Peer Review File

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Reviewer A

The authors are to be commended on a very comprehensive review of a very large topic. I have a few general and specific comments as detailed below.

General comments

- a number of consensus statements are made based on single studies, or very low quality of evidence. The authors may need to temper the statements slightly, given there may not be sufficient evidence to support management one way or another. Examples include the use of theophyllines, or endobronchial valves in LC-COPD and several others. Each consensus statement should include the quality of evidence that it is based upon, and where evidence is lacking, attributed to 'expert opinion'. If there is not sufficient quality evidence, there should not be a strong recommendation made.
- Reply: We have modified the statement for the content without sufficient evidence.
- Changes in the text: We have modified our text as advised (see Page 22, line 703-704; Page 43, line 1438).

- the authors could consider adding a summary of consensus statements at the beginning of the document, with subject headings
- Reply: We have added “Abstract”.
- Changes in the text: We have added some data (see Page 6, line 183-198).

- the methodology should include the use of evidence that led to the consensus statements, i.e., grading of evidence in terms of quality of trials etc and how these informed the statements.
- consider also including in the methods the target audience, the groups covered etc
- this link may be helpful:
https://bestpractice.bmj.com/info/toolkit/ebm-toolbox/critical-appraisal-checklists/
- Reply: The levels of evidence and grades of recommendation in this consensus document set based upon the Oxford Centre of Evidence Based Medicine’s Levels of Evidence (see Page 9, line 278-280). We have added the target population and target audience in the methods.
-Changes in the text: We have added some data “The target population is adults (≥18 years of age) with LC-COPD. The target audience of this consensus are clinicians who diagnose and treat patients with LC-COPD in primary, secondary, and tertiary medical

institutions, such as oncologists, respiratory specialists, radiation therapists, thoracic surgeons, interventional radiologists, etc" (see Page 9, line 265-269).

Specific comments

1. top of p5, an additional important point could be made: that COPD often limits eligibility for radical treatments e.g., surgical resection in patients with lung cancer

-Reply: We have briefly supplemented the relevant content.

-Changes in the text: We have added some data (see Page 8, line 234-237).

2. p8: "EMT" kindly spell out this abbreviation if being mentioned in a heading.

-Changes in the text: We have added some data "Epithelial mesenchymal transition" (see Page 12, line 392).

3. Bottom of p9. Lung cancer screening in COPD is actually not so straightforward. There is data from NLST demonstrating a lack of efficacy of lung cancer screening in patients with advanced COPD (GOLD 3&4), while those with undiagnosed COPD or early COPD may have greater efficacy than those without COPD. This has been the subject of discussion- see refs:

- Young RP, et al. Airflow limitation and mortality during cancer screening in the National Lung Screening Trial: why quantifying airflow limitation matters. Thorax 2023;
- Rivera MP, et al. American Thoracic Society Assembly on Thoracic Oncology. Incorporating Coexisting Chronic Illness into Decisions about Patient Selection for Lung Cancer Screening. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med. 2018;
- Gould MK. Lung Cancer Screening in Individuals with Chronic Obstructive Pulmonary Disease. Finding the Sweet Spot. Am J Respir Crit Care Med. 2015;
- Ruparel M. Lung cancer screening in advanced chronic obstructive pulmonary disease: helpful or harmful? Thorax. 2023

-Reply: Thanks for your insightful comment. There is still controversy over whether severe COPD patients should undergo lung cancer screening. The heterogeneity of the COPD population is significant, and the results from the secondary analysis of "National Lung Screening Trial" may not be applicable to the entire population. Our recommendation for lung cancer screening is not for all severe COPD, but for those with high-risk factors.

-Changes in the text: We have added some data "However, a secondary analysis of 18463 NLST participants reported that that GOLD 3–4 individuals do not benefit from lung cancer screening" (see Page 14, line 451-453).

4. p15 - when discussing antibiotics, the role of macrolides for patients with COPD with >3 exacerbations per year has been found to have benefit, and is recommended by GOLD 2023. This could be added here.

