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[Prognosis Protocol]

Prognosis of surgically resected clinical stage 1A non-small cell lung cancers manifesting as a subsolid nodule on computed tomography including pure ground glass nodules

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ABSTRACT

Objectives

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

To quantify the risk of tumour relapse/recurrence after a surgical resection of stage 1A non-small cell lung cancer (NSCLC) as manifested on computed tomography (CT) imaging as a subsolid nodule.

BACKGROUND

Description of health condition and context

Lung cancer remains the most common cause of cancer death in both sexes across the globe [1]. It is a relatively lethal cancer with a global mortality to incidence ratio of 0.82 (males 0.83; females: 0.79) in 2020, ranging between 0.59 in Japan to 1 in Belize [2]. The incidence of lung cancer is closely related to the prevalence of tobacco smoking, with outdoor air pollution being the second most significant risk factor [1, 3]. With the introduction of immunohistochemistry and molecular testing, the classification of lung tumours has become increasingly sophisticated in recent years; however, the historic dichotomous classification of carcinomas of the lung into either a small cell type or non-small cell type remains clinically relevant. Small cell lung cancer, which makes up about 14% of lung cancers, is an aggressive cancer that tends to grow and metastasise rapidly and surgical resection is generally ineffective [4, 5]. Non-small cell carcinomas consist mainly of adenocarcinomas, squamous cell carcinomas, non-small cell lung cancers not otherwise specified, or large cell carcinomas [6, 7]. Adenocarcinoma is the most common histological subtype of all lung cancers in both sexes representing an increasing proportion of lung cancers in many countries [5, 7].

The prognosis of non-small cell lung cancer (NSCLC) is related to stage at diagnosis with five-year survival ranging from 68% for stage I disease to 6% for stage IV disease in the USA [6]. Treatment recommendations are based on stage at diagnosis, histology, biomarkers, comorbidities, and performance status [6, 8]. In people who are medically operable, surgical resection is recommended for stage I and II disease either as stand-alone therapy or as part of multimodality therapy [8]. While lobar resection has been considered the gold standard treatment for medically operable people with stage I NSCLC [9], two recent randomised controlled trials suggest that there is a role for sublobar resection in some people with small stage IA peripheral NSCLCs [10, 11].

A prognostic factor is a measurable or defined characteristic of a person or disease that is associated with a particular clinical outcome among people with a given health condition [12]. Anatomical stage is a strong predictor of survival. The TNM staging system is regularly updated based on large international data sets to reflect the average prognosis of NSCLC defined by tumour size, nodal status, and the presence of metastasis [13]. In this system, T generally refers to tumour size and any spread to surrounding tissues; N refers to spread to local lymph nodes; and M to metastasis (spread to other parts of the body). The current system can be applied using clinical data alone (such as imaging) or pathological data, which is generally considered the gold standard. Amongst surgically resected NSCLC, age, sex, region, and histology are independent predictors of prognosis in addition to T descriptors [14]. In recent years there has been work undertaken to refine T descriptors in order to incorporate, where relevant, computed tomography (CT) features of subsolid nodules, as evidence has emerged of their prognostic significance [15].

Lung cancers are often detected on CT as a nodule, which is a rounded opacity (well or poorly defined) measuring up to 3 cm, where opacity describes an area of increased attenuation which appears more opaque than the surrounding areas [16]. The term 'ground-glass opacity' is used to describe an area of less marked increased attenuation in which the margins of vessels and airway walls are preserved, whereas consolidation describes a denser opacity in which the margins or vessels and airway walls are obscured [16]. A nodule which contains a ground-glass component is broadly referred to as subsolid as opposed to a solid nodule which has no ground-glass component. Subsolid nodules are further categorised into pure ground-glass nodules (where there is no component of consolidation), or part solid (or mixed), where the nodule contains both areas of consolidation and ground-glass opacity [16]. Although there may be infective, inflammatory, or other benign causes of subsolid nodules, persisting nodules have a high probability of being an adenocarcinoma spectrum lesion [17, 18]. Part-solid nodules usually arise from pure ground-glass nodules [19, 20], which pathologically generally reflects progression of pre-invasive adenocarcinoma in-situ to minimally invasive adenocarcinoma or invasive adenocarcinoma [15, 21]. The ground-glass component on CT will often correlate with lepidic-predominant adenocarcinoma and the solid component with invasive adenocarcinoma; however, this correlation is imperfect [15, 22]. Furthermore, some studies show that up to 40% of nodules which are purely ground glass on CT are invasive adenocarcinomas [23, 24, 25].

