pain (n=2) (Figure 1). In consideration of the intention to treat (ITT) principle, we included these patients in the final analysis." (the 2 patients who stoped due to lack of motivation are part of a 3rd IMT group not included in our systematic review / meta-analysis)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	4.1 "EORTC-QLQ-C30 and EORTC–LC13 scores were also used to analyze the subjective self-evaluation." tool validated n patients with NSCLC
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	4.2 questionnaire completed by the patient himself at the same times
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	4.3 "All participants were assessed and recorded by

			a statistician who was blind to the study design."
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	5.1 Retrospective registration.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	PY	
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	



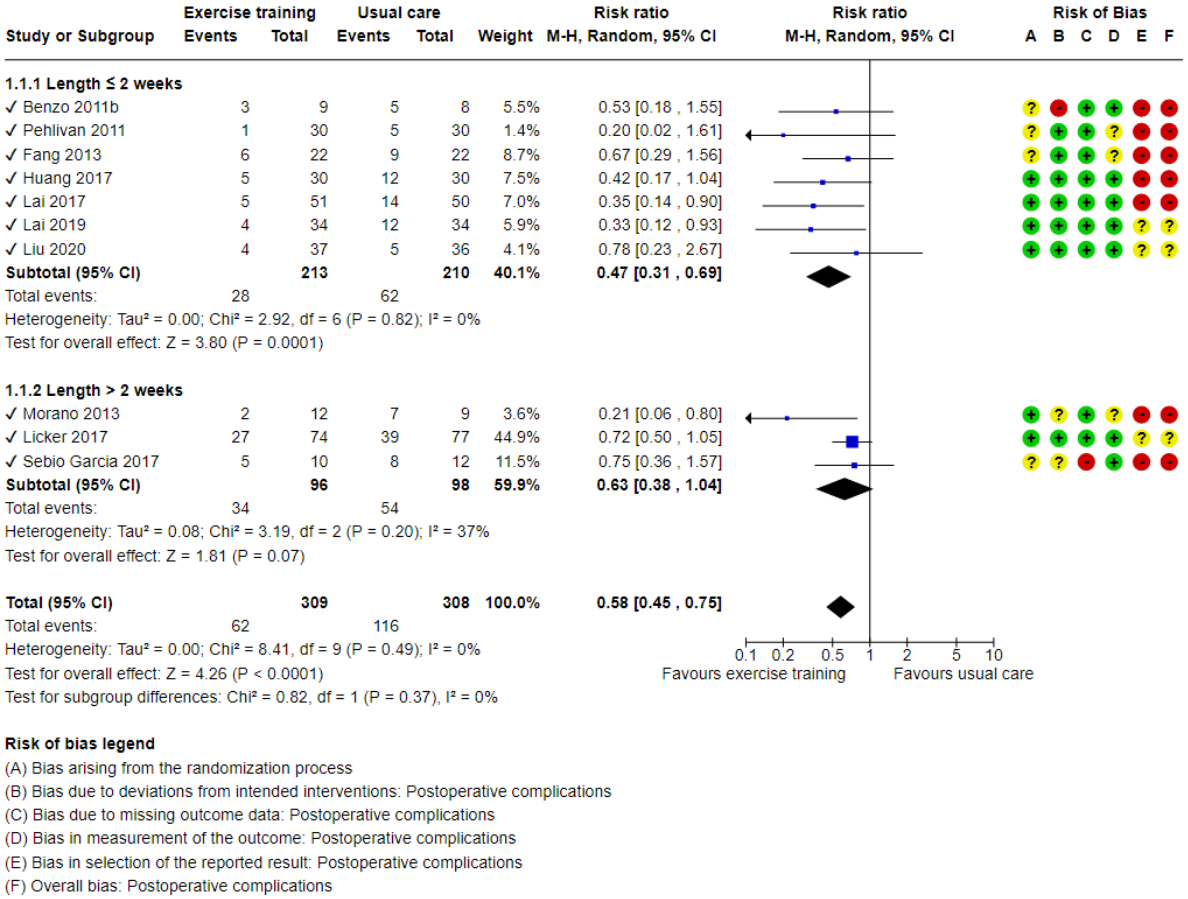


Annexe 3.10. : Analyse des sous-groupes

Appendix 10. Sub-group analysis.

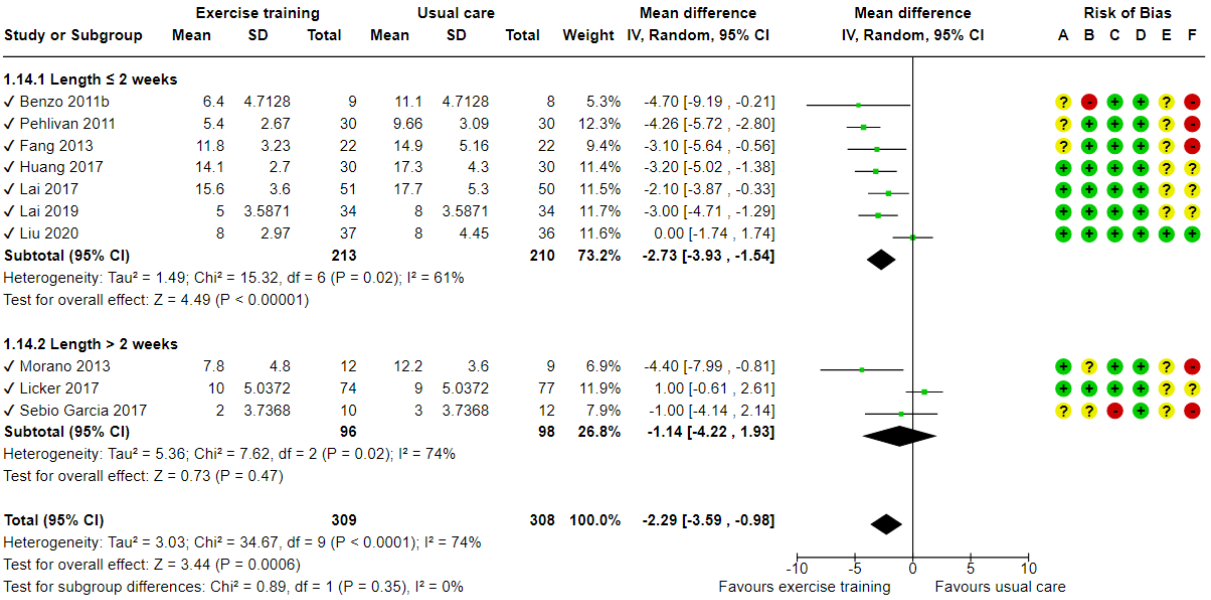
Sub-group analysis n°1: Preoperative exercise training > 2 weeks versus ≤ 2 weeks

- Outcome 1: Postoperative complications (POC)



The subgroup analysis of the seven studies offering short intensive preoperative training (≤ 2 weeks) reported a significative reduction in POC (RR 0.47 [95% CI 0.31 to 0.69]). Paradoxically, the level of certainty concerning programs of longer duration (> 2 weeks) is non significative with a wide confidence interval ranging up to a trivial effect (RR 0.63 [95% CI 0.38 to 1.04])

- Outcome 2: Length of stay (LoS) in the hospital

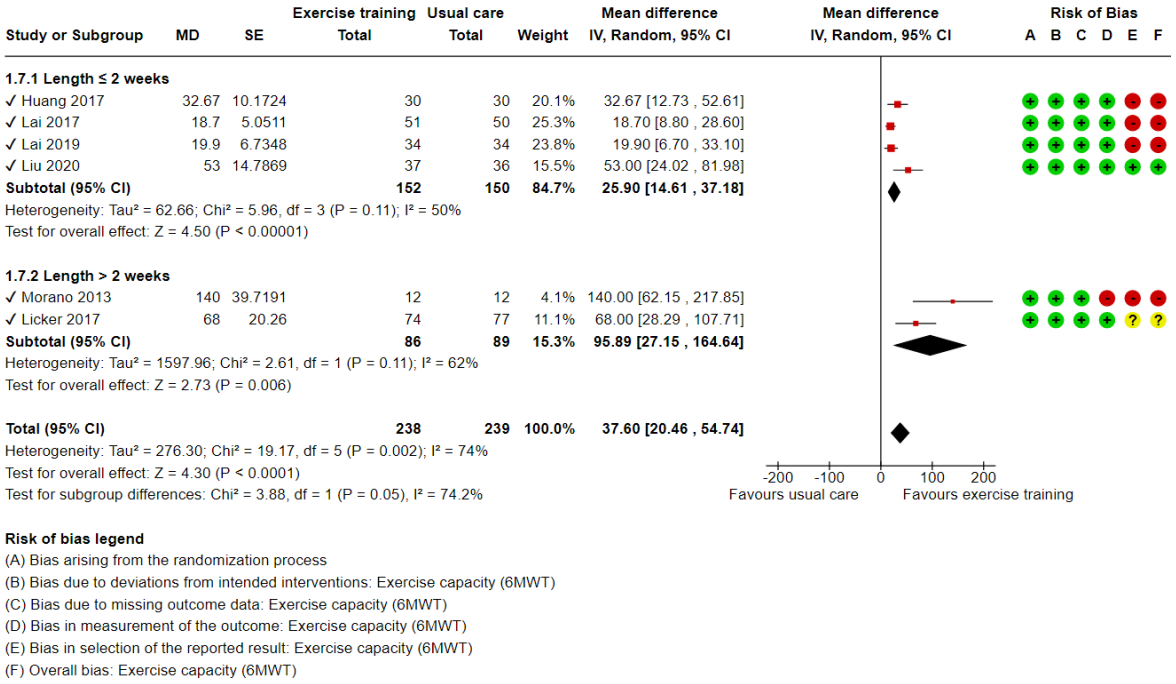


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Length of stay in the hospital
(C) Bias due to missing outcome data: Length of stay in the hospital
(D) Bias in measurement of the outcome: Length of stay in the hospital
(E) Bias in selection of the reported result: Length of stay in the hospital
(F) Overall bias: Length of stay in the hospital

The sub-group analysis of the seven studies offering short intensive preoperative training (≤ 2 weeks) reported a significative reduction in LoS (MD -2.7 days [95% CI -3.9 to 0.-1.5]). Concerning longer programs (> 2 weeks) the sub-group analysis report no significative difference in LoS (MD -1.1 [95% CI -4.2 to 1.9]).