-Reply: We appreciate your perceptive commentary regarding the role of macrolides in patients with COPD (stable) with more than three exacerbations per year. In this part, we only focused on patients currently undergoing AECOPD, rather than those prone to exacerbations.

In addition, the selection of specific antibacterial drugs can be informed by the guidelines and consensus related to COPD, and thus, a detailed explanation is not provided here.

5. The role of mucolytics may also be beneficial.

-Reply: Thanks for your insightful comment. We have revised the manuscript following your recommendations.

-Changes in the text: We have added some data (see Page 21, line 670, 687).

6. Inhaled steroids may protect against lung cancer in COPD- this may also be of relevance. see Adam et al. Inhaled corticosteroids and the risk of lung cancer in COPD: a population-based cohort study. European Respiratory Journal Jun 2019.

-Reply: Thanks for your comment. However, the relationship between inhaled corticosteroids (ICS) and the risk of lung cancer is still inconclusive based on current available data.

Some studies suggested a reduction in lung cancer risk with the use of ICS. (Adam et al. Eur Respir J 2019; 53(6). Seijo LM, et al. Eur Respir J 2019; 53(6). Ge F, et al. Transl Lung Cancer Res 2021; 10(3): 1266-76.)

A systematic review, which examined two observational studies and four RCTs, reported a protective effect of ICS on lung cancer risk in the observational studies that used a higher dose of ICS, but found no benefit in the RCTs. (Raymakers AJ, et al. Respirology 2017; 22(1): 61-70.)

In contrast, one database study reported an increased risk of lung cancer in patients prescribed ICS compared to those not prescribed ICS. (Wu MF, et al. BMC Cancer 2016; 16(1): 778.)

Therefore, based on the available data, ICS do not appear to increase or decrease the risk of lung cancer.

7. bottom p15. Target SpO2 should not be 88-92 unless there is documented hypercapnia. If there is not, target SpO2 should be >92% in patients with COPD.

-Reply: Thanks for your comment. We have revised the manuscript following your

suggestion.
-Changes in the text: We have modified our text as advised (see Page 23, line 739).

8. typo p20 line 894 "should" instead of "shouled"
-Changes in the text: We have modified our text as advised (see Page 29, line 957).

9. Given the extent of discussions around ILD, and toxicities of LC treatments with risk of ILD, perhaps the title/ remit of the paper should be revised to include ILD or chronic lung disease, not just COPD. The introduction would need to be revised accordingly.
-Reply: This section primarily emphasizes that COPD is a risk factor for TKI-ILD, and therefore, LC-COPD patients using TKIs need to be more attentive to the possibility of ILD occurrence. We have made some modifications to these subheadings.
-Changes in the text: We have modified our text as advised (see Page 29-30, line 955, 986).

10. Bottom p22: the use of invasive ventilation in patients with lung disease and lung cancer (be it COPD or ILD) should be carefully considered and weighed up, taking into account prognosis from lung cancer as well as lung disease. And in some cases, palliative care will be more appropriate.
-Changes in the text: We have modified our text as advised (see Page 32-33, line 1071-1073).

11. p27 line 1202- what is the evidence to support the recommendation that ABGs and 6MWT should be regularly performed in these patients? surely clinical and radiological surveillance is enough?
-Reply: We have removed “ABGs” and “6MWT ” .
-Changes in the text: We have modified our text as advised (see Page 36, line 1180-1181, 1194-1195).

12. p30 line 1341- consider changing "multidisciplinary" to "multi-modality"
-Reply: We have changed "multidisciplinary" to "multi-modality".
-Changes in the text: We have modified our text as advised (see Page 43, line 1413).

13. Consensus 15, as mentioned above- These techniques are new and with limited evidence, and likely only to be effective in a narrow select sub-population. The evidence for application of these methods in a LC population is minimal
-Reply: We have modified the level of evidence and strength of recommendation.
-Changes in the text: We have modified our text as advised (see Page 43, line 1426-1427).