In one large systematic review and meta-analysis on recurrence-free survival in people with surgically resected NSCLC, Rajaram and colleagues reported a five-year recurrence-free survival of 86% for stage IA NSCLC [26]. Seventy percent of the studies included in the review were conducted primarily in Asia, and five-year recurrence-free survival was notably better in studies conducted in Asia (87%) compared with those from North America and Europe (60%). The better prognosis observed in Asian studies may have been due to a younger age at diagnosis, a higher proportion of never-smokers, and more frequent ground-glass opacity-related cancers; however, smoking status and the incidence of ground-glass opacity-related cancer could not be controlled for in their meta-regressions [26].

Health outcomes

The purpose of our review is to better understand the natural history of NSCLC presenting as a subsolid nodule postresection. For indolent cancers, the challenge is to document prognosis as best as possible without the potential distortions of competing causes of death. In addition to overall survival, the literature often reports recurrence (or relapse)-free survival. This is defined as the number of days from date of surgery to cancer relapse or death from any cause. In studies with prolonged follow-up, or where competing causes of death are high relative to cancer relapse, recurrence-free survival may not fully reflect the rate of recurrence. However, measures of disease-specific survival, where deaths due to other causes are censored, may be biased in Kaplan-Meier analysis with a tendency to overestimate the cumulative incidence of an event in the presence of competing risks [27]. Therefore, it is important to also understand the locoregional, distant, and overall recurrence rates. It is likely that studies will report recurrences during the period of follow-up, without details on the time of recurrence and with probable variations in duration of follow-up, making it difficult to perform meta-analysis [26]. However, where possible, we will synthesise data on recurrence rates and, if there are sufficient data, the cumulative incidence of recurrence in addition to recurrence-free survival. We will also synthesise data on overall survival, disease-free survival, postoperative mortality, and the proportion of people with clinical stage 1A disease who

had metastases detected in hilar or mediastinal lymph nodes on pathological analysis of surgical resection specimens.

Why is it important to do this review?

Lung cancer screening is currently being implemented in multiple countries throughout the world based on evidence from CT screening studies performed on people with a history of tobacco use [28, 29]. In addition, pulmonary nodules are increasingly being detected incidentally [30]. The highest rates of subsolid nodule detection have been reported in non-smokers in East Asia, particularly women [18, 31]. Recent epidemiological studies from East Asia have identified evidence of substantial overdiagnosis of lung cancer in the setting of screening non-smokers, which is likely due to overtreatment of indolent adenocarcinoma spectrum lesions in this population [32, 33]. Observational studies of ground-glass nodules show that only about 26% of pure ground-glass nodules show growth on follow-up imaging, mostly in the first two years [34]. To our knowledge, there have not been any controlled trials that have compared active surveillance of subsolid nodules with early resection. In the absence of these data, we believe it is pertinent to synthesise the evidence regarding the prognosis of resected stage 1A NSCLC which appear subsolid on CT imaging. Multiple studies have been published with relevant data including some clinical trials and observational studies [35, 36, 37, 38]. The results of this review will be of value to consumers, health professionals, and policymakers, particularly in the setting of lung cancer screening programmes. In addition, our review will likely identify knowledge gaps, which will help inform the ongoing research agenda.

OBJECTIVES

To quantify the risk of tumour relapse/recurrence after a surgical resection of stage 1A non-small cell lung cancer (NSCLC) as manifested on computed tomography (CT) imaging as a subsolid nodule.

METHODS

Criteria for considering studies for review

Population: adults (aged greater than 16 years) with primary clinical stage 1A NSCLC manifesting as a subsolid nodule on CT who have undergone surgical resection including wedge resection, segmentectomy, lobectomy, or pneumonectomy.

Intervention: this will be a review of prognosis following surgical resection and not a review of comparative studies

Comparator: none

Outcome: the primary outcomes will be recurrence-free survival, proportion of participants who develop disease recurrence, and the proportion of participants who die from disease recurrence.