- Outcome 3: exercise capacity measured with 6-minutes' walk distance (6MWD)



The sub-group analysis of the four studies offering short intensive preoperative training (≤ 2 weeks) reported a significative improvement in 6MWD (MD 25.9 meters [95% CI 14.6 to 37.2]). Concerning longer programs (> 2 weeks) the sub-group analysis reported a significative improvement in 6MWD too (MD 95.9 meters [95% CI 27.2 to 164.6]). Although the results were significant in both subgroups, the clinical significance was more marked in favour of longer programs.

Sub-group analysis n°2: Exercise training alone versus comprehensive prehabilitation programs (including education and/or, inspiratory muscle training, and/or chest physiotherapy).

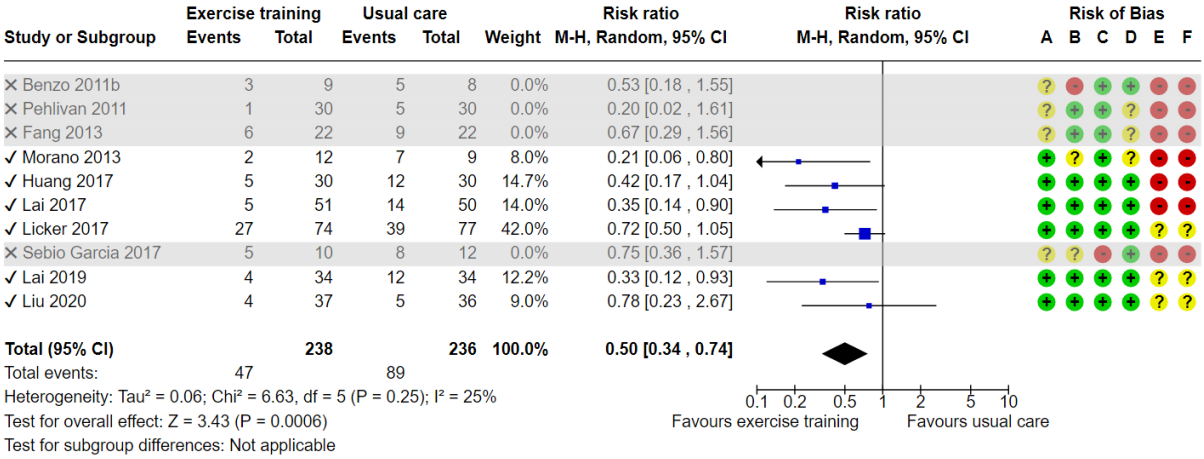
It was not possible to compare exercise training alone with comprehensive prehabilitation programs due to insufficient data for sub-group analysis.

Annexe 3.11. : Analyses de sensibilité

Appendix 3. Sensitivity analysis.

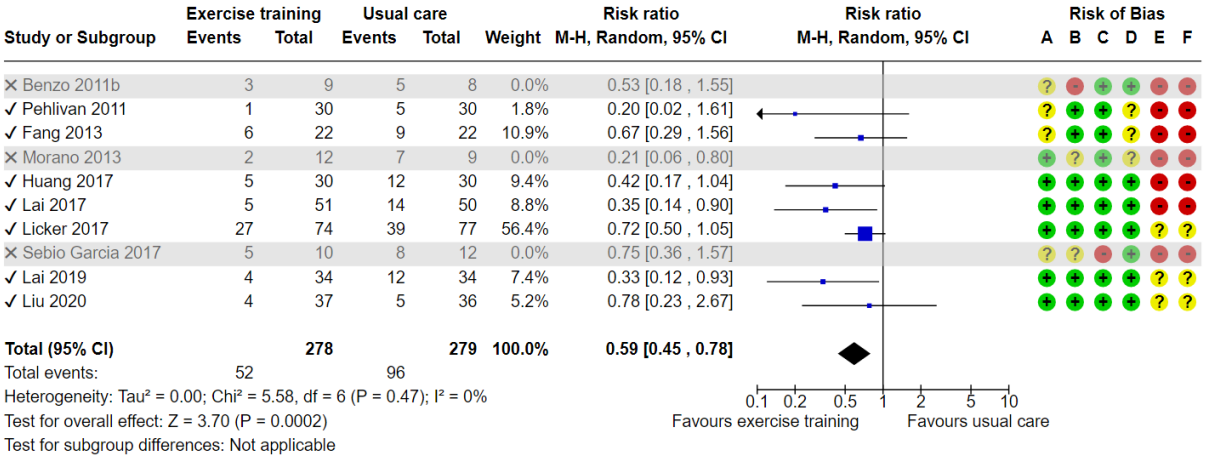
1. **Sensitivity analysis:** Postoperative complications (POC).

1.1 Bias arising from the randomization process (A)



Analysis without the studies of Benzo et al. 2011, Pehlivan et al. 2011, Morano et al. 2013 and Sebio Garcia et al. 2017, with potential bias arising from the randomization process, reported a relative risk (RR) in POC of 0.50 (95% CI 0.34 to 0.74), which does not modify the interpretation of the initial results (RR 0.58, 95% CI 0.45 to 0.75).

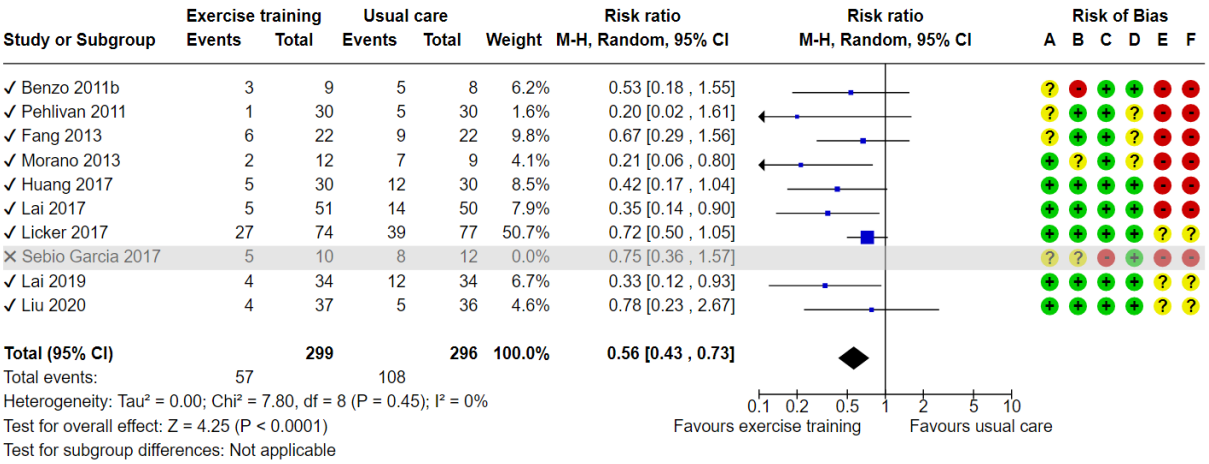
1.2 Bias due to deviations from intended interventions (B)



Analysis without the studies of Benzo et al. 2011, Morano et al. 2013 and Sebio Garcia et al. 2017, with potential bias due to deviations from intended interventions, reported a RR in POC

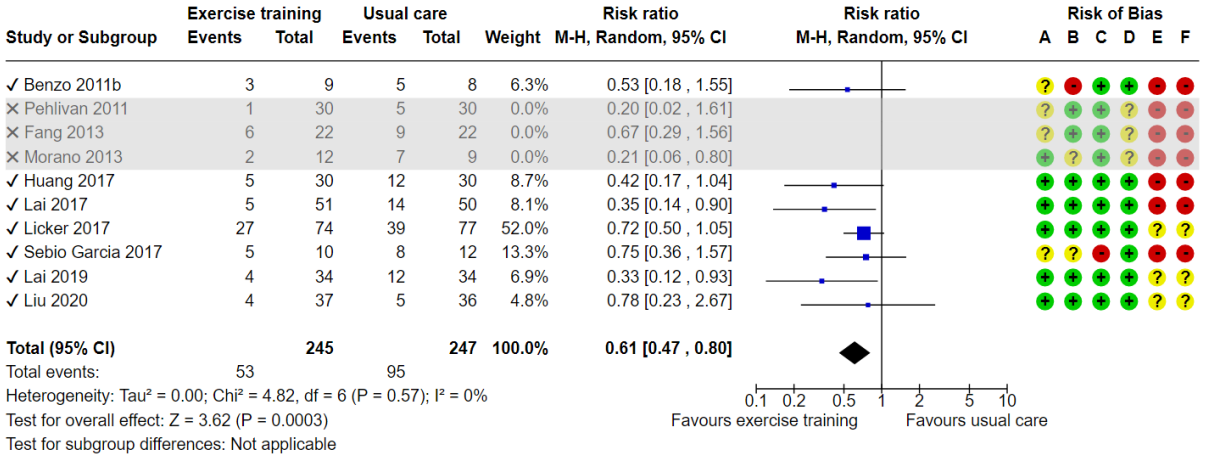
of 0.59 (95% CI 0.45 to 0.78), which does not modify the interpretation of the initial results (RR 0.58, 95% CI 0.45 to 0.75).