14. The use of SBRT is one of the single most exciting developments in lung cancer care that is most relevant to those with COPD. It offers a curative treatment option which has good outcomes irrespective of baseline lung function and doesn't worsen lung function/ toxicity. This is a huge development in lung cancer and can benefit those with COPD more than other groups as they may not have been fit for other treatment options including conventional RT and surgery. Perhaps this point should be given more prominence in the paper- consider moving forward to an earlier consensus.
-Reply: Thank you for your feedback on our paper. While we appreciate your perspective on the significance of SBRT as a treatment option for lung cancer patients with COPD, we have decided to maintain the current structure of the paper.
We believe that the current placement of information regarding SBRT is appropriate and sufficiently highlights its value as a treatment option for patients with COPD. We have carefully considered your suggestion, but we feel that moving it to an earlier consensus is not necessary, as we have already addressed this topic in detail in the relevant sections.

15. p35- use of theophylline has very limited evidence of benefit in COPD. This statement should be reworded to reflect the low quality of available evidence. Furthermore, these drugs carry significant risk of toxicity and cardiac arrhythmias. The authors have quoted a single study here - poor evidence quality. This should be reworded to not given a recommendation for or against. There are a few other recommendations such as this elsewhere in the document.
-Reply: We have removed the relevant content.

Reviewer B

1. This reads as an attempt, in the main, at a comprehensive narrative overview of lung cancer, which deals with management of COPD in that context. But there is internal ambivalence and indeed incoherence about the emphasis really. Could I suggest that a better approach should start in a more logical title to set the platform for what follows: “Lung cancer in the context of COPD”. They should start and continue with that strict focus, which currently is sort of there at the moment, but it rather comes and goes.
-Reply: Thank you for your feedback on our paper. Our focus is to draw readers' attention to the population with the co-occurring conditions of lung cancer and COPD, and to provide treatment guidance to this population. We always pay attention to the impact of lung cancer on COPD treatment or the impact of COPD on lung cancer, and guide how to manage this situation. Due to the variety of treatment types for lung cancer, the article may appear to be overly focused on lung cancer, although we aim to maintain

a balanced approach to both conditions.

2. They do very well with epidemiology but much less so with pathology/pathogenesis which is actually fundamental, once the case is made that COPD itself is a major risk-factor for NSC lung cancer. They need to point out that the underlying COPD disease process starts with airway fibrosis and destruction, probably due to oxidant damage (from smoking, airway luminal inflammation etc), with >40% of small airways "lost" before FEV1 begins to fall or symptoms appear, i.e., in a long pre-COPD disease phase. They are right in saying that gene "reprogramming" in the airway epithelial basal/stem cell is fundamental to changes in epithelial morphology, but also active EMT and related sub-epithelial myo-fibroblast accumulation, airway wall thickening with changed and excessive matrix protein accumulation...all these changes related to loss of airflow function (e.g., Eapen MS, etal. ERJ Open Res 2021 7;7(2):00876-2020; Walters EH, Shukla SD, Mahmood MQ, Ward C. Eur Respir Rev. 2021 May 25;30(160):200364).
-Reply: Thank you for your review comments. The section on pathogenic mechanisms mainly provides a simple explanation of the common mechanisms between lung cancer and COPD, without detailed elaboration on the mechanisms of COPD as a risk factor for lung cancer. We believe that this is not the focus of this consensus statement.

3. Further, there is now good evidence that the common classic smokers` centrilobular emphysema in COPD starts with peri-bronchial air-trapping secondary to small airway narrowing and destruction, and it is in these very areas that emphysema occurs, albeit slowly and over years. (Xu F etal Broadening concepts of core pathobiology in various aspects of COPD development. Eur Respir J. 2022 Oct 6:2201796)
-Reply: Thank you for your comments, but this consensus primarily focuses on the common risk factors and pathogenic mechanisms between lung cancer and COPD, and does not provide a detailed elaboration on the specific mechanisms underlying the development of COPD.