Timing: any disease recurrence during the follow-up period (at five years or more) with no upper limit for follow-up period.

Setting: all settings, including hospital outpatients and community.

Types of studies

We will include published, peer-reviewed, prospective, or retrospective longitudinal studies (such as observational cohorts, registry studies, electronic health records studies, or relevant comparative epidemiology studies). We will include case series with at least 50 included participants. We will also include single arm clinical trials or randomised controlled trials, including feasibility or pilot studies.

We will exclude case reports, cross-sectional studies, and case control studies as these studies will not provide relevant data regarding prognosis. We will exclude research papers not based on original data such as expert opinions, narrative reviews, or letters to the editor.

Targeted population

Adults (aged greater than 16 years) with primary clinical stage 1A NSCLC (including carcinoma in-situ) manifesting as a subsolid nodule (including pure ground-glass nodules) on CT who have undergone surgical resection including wedge resection, segmentectomy, lobectomy, or pneumonectomy (with or without hilar or mediastinal lymph node sampling or dissection). We will include all surgical approaches such as thoracotomy, video-assisted thoracoscopic surgery, robotic-assisted thoracoscopic surgery, or any combination of these. We will include studies in which some or all participants have had neoadjuvant or adjuvant therapy. We will exclude studies including participants undergoing surgery for recurrent tumours or purely for diagnostic purposes. We will exclude studies including participants with small cell lung cancer if results for participants with small cell lung cancer and NSCLC are not presented separately. We will define clinical stage 1A as a tumour size less than 3 cm on CT in maximum dimension with a TNM stage of T1N0M0. We will include studies using any staging system from the 5th edition Union for International Cancer Control (UICC) or 5th edition American Joint Committee on Cancer (AJCC) TNM onwards [39].

We will not exclude studies that have included participants with incomplete resections, but will extract and describe these data in the description of included studies.

Where studies include prognostic details for both solid and subsolid nodules, we will only extract data relevant for the subsolid group.

We anticipate that there will be variations in the terminology used to describe NSCLC manifesting as a subsolid nodule on CT, including but not limited to: pure ground-glass opacity; pure ground-glass nodule/lung cancer; localised or focal ground-glass opacity; ground-glass opacity-dominant nodule/lung cancer; subsolid nodules/lung cancers; part-solid nodule/lung cancers; semi-solid nodules; or nodules or cancers with a consolidation to tumour ratio of any value less than 1.

We will describe in the characteristics of included studies table the type of radiological evaluation studies used to assess nodules and the criteria used to define the nodule characteristics. This will also be evaluated in our risk of bias assessment.

Types of outcomes to be predicted

Primary outcomes

- **Relapse (recurrence)-free survival** at five or more years of follow-up. Defined as the number of days from enrolment/registration or from date of surgery to cancer relapse or death from any cause.
- **Proportion of participants who develop disease recurrence (including lung cancer-related death)** at five or more years of follow-up.
- **Proportion of participants who die from disease recurrence** at five or more years of follow-up.

Secondary outcomes

- **Overall survival** at five years or more.
- **Disease-free survival** at five years or more. This is the same as relapse- or recurrence-free survival but will include second primary lung cancers.
- **Proportion of resections with hilar or mediastinal node involvement detected at time of surgery**.
- **Distant (excluding locoregional) recurrence rate** at any follow-up time from one year onwards.
- **90-day postoperative mortality**.

We will also record in the description of studies where possible whether studies detected disease recurrence by symptoms or surveillance.

We will exclude studies that do not report on at least one survival or recurrence rate outcome measure and with less than two years of follow-up.

Search methods for identification of studies

Electronic searches

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

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library)
- MEDLINE (via PubMed)
- Embase (via Elsevier)

Our search will be conducted from 1971 (when CT imaging became available).

We will perform the electronic searches according to the recommendations of the Cochrane Methods Prognosis Group. The search strategies for CENTRAL, MEDLINE, and Embase are presented in Supplementary material 1. Considering the low number of references retrieved when testing the search strategies, we will use no filters.

We will use functionality available in Endnote to reassess included studies just prior to publication of the systematic review for any retractions that may have been published while the review work was being undertaken.

Searching other resources

We will handsearch the references of eligible studies to identify additional studies for inclusion.

We will search for abstracts/proceedings of conferences from the following sources (from 2022 to date of search).