1.3 Bias due to missing outcome data (C)



Analysis without the study of Sebio Garcia et al. 2017, with potential bias due to missing outcome data, reported a RR in POC of 0.56 (95% CI 0.43 to 0.73), which does not modify the interpretation of the initial results RR 0.58 (95% CI 0.45 to 0.75).

1.4 Bias in measurement of the outcome (D)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Postoperative complications
(C) Bias due to missing outcome data: Postoperative complications
(D) Bias in measurement of the outcome: Postoperative complications
(E) Bias in selection of the reported result: Postoperative complications
(F) Overall bias: Postoperative complications

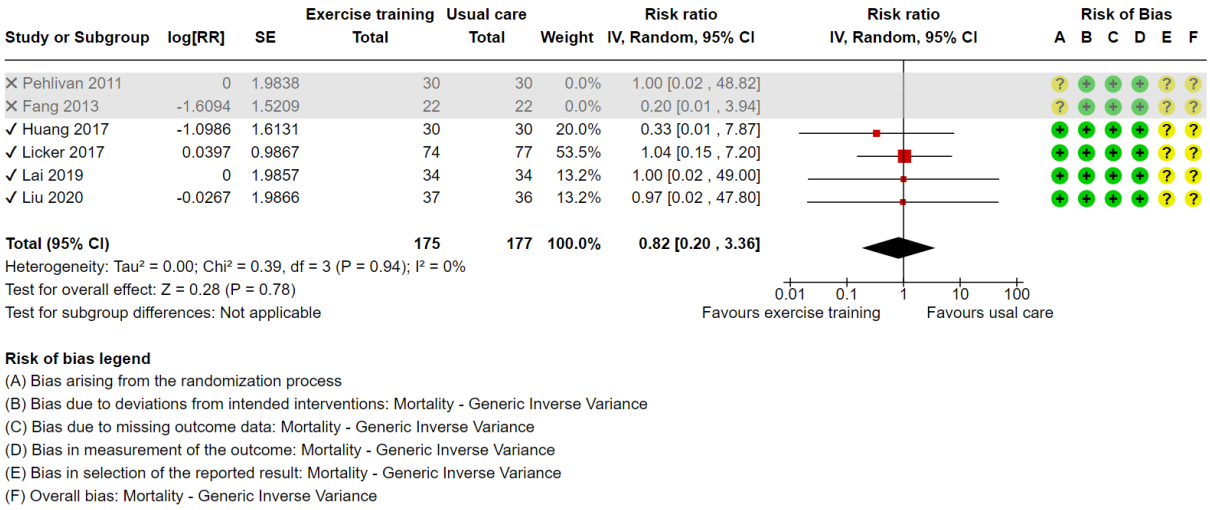
Analysis without the studies of Pehlivan et al. 2011, Fang et al. 2013, and Morano et al. 2013, with potential bias in measurement of the outcome, reported a relative risk (RR) in POC of 0.61 (95% CI 0.47 to 0.80), which does not modify the interpretation of the initial results RR 0.58 (95% CI 0.45 to 0.75).

1.5 Bias in selection of the reported result (E)

All studies had potential bias in selection of the reported result, consequently the sensitivity analysis was not carried out for this risk of bias.

Sensitivity analysis n°2: Mortality

1.1 Bias arising from the randomization process (A)



Risk of bias legend

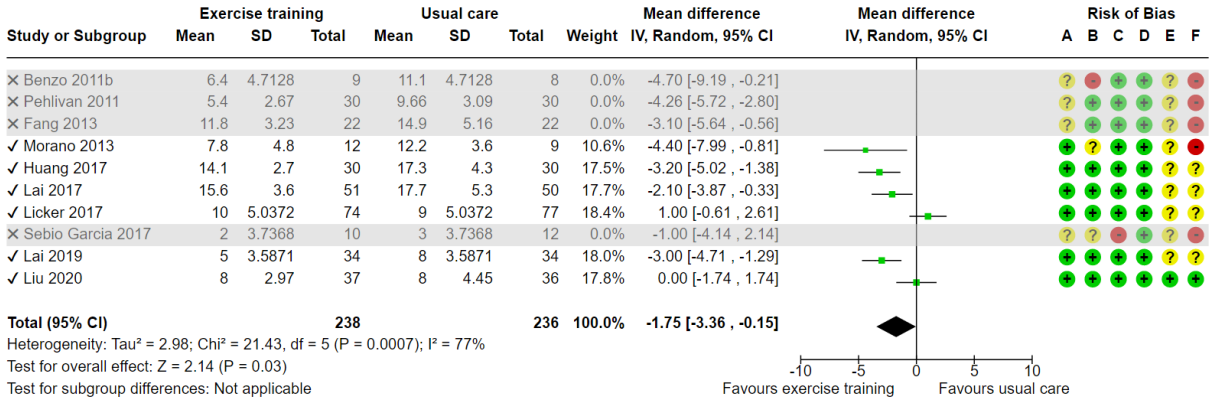
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Mortality - Generic Inverse Variance
(C) Bias due to missing outcome data: Mortality - Generic Inverse Variance
(D) Bias in measurement of the outcome: Mortality - Generic Inverse Variance
(E) Bias in selection of the reported result: Mortality - Generic Inverse Variance
(F) Overall bias: Mortality - Generic Inverse Variance

Analysis without the study of Pehlivan et al. 2011, and Fang et al. 2013, with potential bias arising from the randomization process, reported no significative modification in mortality with a RR of 0.82 (95% CI 0.20 to 3.36), which does not modify the interpretation of the initial results (RR 0.66; 95% CI 0.20 to 2.22).

The sensitivity analysis was not carried out for the other risks of bias.

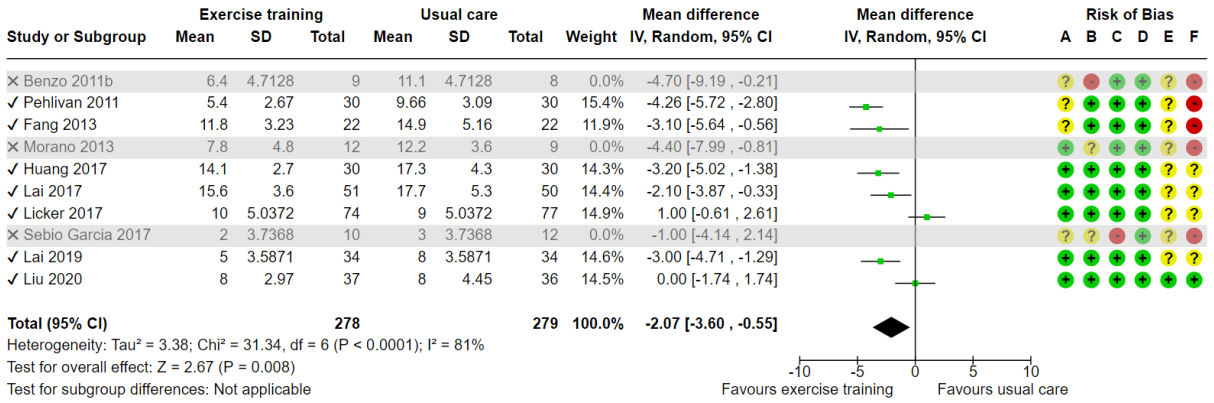
Sensitivity analysis n°3: Length of stay in the hospital (LoS).