4. More broadly, there needs to be reference to the accepted now concept that epithelia in general are unstable and in the face of oxidant insult they are pre-cancerous as well as pro-fibrotic. Fibrosis and cancer just go together; >90% of human cancers are epithelial in origin, with what happens in COPD in the airways being a paradigm of what happens in all organs with epithelia. EMT is a common and vital ingredient in all this pathology, involved in cancer formation and well as aggressiveness (Mahmood MQ etl. Biomolecules. 2021 Sep 21;11(9):1394).
-Reply: Thank you for your review comments. This consensus has briefly described the role of EMT in the pathogenesis of lung cancer or COPD. However, the specific

mechanism is not the focus of this consensus.

Other specific major issues.

5. It seems to me that the review is just too long and too “wordy”. I suggest that it should not bother too much with standard management of either lung cancer or COPD in the general case, but instead really focuses on what is different and/or the special particular approaches needed where cancer occurs in the context of COPD. Most if this is there somewhere, but needs to stand out more, to be the very basis of the clinical aspects of the review. Thus, core issues are indeed: careful MDT selection of patents for a curative intent to management, QoL as central which might well involve some gentle and relatively non-toxic chemotherapy or immunotherapy, AND early consideration of referral to specialised medical palliative care services. Details of therapeutic algorithms or lists of drugs etc are far less important than getting the overarching principles right, especially for the more elderly, the more frail or unfit, and those with more advanced cancers.

-Reply: This article has been streamlined to focus on the unique challenges associated with managing COPD and lung cancer concurrently. Specifically, this consensus has emphasized the importance of tailoring treatment strategies to address the specific needs of patients who have both conditions. When managing COPD in the presence of lung cancer, healthcare professionals must consider the potential impact of COPD on treatment outcomes, such as addressing symptoms that can affect quality of life. Conversely, when managing lung cancer in the presence of COPD, treatment decisions must take into account the potential impact of cancer treatments on lung function and COPD symptoms. A multidisciplinary approach involving pulmonologists, oncologists, and other healthcare professionals is essential to optimize outcomes for patients with both COPD and lung cancer.

Lesser and miscellaneous issues

6. There are a great number of authors. Would it be better to have a named core group of activists, with others acknowledged by their working group or society?

-Reply: The authors of this article are experts and scholars from different fields, countries, and regions. Listing all the authors helps to increase the credibility and applicability of the article.

7. Line 278: I`m not sure asbestos should be included in a COPd review?

-Reply: Some studies have shown a correlation between asbestos exposure and the development of COPD (e.g., Int J Environ Res Public Health. 2020;17(19):7085; 1998;55(10):678-683; Clin Respir J. 2018;12(4):1676-1684)

8. Line 290: how much risk of cancer is there in asthma per se? What co-factors may here be?
-Reply: We have now added the word 'adjusted' in the text to clarify that the HR reported by Fan et al. is adjusted.
-Changes in the text: we have modified our text as advised (see Page 11, line 332).

9. The point about the association of emphysema and lung cancer is that more emphysema there is more severe the small airway disease that it reflects. Is there evidence for example of lung cancer caused by anti-proteinase deficiency only? Line 357: Studies of genes more generally tend to poorly differentiate airway disease from parenchymal disease in COPD; my reading is that genetic influences tend to group with IPF/emphysema/cancer/lung ageing and not airways fibrosis/destruction (which looks nothing like “pure” airway ageing).
-Reply: A dual case-control study, which adjust for the effects of COPD and tobacco smoke exposure, found an association between alpha-1 antitrypsin deficiency and the occurrence of lung cancer. (Arch Intern Med. 2008;168(10):1097-1103).

10. Line 538: what do you mean by decreased lung compliance in COPD...airways do become less compliant but not the parenchyma. If this refers to FVC, then a low FVC is due to lung air trapping increasing RV.
-Reply: The static compliance of COPD patients increases due to the presence of emphysema, but the dynamic compliance decreases due to the presence of airway obstruction. Therefore, we have changed the phrase 'poor lung compliance' to 'abnormal lung compliance'.
-Changes in the text: we have modified our text as advised (see Page 18, line 582).