- World Conference on Lung Cancer (WCLC)
- International Lung Cancer Research Association (IASLC)
- European Society for Medical Oncology (ESMO)
- European Lung Cancer Conference (ELCC)
- American Association of Cancer Research (AACR)
- European Society of Thoracic Surgery (ESTS)
- American Association of Thoracic Surgery (AATS)

Data collection

Selection of studies

We will enter the search results into Covidence [40]. After removal of duplicates, two review authors will independently screen titles and abstracts to exclude studies that are irrelevant or do not fit inclusion criteria. Two review authors will then obtain the full texts of the remaining studies and independently check the eligibility of each against our inclusion and exclusion criteria. We will discuss any discordant evaluations to reach consensus, and consult a third review author if this is not possible.

Data extraction and management

We will extract data from included studies into a modified CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) [41].

We will pilot test the data extraction form and modify it where necessary before completing data extraction in all included studies. Where there are multiple reports that relate to a single study, we will collate them to represent a single study in the review.

We will conduct data management and analysis according to the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* [42].

Two review authors (RM and AB) will extract data onto an Excel spreadsheet [43]. We will resolve any disagreements through discussion or by involving a third review author (RSM), if necessary.

All the information we will be extracting from each included study is listed in Supplementary material 2. We will contact trial authors for any missing information.

Assessment of risk of bias in included studies

Two review authors (RM and AB) will independently assess risk of bias in included studies. When there is discordance between risk of bias judgements, the review authors will reach consensus by discussion. If necessary, a third author will resolve disagreements where a consensus cannot be reached.

There is currently no tool to assess the biases of overall prognosis reviews. Therefore, we designed a tool by including items from the Quality in Prognostic Studies (QUIPS) tool [44, 45] and the Prediction model Risk Of Bias ASsessment Tool (PROBAST) (see Supplementary material 3). We have decided to assess the bias across four domains that are relevant to reviews of overall prognosis: study participation; study attrition; outcome measurement; and statistical analysis and reporting.

For the statistical analysis and reporting domain, we have excluded the questions around model development that do not relate to this review. For each domain, we will extract relevant methodological data and rate the adequacy of reporting for prespecified items for each domain as yes, partly yes, no, and unclear. Based on these items, we will then rate the potential risk of bias for each of the four domains as high risk of bias, moderate risk of bias, or low risk of bias.

We will rate studies with a low risk of bias in all four domains as having an overall low risk bias. We will assess studies with a high risk of bias in any of the four domains as having an overall high risk of bias. We will conduct a sensitivity analysis that will limit the pooled analysis for primary outcomes to studies with an overall low risk of bias [45].

Measures of association or predictive performance measures to be extracted

We will extract survival statistics from a single-arm study at five years or more using a non-parametric approach for survival probability — Kaplan–Meier estimate with their corresponding 95% confidence intervals (CI), calculated using Stata's mvmeta command [46]. We will assess the proportion of people who develop recurrence at two years or more by extracting the number of those with events or risk ratios or odds ratios and their 95% CIs. We will extract the unadjusted and adjusted measure of association for each study, when they are available.

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

Dealing with missing data

We will include studies with data on our primary outcomes and overall survival even if data are not complete for all individuals in the study. We will attempt to contact study authors to clarify details regarding missing data. Where required, we will estimate or calculate outcome measures from any data reported, such as Kaplan-Meier curves using indirect measures [47, 48].

Assessment of heterogeneity

We will assess statistical heterogeneity between included studies in each meta-analysis by inspecting forest plots and quantifying heterogeneity statistically using the I^2 statistic, Tau^2 statistic, and the prediction intervals [49].

We will assess clinical heterogeneity of included studies based on study design, duration of follow-up, participant population, types of subsolid nodules included in study, and variations in extent of surgery. We will assess methodological heterogeneity by comparing the risk of bias in studies based on study participation, participant attrition, outcome measurement, and statistical analysis and reporting.

Assessment of reporting deficiencies

For each meta-analysis, we will examine publication bias (where there are at least 10 studies) by visually inspecting the asymmetry of funnel plots [50].