1.1 Bias arising from the randomization process (A)



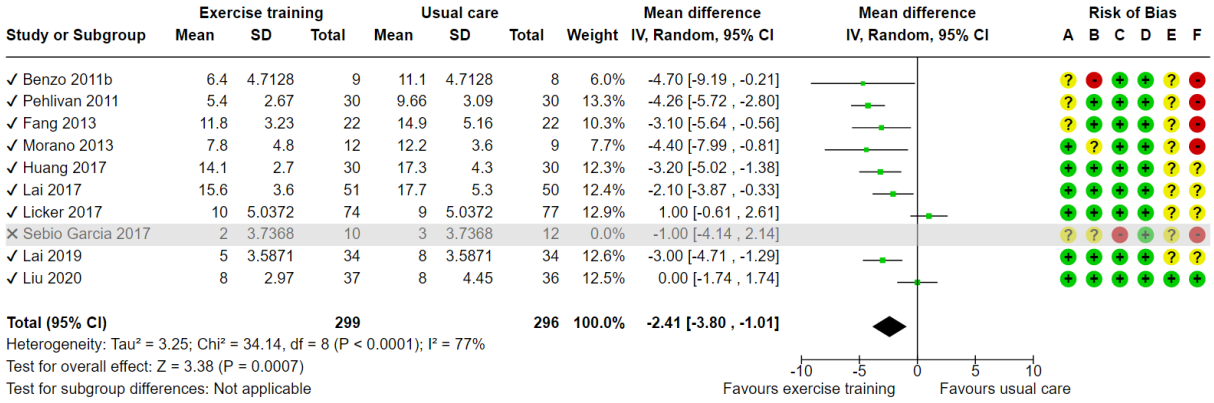
Analysis without the studies of Benzo et al. 2011, Pehlivan et al. 2011, Fang et al. 2013 and Sebio Garcia et al. 2017, with potential bias arising from the randomization process, reported a significative mean difference (MD) in LoS of -1.75 days (95% CI -3.36 to -0.15), consequently the certainty of the worthwhileness effect may not be clinically any more. As a reminder the initial results report a MD of -2.29 days (95% CI -3.59 to -0.98).

1.2 Bias due to deviations from intended interventions (B)



Analysis without the studies of Benzo et al. 2011, Morano et al. 2013, and Sebio Garcia et al. 2017, with potential bias due to deviations from intended interventions, reported a significative mean difference (MD) in LoS of -2.07 days (95% CI -3.60 to -0.55), which does not modify the interpretation of the initial results (MD -2.29 days 95% CI -3.59 to -0.98).

1.3 Bias due to missing outcome data (C)

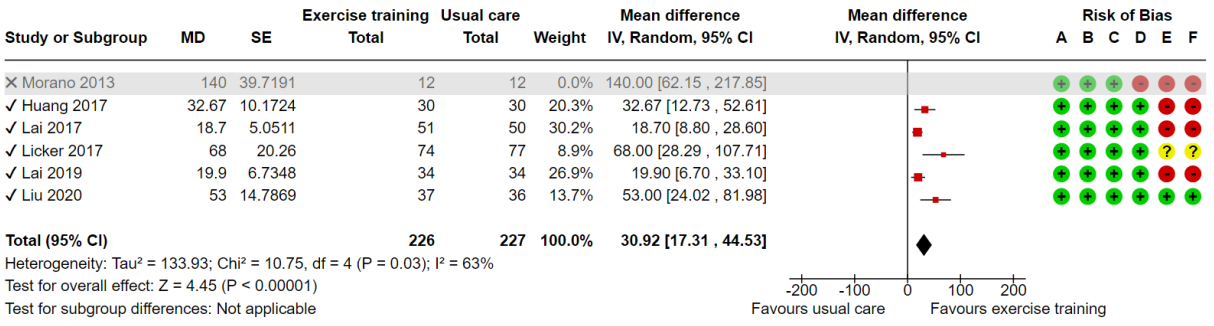


Analysis without the studies of Sebio Garcia et al. 2017, with potential bias due to missing outcome data, reported a significative mean difference (MD) in LoS of -2.41 days (95% CI -3.80 to -1.01), which does not modify the interpretation of the initial results (MD -2.29 days 95% CI -3.59 to -0.98).

The sensitivity analysis was not carried out for the other risks of bias.

Sensitivity analysis n°3: Exercise capacity assessed with six-minute walk distance (6MWD).

1.4 Bias in measurement of the outcome (D)



Analysis without the study of Morano et al. 2013, with potential bias in measurement of the outcome, reported a MD in 6MWD of 30.92 meters (95% CI 17.31 to 44.53), which does not modify the interpretation of the initial results (MD 37.60 meters, 95% CI 20.46 to 54.74).

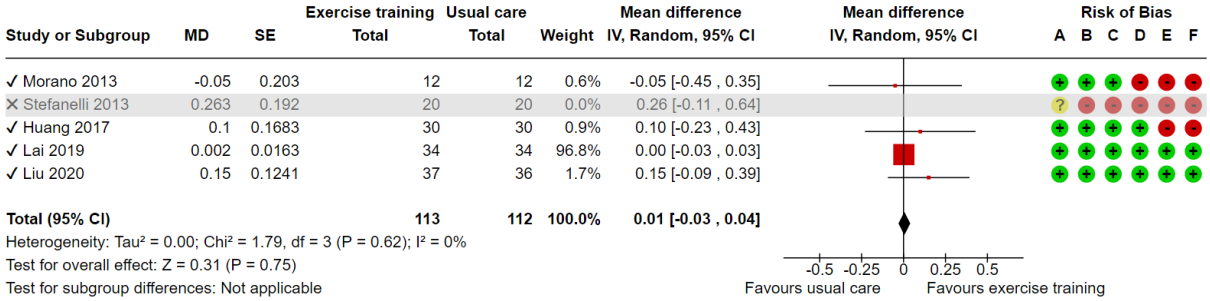
The sensitivity analysis was not carried out for the other risks of bias.

Sensitivity analysis n°4: Pulmonary function assessed with forced expiratory volume in 1 second (FEV1) measured in litter (L).

1.1 Bias arising from the randomization process (A)

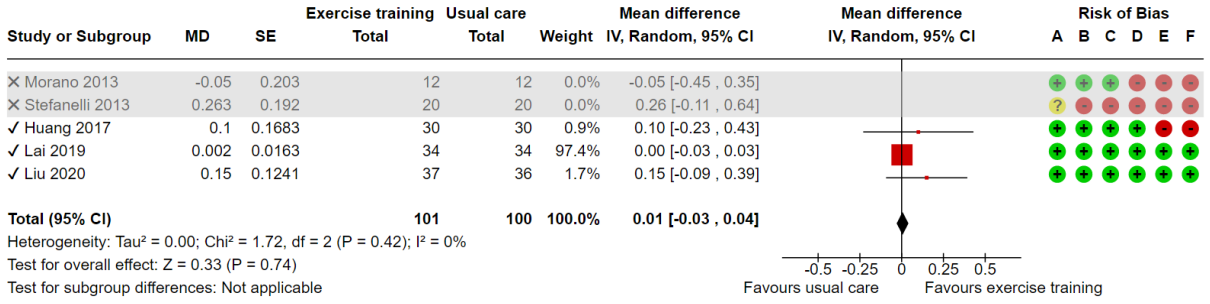
1.2 Bias due to deviations from intended interventions (B)

1.3 Bias due to missing outcome data (C)



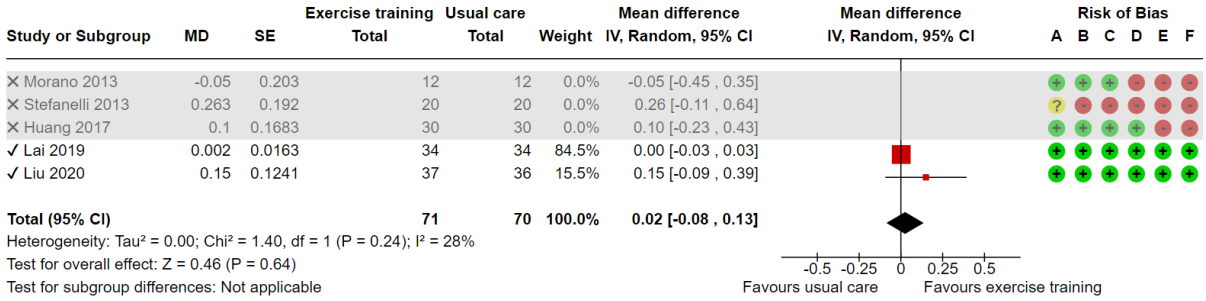
Analysis without the studies of Stefanelli et al. 2013 with potential bias arising from the randomization process, and due to deviations from intended interventions or missing outcome data, reported a non significative MD in FEV1 of 0.01 L (95% -0.03 to 0.04), which does not modify the interpretation of the initial results (MD 0.01 L, 95% CI -0.02, 0.04).

1.4 Bias in measurement of the outcome (D)



Analysis without the studies of Morano et al. 2013, and Stefanelli et al. 2013, with potential bias in measurement of the outcome, reported a non significative MD in FEV1 of 0.01 L (95% -0.03 to 0.04), which does not modify the interpretation of the initial results (MD 0.01 L, 95% CI -0.02, 0.04).

1.5 Bias in selection of the reported result (E)



Analysis without the studies of Morano et al. 2013, Stefanelli et al. 2013, and Huang 2013, with potential bias in selection of the reported result, reported a non significative MD in FEV1 of 0.02 L (95% -0.08 to 0.13), which does not modify the interpretation of the initial results (MD 0.01 L, 95% CI -0.02, 0.04).