11. Consensus 7 and line 542: the sputum/blood eosinophil issue in COPD management should probably have more prominence and discussion, and earler.
-Reply: Relevant content exists in the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which is not extensively discussed in this consensus.

12. Line 609: what do you mean by “inducements”?
-Reply: We replaced "inducements" with "triggers".

13. Line 677: Use of ICU in someone with lung cancer and COPD needs thinking about very carefully! Common sense and humanity need to reign.
-Reply: We fully agree with your point of view. We have made some modifications to the wording.
-Changes in the text: We have modified our text as advised (see Page 23, line 742, 746).

14. There are many abbreviations introduced without any or enough explanation.
-Reply: We have reviewed the article and added the full names for the abbreviations.

15. Lines 1191-8; antibiotics and chemoRx: I found this section difficult to interpret.
-Reply: The antibiotics discussed here may affect the efficacy of immunotherapy, and some AECOPD patients may require antibiotic treatment, so the use of antibiotics should be standardized.

16. Line 1500: s EEV1 a typo?
-Reply: Thank you for your reminder. We have modified it to 'FEV1'.

17. Lines: 1527-8: “Intra-operative hypoxic preconditioning” and “IV perioperative theophylline seem rather poorly evidence-based and too speculative for inclusion”.
-Reply: We have removed these two sections after discussion.

18. Are figs 1-3 or Table 2 really needed in a more focused review? Tables 6/7 could be amalgamated.
-Reply: We have removed these figures and table 2. However, Figure 6 is about TKI-ILD, while Figure 7 is about surgical risk assessment, and they cannot be merged together.

Needs a lot more focus on the key issues. lots of unexplained abbreviations and quite a lot of jargon phases in later parts...presumably writing-group related; these could do with a good edit by a single senior author.

Reviewer C

The paper titled “International expert consensus on diagnosis and treatment of lung cancer complicated by chronic obstructive pulmonary disease” is interesting. The Chinese Medical Association Lung Cancer and COPD Groups have developed this consensus document after extensive discussion. However, there are several minor issues that if addressed would significantly improve the manuscript.
1) What is the correlation between Treg/Thl7 and the efficacy of receiving a PD-1 monoclonal antibody in patients with lung cancer complicated by chronic obstructive pulmonary disease? It is recommended to add relevant content.
-Reply: There are few articles that correlate Treg/Th17 with PD-1 inhibitor efficacy. We

found an article titled 'Correlation between the Treg/Thl7 Index and the Efficacy of PD-1 Monoclonal Antibody in Patients with Advanced Non-Small-Cell Lung Cancer Complicated with Chronic Obstructive Pulmonary Disease', but it is not included in this consensus because the control group used in the study consisted of healthy subjects rather than lung cancer patients, and no direct relationship was observed between Treg/Th17 and PD-1 inhibitor efficacy.

2) What are the effects of postoperative exercise training on exercise endurance, daily activity and lung function of lung cancer complicated by chronic obstructive pulmonary disease? It is recommended to add relevant content.
-Reply: This consensus has addressed respiratory rehabilitation, but there are few articles on pre- or post-operative exercise training for LC-COPD patients. A meta-analysis showed that preoperative exercise training can reduce postoperative complications in lung cancer patients, but the benefits for patients with coexisting COPD were not significant (Cancer Manag Res. 2019;11:1765-1777). Another study demonstrated that postoperative exercise training can improve exercise tolerance and daily activity in LC-COPD patients (Zhongguo Fei Ai Za Zhi. 2022;25(1):14-20). However, the evidence level for postoperative exercise training is not sufficient, and therefore, it has not been included in this consensus.

3) What guidance can this research provide for the early identification and management of lung cancer complicated by chronic obstructive pulmonary disease? It is recommended to add relevant content.
-Reply: Consensus 3 and 4 are strategies for early identification. As for management, we have addressed the simultaneous treatment of lung cancer and COPD in Consensus 5.