Data synthesis

Where there are three or more sufficiently clinically homogeneous studies, we will conduct a single-arm meta-analysis. As there is often between-study heterogeneity in prognostic studies, we will conduct a meta-analysis using a random-effects generic inverse variance model to account for this [51]. We will summarise meta-analyses with a pooled estimate (average prognostic effect), with 95% CIs, the estimates of the I^2 and Tau^2 statistics, and a 95% prediction interval for the prognostic effect in a single study [52].

Where it is inappropriate to pool results (e.g. presence of clinical heterogeneity or insufficient data), we will summarise the results narratively and in tables.

For disease recurrence rate, death from disease recurrence, proportion of resections with hilar or mediastinal node involvement, distant recurrent rate, and 90-day mortality rate, if studies are sufficiently homogeneous, we will pool the proportion of participants with an event (disease recurrence, death) across studies at similar time points. We will pool the proportion rates per time point using the generic inverse-variance random-effects model. We will present the overall proportion rate and the 95% CIs for each outcome.

For the other review time-to-event outcomes, such as overall survival, we will pool data using a random-effects approach at various time points and present the pooled overall estimate as hazard ratios and 95% CIs.

We will conduct all analyses in Stata 18 [53].

When meta-analysis is inappropriate, we will synthesise results narratively. Where data are sufficiently similar to permit pooling, we will use a random-effects approach, given our expectation of high heterogeneity between studies.

We will synthesise data for pure ground-glass lesions and part-solid lesions separately where possible. If this is not feasible, because studies have only reported data combined as a single group, we will report them as a single group.

Subgroup analysis and investigation of heterogeneity

We will consider factors such as sex, age, extent of surgery, region in which study was conducted, histological subtypes included, and duration of follow-up in the interpretation of heterogeneity.

We will synthesise data for pure ground-glass lesions and part-solid lesions separately where possible.

When there is evidence of heterogeneity and we have 10 or more included studies in the meta-analysis, we will investigate heterogeneity by conducting a meta-regression analysis [54].

Sensitivity analyses

We will perform a sensitivity analysis that restricts the analysis to studies judged without any high risk of bias in any of the four domains.

Conclusions and summary of findings

We will present summary of findings tables including the following outcomes.

- Relapse (recurrence)-free survival at five or more years of follow-up
- Proportion of participants who develop disease recurrence (including lung cancer-related death) at five or more years of follow-up
- Proportion of participants who die from disease recurrence at five or more years of follow-up
- Overall survival at five years or more
- Distant (excluding locoregional) recurrence rate at any follow-up time from one year onwards
- 90-day postoperative mortality

Two review authors will independently use a modified GRADE framework to assess the overall certainty of the evidence. We will present these results for pure ground-glass nodules and part-solid nodules in two separate summary of findings tables [44, 55].

We will rate the overall certainty of evidence as high, moderate, low, or very low, based on the phase of prognostic study, internal validity, size and precision of effect, heterogeneity, generalisability, and potential reporting bias.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016091.

Supplementary material 1 Search strategies

Supplementary material 2 Data extraction

Supplementary material 3 Risk of bias assessment from QUIPS and PROBAST tools

ADDITIONAL INFORMATION

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The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Toby Lasserson, Deputy Editor-in-Chief
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sara Hales-Brittain, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Jennifer Hilgart, Cochrane (methods); George Eapen, MD Anderson Cancer Center (clinical); Zosia Beckles, University of Bristol (search)

Contributions of authors

Conceptualisation: RM, DP, GW, AB

Methodology: RM, RSM, CM, AB

Writing of the protocol: RM, RSM, CM, DP, GW, AB

Declarations of interest

RM: none. Renee has a Cochrane Lung Cancer Group editorial role and was not involved in the editorial process for this protocol. Her institution received a National Health and Medical Research Council (NHMRC) grant for an observational study of low-dose screening for lung cancer in 2016. She is a member of the Thoracic Society of Australia and New Zealand (TSANZ), an organisation advocating for lung cancer screening.

RSM: none.

CM: none. She is Managing Editor for the Cochrane Lung Cancer Group and was not involved in the editorial process.

DP received personal payment from Cancer Australia. She was a Royal Australian and New Zealand College of Radiologists representative on the Expert Advisory Committee for the National Lung Cancer Screening Program.

GW: none.

AB: none.

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Registration and protocol

Cochrane approved the proposal for this review in December 2023.

Data, code and other materials

Data sharing not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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