Annexe 4. : Réponse lettre à l'éditeur : Prehabilitation versus standard care-What impact on complications ?

PREOPERATIVE PULMONARY REHABILITATION

To the Editor:

I enjoyed the recent article by Gravier and colleagues[1] in the June issue of *The Journal of Thoracic and Cardiovascular Surgery*, "Effect of Prehabilitation on Ventilatory Efficiency in Non–Small Cell Lung Cancer Patients: A Cohort Study." Our group did extensive outpatient preoperative pulmonary rehabilitation in patients with lung cancer with forced expiratory volume in 1 second < 1.56 L/s who underwent subsequent lung resection. The study compared those receiving preoperative pulmonary rehabilitation with a second group without any preoperative pulmonary therapy.

The group receiving pulmonary rehabilitation improved their forced expiratory volume in 1 second significantly

Author has nothing to disclose with regard to commercial support.

before lung resection. The average intensive care unit stay, morbidity, and mortality, however, were unchanged between the cohorts.[2]

Gravier and colleagues[1] presented a more extensive plan of preoperative rehabilitation and a much more elegant measure of pulmonary function. Patients can be enrolled in preoperative rehabilitation, but their participation is effort dependent. How did the postoperative course and complications of the treated patients (whether more or fewer than 15 treatments) compare with those of patients who did not receive any preoperative therapy?

We await the results of current prospective efforts at preoperative pulmonary rehabilitation, including muscle training, avoiding smoking, and adjustment of patient medications, to see whether there will be a substantial effect on lung resection outcomes in patients with lung cancer.

Frank A. Baciewicz Jr, MD
Department of Cardiothoracic Surgery
Michael and Marian Ilitch Department of Surgery
Wayne State University School of Medicine
Detroit, Mich

References

1. Gravier FE, Bonnevie T, Boujibar F, Médrinal C, Prieur G, Combret Y, et al. Effect of prehabilitation on ventilatory efficiency in non–small cell lung cancer patients: a cohort study. *J Thorac Cardiovasc Surg*. 2019;157:2504-12.
2. Hasmi A, Baciewicz FA Jr, Soubani AO, Gadgeel SM. Preoperative pulmonary rehabilitation for marginal-function lung cancer patients. *Asian Cardiovasc Thorac Ann*. 2017;25:47-51.

https://doi.org/10.1016/j.jtcvs.2019.07.137

REPLY: PREHABILITATION FOR INCREASING VENTILATORY EFFICIENCY BEFORE LUNG RESECTION—AMAZING CONCEPT, BUT WE ARE NOT THERE YET!

Reply to the Editor:

We thank you for the opportunity to comment on the letter to the Editor sent by Dr Baciewicz. We concur with Dr Baciewicz that the proposed comparison between the cohort of the study from Gravier and colleagues[1] and patients who did not receive preoperative prehabilitation in terms of postoperative course and clinical complications could be of interest. They could run this analysis with or without propensity matching with the 138 patients who did not receive pulmonary prehabilitation in their center during the same study period as a comparator. Nevertheless, this analysis would likely be underpowered because the small sample size in each subgroup. Moreover, conclusions drawn from this analysis, even if positive, should be viewed with caution, because the threshold of 15 sessions was decided on arbitrarily, more on the basis expert opinion than on the basis of robust statistical analysis (area under the curve, 0.68).

Authors have nothing to disclose with regard to commercial support.

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Reference

1. Gravier FE, Bonnevie T, Boujibar F, Médrinal C, Prieur G, Combret Y, et al. Effect of prehabilitation on ventilatory efficiency in non–small cell lung cancer patients: a cohort study. *J Thorac Cardiovasc Surg*. 2019;157:2504-12.

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REPLY FROM THE AUTHORS: PREHABILITATION VERSUS STANDARD CARE—WHAT IMPACT ON COMPLICATIONS?

Reply to the Editor:

We thank Dr Baciewicz for his interest in our article. Indeed, our retrospective cohort study of 50 patients focused on the impact of prehabilitation with analysis of cardiopulmonary exercise testing before and after prehabilitation. Results report that patients included in our prehabilitation program had better physiologic benefits and suggest fewer complications from 15 treatment sessions. As is underlined, however, there remains the question of comparison with patients who have not benefited

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from the proposed program. Unfortunately, because of organizational constraints of our rehabilitation center, patients who were not referred for prehabilitation were not included in our follow-up. In consequence, we do not have data to answer the question, but we can expose some adjuvant elements.

First, we can report previous results from a cohort study in which some patients received the same prehabilitation program. Boujibar and colleagues[1] analyzed data from 34 patients with non–small cell cancer (median forced expiratory volume in 1 second 61% [58%-67%] predicted, and peak oxygen uptake 15.4 mL/kg/min [13.8-17.1 mL/kg/min]) who underwent video-assisted or robot-assisted resection surgery in the thoracic surgery department of Rouen University Hospital from 2014 to 2015 after having benefited from a cardiopulmonary exercise testing in their preoperative evaluation. Nineteen patients among them were referred for preoperative rehabilitation in the same conditions as our work. Their analysis showed significant decreases not only in the occurrence of complications but also in their severity according to the Clavien-Dindo score.

Furthermore, with regard to the effects of preoperative exercise training, Sebio Garcia and colleagues[2] published in 2016 a meta-analysis of 8 studies reporting a relative risk reduction of 55% in those patients undergoing rehabilitation in comparison with the patients receiving the standard care (relative risk, 0.45; 95% confidence interval, 0.28-0.73).

More recently, Licker and assoicates[3] published a prospective study focusing on postoperative complications. Their analysis of 151 patients randomized in 2 groups (preoperative high-intensity exercise training versus usual care) provided evidence to support a decreased number of complications within the postoperative 30 days (relative risk, 0.70; 95% confidence interval, 0.48-1.02). Note that this study included patients with less severe impairment than in most other studies evaluating preoperative exercise training (forced expiratory volume in second >80% predicted, and peak oxygen uptake around 20 mL/kg/min), which theoretically is associated with a lower postoperative risk.[4] This suggests that even patients considered to be at lesser risk can benefit from preoperative training.

In total, the few previously stated elements indicate potential benefits of physical preoperative management regardless of the number of treatments offered. We are convinced of the need to include prehabilitation in the care of patients with non–small cell lung cancer referred for thoracic surgery. In parallel with the implication for practice and research provided by the Cochrane collaboration about rehabilitation in chronic obstructive pulmonary disease,[5] the question is no longer whether prehabilitation is beneficial relative to conventional care for patients with lung cancer but rather what the optimal way is to apply it. New research should now be directed toward the evaluation of the most efficient methods to apply preoperative exercise training in terms of duration, frequency, intensity, and adjuvants.

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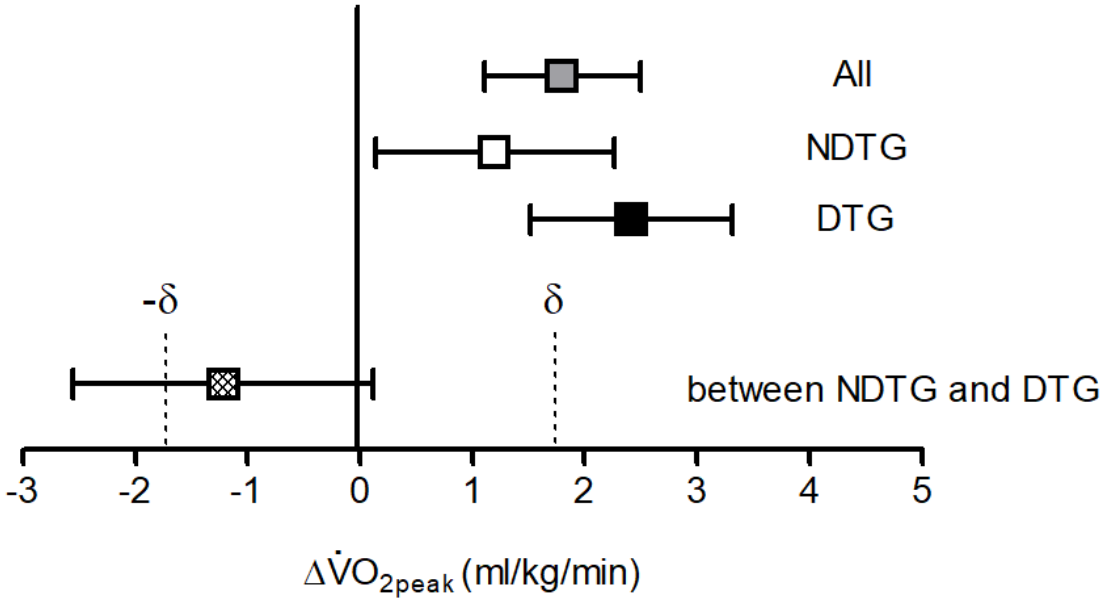
https://doi.org/10.1016/j.jtcvs.2019.07.138

Annexe 5 : données en ligne complémentaires étude Preo-Dens

Annexe 5.1.: Intention to treat analysis (ITT), using the last observation carried forward (LOCF) method



Appendix 1 ITT analysis Figure 1: variation (Δ) of peak oxygen uptake ($\dot{V}O_2peak$) after prehabilitation for all patients, non-dense-training group (NDTG: 3 sessions/week during 5 weeks), dense-training group (DTG: 5 sessions/week during 3 weeks), and difference between groups. The 2-sided 95% Confidence Interval (95% CI -2.6 to 0.1) exceeded the pre-set margin of equivalence (δ) of 1.75 ml/kg/min in favour of dense training.

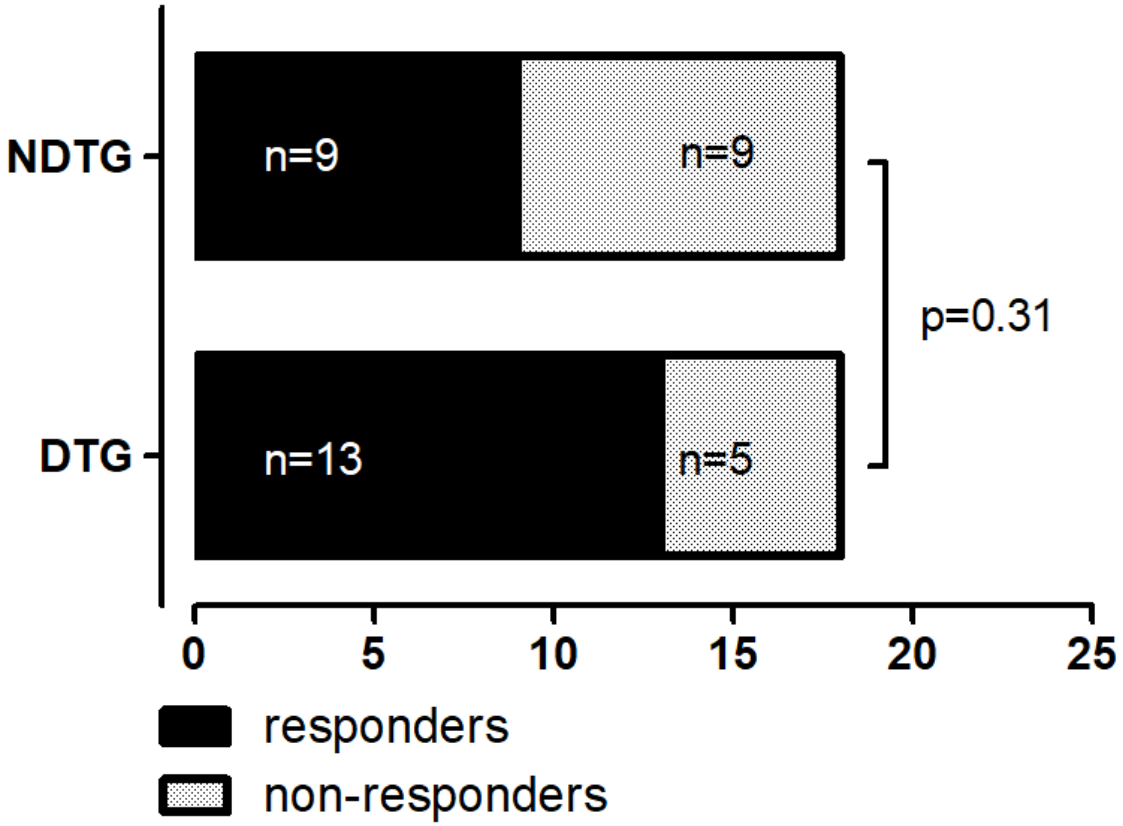
Appendix 1 ITT analysis Table 1: prehabilitation program response (Δ pre/post) for all patients, each group, and between group p-value.

Variable (units)	Δ All	Δ NDTG	Δ DTG	p-value
CPET	*n=36*	*n=18*	*n=18*	
$\dot{V}O_2$peak (mL/kg/min)	1.8 ± 2.1	1.2 ± 2.2	2.4 ± 1.8	0.07
$\dot{V}O_2$peak (% pred.)	8.4 ± 8.1	6.4 ± 8.9	10.4 ± 6.8	0.13
$\dot{V}O_2$VT (mL/kg/min)	1.0 ± 1.5	0.9 ± 1.5	1.1 ± 1.6	0.78
$\dot{V}E/\dot{V}CO_2$ slope	0.0 (-4.6 to 2.0)	0.8 (-6.7 to 3.0)	-0.6 (-4.0 to 0.9)	0.35
WRpeak (Watts)	10.0 (0.0 to 15.0)	15.0 (0.0 to 15.0)	10.0 (0.0 to 15.0)	0.89
WRpeak (% pred.)	9.0 (0.0 to 17.3)	9.5 (0.8 to 18.0)	8.5 (0.0 to 15.3)	0.74
Pulmonary Function	*n=36*	*n=18*	*n=18*	
FEV1 (L)	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.2	0.87
FEV1 (% pred.)	1.9 ± 10.2	3.6 ± 12.4	0.2 ± 7.4	0.31
FVC (L)	-0.1 ± 0.4	-0.1 ± 0.5	-0.1 ± 0.2	0.68
FVC (% pred.)	-0.7 ± 14.1	1.1 ± 17.8	-2.5 ± 9.2	0.45
MIP (cmH_2O)	10.1 ± 13.0	10.6 ± 16.2	9.6 ± 9.3	0.82
Nutrition	*n=36*	*n=18*	*n=18*	
Weight (kg)	0.3 ± 1.4	0.6 ± 1.4	0.0 ± 1.5	0.26
Fat mass (%)	0.2 ± 2.3	0.1 ± 2.8	0.3 ± 1.5	0.78
Water (%)	-0.4 ± 2.2	-0.2 ± 2.6	-0.5 ± 1.8	0.76
Lean dry mass (%)	0.1 ± 0.5	0.1 ± 0.7	0.2 ± 0.3	0.77
QoL (EORTC)	*n=36*	*n=18*	*n=18*	
Functional score	5.6 (0.6 to 15.6)	5.6 (0.0 to 17.7)	5.6 (2.2 to 13.9)	0.98
Symptom score	2.5 (-5.1 to 5.1)	2.5 (-3.2 to 5.1)	1.3 (-5.1 to 7.7)	0.99
Global score	8.3 (0.0 to 16.7)	8.3 (-2.1 to 16.7)	8.3 (0.0 to 16.7)	0.77
LC13 score	2.6 (-2.6 to 5.2)	1.3 (-5.1 to 5.1)	2.6 (-2.5 to 7.6)	0.56
Quadriceps strength*	*n=34*	*n=18*	*n=16*	
QMVIC right (Nm)	8.0 ± 14.5	5.7 ± 13.8	10.6 ± 15.2	0.34
QMVIC right (% pred.)	6.5 ± 12.2	5.9 ± 12.2	7.1 ± 12.7	0.77
QMVIC left (Nm)	8.4 ± 15.6	8.2 ± 18.3	8.5 ± 12.5	0.96
QMVIC left (% pred.)	7.1 ± 12.5	7.9 ± 15.4	6.4 ± 8.5	0.89

Data are presented as mean ± SD or median (25th to 75th percentile); NDTG: non-dense-training group (3 sessions/week during 5 weeks); DTG: dense-training group (5 sessions/week during 3 weeks); $\dot{V}$O2peak: peak of oxygen uptake; $\dot{V}$O2VT: oxygen uptake at ventilatory threshold; $\dot{V}E/\dot{V}CO2$ slope: linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO2$); WRpeak: peak power on cyclo-ergometer; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; MIP: maximal inspiratory pressure; QoL: quality of life; QMVIC: quadriceps' maximal voluntary isometric contractions.

*QMVIC was not measured at baseline in two patients with an history of skin ulcer on the anterior side of the tibia, no pre/post data was therefore imputed.

Annexe 5.2.: Appendix 2 comparison of the proportion of responders and non-responders



Appendix 2: comparison of the proportion of responders ($\Delta\dot{V}O_2$peak ≥ 10% from baseline) and non-responders ($\Delta\dot{V}O_2$peak < 10% from baseline), for non-dense-training group (NDTG: 3 sessions/week during 5 weeks), and dense-training group (DTG: 5 sessions/week during 3 weeks).

Annexe 5.3.: intra-group evolution over the course of the prehabilitation program

Variable (units)	All (n=36)		NDTG (n=18)		DTG (n=18)	
	Pre	Post	Pre	Post	Pre	Post
Cardiopulmonary exercise testing						
$\dot{V}O_2$peak (mL/kg/min)	13.5 ± 3.3	15.2 ± 3.7 ***	14.1 ± 3.2	15.1 ± 3.7 *	12.9 ± 3.3	15.2 ± 3.7 ***
$\dot{V}O_2$peak (% pred.)	63.6 ± 15.3	72.1 ± 17.2 ***	66.6 ± 15.4	73.2 ± 17.8 **	60.7 ± 15.1	70.9 ± 16.9 ***
$\dot{V}O_2$VT (mL/kg/min)	9.6 ± 1.7	10.6 ± 1.9 ***	9.8 ± 1.7	10.7 ± 1.8 *	9.5 ± 1.8	10.5 ± 2.0 *
$\dot{V}E/\dot{V}CO_2$ slope	37.3 (32.0-44.0)	35.2 (30.4-42.5)	37.3 (31.5-44.9)	35.4 (30.2-44.5)	35.7 (31.1-43.2)	35.0 (30.5-41.9)
WRpeak (Watts)	76.6 ± 22.8	85.3 ± 26.4 ***	77.2 ± 26.4	86.5 ± 32.3 ***	73.4 ±19.2	84.1 ± 19.5 ***
WRpeak (% pred.)	65.8 ± 18.3	74.7 ± 22.9 ***	68.8 ± 19.6	77.4 ± 23.3 ***	62.9 ± 17.0	72.1 ± 22.9 **
Pulmonary Function						
FEV1 (L)	1.9 ± 0.7	1.9 ± 0.7	1.9 ± 0.7	1.9 ± 0.7	1.9 ± 0.7	1.9 ± 0.7
FEV1 (% pred.)	74.0 ± 27.9	75.7 ± 29.6	75.4 ± 25.9	79.1 ± 30.4	72.6 ± 30.6	71.9 ± 29.2
FVC (L)	3.0 ± 0.8	2.9 ± 0.9	2.9 ± 0.8	2.8 ± 1.0	3.2 ± 0.9	3.0 ± 0.8
FVC (% pred.)	89.6 ± 22.1	89.3 ± 24.8	89.6 ± 18.6	90.8 ± 25.6	89.5 ± 25.7	87.6 ± 24.6
MIP (cmH_2O)	60.7 ± 18.3	70.5 ± 17.8 ***	60.5 ± 20.6	71.1 ± 18.6 *	60.9 ± 16.3	69.8 ± 17.3
Nutrition						
Weight (kg)	82.0 ± 17.6	82.3 ± 17.6	79.8 ± 16.7	80.4 ± 16.8	84.2 ± 18.6	84.3 ± 18.7
Fat mass (%)	35.8 ± 8.6	36.1 ± 8.1	37.8 ± 8.6	38.0 ± 7.9	33.7 ± 8.4	34.1 ± 8.1
Total body water (%)	50.2 ± 6.6	49.8 ± 6.3	48.8 ± 6.0	48.6 ± 5.9	51.6 ± 7.0	51.1 ± 6.6
Lean body mass (%)	14.0 ± 4.0	14.1 ± 3.9	13.3 ± 4.6	13.4 ± 4.5	14.8 ± 3.2	14.8 ± 3.2
Quality of Life (EORTC-QLQ-C30 / LC13)						
Functional score	77.8 (64.4-88.9)	86.7 (77.8-93.3) ***	75.6 (55.0-91.1)	91.1 (71.7-93.3) **	78.9 (66.7-88.9)	84.4 (78.9-93.3) **
Symptom score	84.6 (75.0-91.7)	89.7 (54.6-89.7)	87.2 (73.1-94.9)	89.7 (71.2-95.5)	83.3 (76.3-87.3)	84.6 (74.4-92.3)
Global score	66.7 (50.0-83.3)	75.0 (58.3-83.3) **	66.7 (45.8-83.3)	83.3 (56.2-83.3)	66.7 (50.0-75.0)	75.0 (58.3-83.3) *
LC13 score	85.9 (79.5-92.3)	89.7 (79.5-94.9)	87.2 (76.9-92.3)	89.7 (76.3-94.9)	83.4 (78.9-92.8)	89.7 (79.5-94.9)
Quadriceps strength						
QMVIC right (Nm)	80.2 ± 34.3	87.8 ± 32.3 **	83.5 ± 43.0	89.2 ± 39.2	76.4 ± 21.7	86.1 ± 22.4 *
QMVIC right (% pred.)	59.0 ± 19.6	65.4 ± 18.9 **	61.1 ± 20.8	67.0 ± 20.7	56.6 ± 18.6	63.6 ± 17.0 *
QMVIC left (Nm)	84.8 ± 33.6	92.5 ± 32.3 **	86.7 ± 42.6	94.9 ± 39.5	82.7 ± 20.7	89.7 ± 21.6 *
QMVIC left (% pred.)	64.9 ± 19.4	71.9 ± 18.9 **	66.8 ± 21.3	74.4 ± 19.8 *	63.0 ± 17.5	68.9 ± 17.9 **

Data are presented as mean ± SD or median (25th–75th percentile); pre/post p-value :* p<0.05 ** p<0.01 *** p<0.001; NDTG: non-dense-training group (3 sessions/week during 5 weeks); DTG: dense-training group (5 sessions/week during 3 weeks); $\dot{V}O_2$peak: peak of oxygen uptake; $\dot{V}O_2$VT: oxygen uptake at ventilatory threshold; $\dot{V}E/\dot{V}CO_2$ slope: linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO2$); WRpeak: peak power on cyclo-ergometer; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; MIP: maximal inspiratory pressure; QoL: quality of life; QMVIC: quadriceps' maximal voluntary isometric contractions

Curriculum Vitae

CURRICULUM VITAE

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Etudes - Diplômes

- **2018 :** Master 2 STAPS : Activité Physique Adaptée et Santé, Université de Rouen
- **2016 :** Diplôme Universitaire Éducation des Patients, Université de Rouen
- **2012** : Diplôme Inter-Universitaire Kinésithérapie Respiratoire et Cardio-Vasculaire, Université Paris Descartes, Paris V
- **2010** : Diplôme d'état de Masseur Kinésithérapeute, IFMK de Rouen

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Langues et informatique

- Espagnol : capacité de présentation orale, lecture
- Anglais : capacité de présentation orale, lecture, publication
- Maitrise outils informatiques courants (MS Office), et internet
- Logiciels statistiques : R (Rcmdr ; EZR) ; Graphpad Prisme ; RevMan

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Expérience Professionnelle

- **Mai 2014 à Aujourd'hui :** Kinésithérapeute, ADIR Association, Bois-Guillaume. CHU Hôpitaux de Rouen.
- **Septembre 2011 à Janvier 2014 :** Kinésithérapeute en service de réanimation médicale et chirurgicale, Hôpital Charles Nicolle, CHU Hôpitaux de Rouen.
- **Juillet 2010 - Septembre 2011 :** Kinésithérapeute polyvalent, Hôpital Charles Nicolle
    - Alternance entre les services de : chirurgie thoracique, vasculaire et cardiaque, dermatologie et pneumologie.
    - Encadrement de Stagiaires Kinésithérapeutes au cours de l'exercice hospitalier.

Formation continue

- **Octobre 2010** : Actualisation de la pratique de kinésithérapie respiratoire du bilan diagnostic aux techniques, par M. GOUILLY Pascal, Bois-Guillaume.
- **Novembre 2010 :** Journées Lyonnaises Paramédicales Réanimation, Lyon.
- **Janvier 2011 :** 15ème Congrès de Pneumologie de Langue Française, SPLF, Lille.
- **Mars 2011 :** actualisation de la pratique de rééducation du sujet hémiplégique, par Mr PICARD, Bois-Guillaume.
- **Janvier 2012** : 16ème Congrès de Pneumologie de Langue Française, SPLF, Lyon.
- **Novembre 2011 à Juin 2012** : Diplôme Inter-Universitaire de spécialité en kinésithérapie, mention kinésithérapie respiratoire et cardio-vasculaire, Université Paris Descartes V, Paris.
- **Mars 2012 :**
    - Stage de pratique en service de réanimation aux Cliniques Universitaires St-Luc à Bruxelles, encadrement J. ROESELER.
    - 13èmes Journées Internationales de Ventilation à Domicile / 4ème Congrès de l'European Respiratory Care Association (ERCA), Barcelone.
- **Octobre 2012 :** "Actualités en ventilation mécanique", Cliniques Universitaires St-Luc à Bruxelles.

- **Novembre 2013 :** Actualités en ventilation 2013, Clinique Universitaire Saint Luc, Bruxelles.
- **Mai 2014** : Le muscle en réanimation, de la dysfonction à la réhabilitation, Société de Kinésithérapie de Réanimation, Paris.
- **Janvier 2015** :
    - 15e Congrès de la Société de Réanimation de Langue Française, SRLF, Paris.
    - 19e Congrès de la Société de Pneumologie de Langue Française, SPLF, Lille.
- **Octobre 2015 :** formation à la rééducation du syndrome d'hyperventilation, par Mr MORALES Adrian, organisme UKR, Bois-Guillaume.
- **Janvier 2016 :** 20e Congrès de la Société de Pneumologie de Langue Française, SPLF, Lille.
- **Janvier – février 2016 :** Introduction to Applied Biostatistics: Statistics for Medical Research. Formation en ligne, plateforme EDX, Osaka University.
- **Mars 2016 :** 11e congrès des Journées Francophones Alvéole, Groupe Alvéole de la SPLF, Lyon
- **Mai 2016 :** 1ère Journée Francophone en Kinésithérapie Respiratoire, Paris
- **Janvier 2017 :** 21e Congrès de la Société de Pneumologie de Langue Française, SPLF, Marseille.
- **Mars 2017 :** Congrès de la Société de Pneumologie de l'Ouest, SPO, Poumon et cœur à l'effort, 2017, La Baule.
- **Mars 2018 :** Journées Internationales de Ventilation à Domicile (JIVD) / European Respiratory Care Association (ERCA), Lyon.
- **Septembre 2018 :** European Respiratory Society Congress, Paris.
- **Octobre 2018 :** inscription doctorat en science médicale auprès de l'Ecole Doctorale Normande de Biologie Intégrative Santé Environnement (EDnBISE 497), Normandie Université.
- **Septembre 2019 :** European Respiratory Society Congress, Madrid.
- **Janvier 2019 :** 24e Congrès de la Société de Pneumologie de Langue Française, SPLF, Paris.

- **Septembre 2020 :** Congrès Virtuel de l'European Respiratory Society.
- **Octobre 2020 :** Congrès virtuel, Journées Francophones Alvéole, congrès de réhabilitation respiratoire, Groupe Alvéole de la SPLF.
- **Septembre 2021 :** Congrès Virtuel de l'European Respiratory Society.

Enseignement

- **Depuis 2012 :** Encadrement stagiaires d'étudiantes en kinésithérapie(2 à 3 stagiaires / an)
- **Depuis 2013 :** Intervenant dans l'équipe pédagogique du module de pneumologie de l'IFMK de Rouen,
    - Cours magistraux
    - Encadrement de travaux dirigés, travaux pratiques
    - Direction de mémoire
    - Jury Diplôme d'Etat de Masso-Kinésithérapie
- **Depuis Novembre 2018** : enseignant vacataire auprès de la faculté de STPAS de l'Université de Rouen Normandie. Thème réhabilitation respiratoire, Master 2 Activité Physique Adaptée à la Santé (APAS).
    - Cours magistral et travaux dirigés

Présentations en congrès scientifiques

- **Mai 2014** : Communication orale lors de la formation « Le muscle en réanimation, du dysfonctionnement à la réhabilitation », sur le thème « L'IMT en pratique : évaluation du diaphragme et moyens techniques de préventions et de rééducation », Société de Kinésithérapie de Réanimation, Paris.
- **Janvier 2015 :** Communication orale lors du 15^{e} Congrès de la Société de Réanimation de langue Française, dans la session thématique "Autour du diaphragme" sur la « réhabilitation précoce », Paris

- **Avril 2015** : Communication orale lors de la « journée de sensibilisation à l'obésité destinée aux clubs sportifs de Haute-Normandie », sur le thème de la Réhabilitation, CHU Hôpitaux de Rouen, Rouen.

- **Mars 2016** : Communication orale lors du 11e congrès des Journées Francophones Alvéole, sur le thème « Améliorer la tolérance à l'exercice des insuffisants respiratoires par des moyens mécaniques », Groupe Alvéole de la SPLF, Lyon.

- **Mai 2016** : Communication orale lors de la 1ère Journée Francophone en Kinésithérapie Respiratoire, Controverse : « Les adjuvants au réentrainement à l'effort : Pour », Société de Kinésithérapie en Réanimation (SKR), Paris

- **Mars 2018** : Communication orale « Workshop : Exercise retraining under NIV: from theory to practice », lors des Journées Internationales de Ventilation à Domicile (JIVD) / European Respiratory Care Association (ERCA), Lyon.

- **Janvier 2019** : Communication orale « Activité Physique et Asthme », Congrès de Pneumologie de Langue Française, SPLF, Paris.

- **Septembre 2021** : Poster présenté sous forme de communication orale « Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis. », congrès international de l'European Respiratory Society (ERS) 2021, online.

Actions associatives

- **Septembre 2013 – septembre 2017 :** membre de l'Union des Kinésithérapeutes Respiratoires (UKR), membre du bureau de l'UKR septembre 2014 à 2017.

- **Avril 2015 :** adhésion à la Société Française de Physiothérapie (SFP).

Participation à des projets scientifiques et publications

- Bonnevie T ; Villiot-Danger JC ; **Gravier FE** ; Dupuis J ; Prieur G ; Médrinal, C. Inspiratory muscle training is used in some intensive care units, but many training methods have uncertain efficacy: a survey of French physiotherapists. Journal Of Physiotherapy. J Physiother. 2015 Oct;61(4):204-9. DOI: 10.1016/j.jphys.2015.08.003.

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- **Gravier FE** *(présentation anglais)*, Bonnevie T, Boujibar F, Médrinal C, Prieur G, Combret Y, Muir JF, Baste JM, Debeaumont D, Cuvelier A. Cardiopulmonary exercise testing in patients with non-small cell lung cancer: maximality criteria analysis. September 2020 ERS International Congress 2020 abstracts

Résumé

La résection pulmonaire oncologique est le geste chirurgical le plus pratiqué en chirurgie thoracique pulmonaire, et constitue le traitement curatif de référence des stades précoces de cancer bronchique non à petites cellules (CBNPC). Au-delà de la faisabilité technique du geste chirurgical, la fonctions cardiaque, respiratoire, ainsi que la capacité à l'exercice conditionnent l'opérabilité. Ce manuscrit de thèse aborde successivement les thématiques de l'évaluation préopératoire, des effets du réentrainement à l'effort préopératoire, et l'optimisation de ces programmes dits de préhabilitation.

Tout d'abord, concernant l'évaluation de la capacité à l'exercice préopératoire, nous avons identifié qu'environ 30% des patients adressés en épreuve fonctionnelle à l'exercice avant chirurgie pulmonaire oncologique fournissaient des niveaux d'effort objectivement sous-maximaux. L'adaptation du mode d'évaluation, ou l'identification de marqueurs sous-maximaux fiables est donc potentiellement nécessaire. De plus, nous nous sommes intéressés à l'identification de nouveaux tests de terrain, aisément réalisables en pratique clinique, comme le test de levers de chaise de 3 minutes, pour identifier les patients les plus fragiles.

Deuxièmement, nous avons évalué les effets physiologiques d'un programme de préhabilitation ambulatoire local. Les effets positifs mesurés ont été confortés par la suite, via une revue systématique et méta-analyse incitant à intégrer ces programmes de manière systématique dans les parcours thérapeutiques.

Enfin, malgré un niveau de preuve grandissant, l'hétérogénéité des programmes de préhabilitation reste importante. Nous nous sommes donc intéressés à la structuration du réentrainement préopératoire, et notamment le paramètre de la densité (rapport fréquence séance / durée entrainement). Bien que les résultats obtenus ne soient pas équivalents (en faveur de l'entrainement le plus dense), la supériorité d'une modalité sur l'autre n'a pas été démontrée.

Au total, les cinq articles originaux inclus dans ce manuscrit de thèse nous ont permis de valider ou invalider scientifiquement nos hypothèses autour de l'évaluation et de l'entrainement préopératoire des patients atteints de CBNPC. Ces résultats nous aident à optimiser notre pratique clinique et à préparer de futurs projets autour de l'entrainement préopératoire avant résection pulmonaire oncologique.

Mots clés : Chirurgie Pulmonaire ; Préhabilitation ; Evaluation fonctionnelle à l'exercice ; Réentrainement à l'effort ; Soins préopératoires ; Cancer bronchique non à petites cellules.

Summary

Oncological pulmonary resection is the most common surgical procedure in thoracic pulmonary surgery, and is the gold standard treatment for early stages of non-small cell lung cancer (NSCLC). Beyond the technical feasibility of the surgical procedure, the general condition of the patient determines his operability and his recovery. This thesis manuscript successively addresses the themes of preoperative assessment, the effects of preoperative exercise training, and the optimisation of these prehabilitation programs.

First, regarding the assessment of preoperative exercise capacity, we identified that approximately 30% of patients referred for cardiopulmonary exercise testing before oncologic lung surgery provided submaximal effort. Adaptation of the assessment method, or validation of reliable submaximal markers is therefore potentially necessary. In addition, we were interested in identifying new field tests, easily performed in clinical practice in patients with scheduled NSCLC resection, such as the 3-minute chair rise test, to identify the frailer patients.

Second, we evaluated the physiological effects of a local outpatient prehabilitation program. The positive effects locally observed were subsequently confirmed with a systematic review and meta-analysis, prompting the inclusion of these programs in preoperative care pathway of patients with scheduled lung resection for NSCLC.

Finally, despite a growing level of evidence, the heterogeneity of prehabilitation programs remains a difficulty for its development in clinical practice. We therefore focused on structuring preoperative exercise training, and in particular the density parameter (session frequency / training duration ratio). Although the results were not equivalent (in favour of the denser training), the superiority of one modality over the other has not been demonstrated.

In total, the five original articles included in this thesis manuscript have enabled us to scientifically validate or invalidate our hypotheses around the preoperative assessment and training of patients with NSCLC. These results help us to optimize our clinical practice and to prepare future projects around preoperative oncological lung resection training.

Keywords: Lung surgery; Prehabilitation; Cardiopulmonary exercise testing; Exercise training; Preoperative care; Non-small cell lung cancer.