4) What are the risk factors affecting the prognosis of elderly patients with lung cancer complicated by chronic obstructive pulmonary disease? It is recommended to add relevant content.
-Reply: Patients with lung cancer complicated by COPD are mostly elderly. As for the prognostic risk factors of elderly patients with lung cancer complicated by COPD, there are many factors involved, such as tumor staging, tumor type, COPD grading, PS score, etc. Moreover, the prognostic risk factors may differ with different treatments. Therefore, this consensus does not provide detailed information on this topic

5) How to choose patients to better meet the value of treatment strategies?
-Reply: This is a very good question, but the treatment of LC-COPD is quite complex and requires consideration of both the tumor and COPD condition. It is difficult to

summarize the treatment strategies for LC-COPD, but in the "Consensus on clinical applications" chapter, we have listed what needs to be considered for each treatment and which patients are suitable for these treatments.

Reviewer D

I have some minor comments for this interesting expert consensus.

1) First, in the background of this expert consensus, the authors need to explain the negative consequences of the LC-COPD, challenges in the clinical management, and the negative consequences of the under-recognition of LC-COPD. This information is important for this expert consensus.

-Reply: We have added relevant content in the background section.

-Changes in the text: We have added some data (see Page 8, line 234-240).

2) Second, in the methodology of the main text, please briefly describe the compositions of the expert panel, to support their expertise, authority, and international representativeness. My major concern is that there are many Chinese experts in the group who developed the consensus.

-Reply: We have added relevant content in the methodology section.

-Changes in the text: We have added some data (see Page 9, line 259-260).

Reviewer E

This article is very well written.

Regarding the content, there is nothing to revise.

At the beginning, a list of considerations will make it easier for readers to access the information they need.

Great job.

-Reply: This is a great suggestion. We have added a "Highlight Box" at the beginning of the consensus.

Reviewer F

References/Citations

a) Please move the citations to the main text, and check the other subtitles.

###Anlotinib plus chemotherapy can be used in patients with ES-SCLC complicated with COPD, and many studies have shown that elderly patients with ES-SCLC can benefit from anlotinib-based combinations (175,176)

###For intermediate and advanced lung cancer combined with COPD, feasible interventional palliative treatment can include argon plasma coagulation, photodynamic therapy, and CRYO (211)

Reply: We have modified the subtitle, and references 175 and 176 are not included in the subtitle. We have deleted reference 211.

b) There are 2 reference lists in the file, please keep the correct one and delete another one.
*Please note that there are **298** citations in the text.

1822 disease progression, and improve the quality of life (296). According to the US
1823 National Comprehensive Cancer Network (NCCN) guidelines (297,298), the

Reply: We have revised the content and citations.

c) Please add the citations for Borst et al. at the end of the sentence.

1590 severe/very severe COPD and ILD (250). Borst *et al.* measured pulmonary function in

Reply: We have added a citation.

d) Please double check if the author's name matches with the citation.

521 cancer screening and management", Wang *et al.* (50) defined patients with lung

1699 Kobayashi *et al.* (283) in their retrospective study revealed that use of inhaled

Reply: We have modified our text as advised.

e) Please double-check if citations should be added as you mentioned "ADAURA and FLAURA studies".

1038 are approximately 1–2%. ADAURA and FLAURA studies reported that the incidence
1039 of osimertinib-related ILD was 3% and 4%, respectively. Patients who have
1040 previously received EGFR-TKI treatment appear to have a higher probability of
1041 developing ILD after osimertinib readministration (150). For patients receiving

Reply: We have added the citations.

f) Please double-check if citations should be added as you mentioned "studies".
*Please note that the references should be cited in order of their appearance in the text. If the studies are not included in the reference list, please also update the current version.

evidence: IV; grade of recommendation: C). Few studies have explored the combination of anti-angiogenic drugs with ICIs in elderly patients, and only a few retrospective studies have shown that the combination of pembrolizumab with anlotinib increased both PFS and OS in patients with NSCLC and EGFR mutations who had failed previous treatment compared with pembrolizumab monotherapy.

with PD-L1 ≥50%

Retrospective studies have shown that the incidence of CIP in patients with lung cancer and COPD was higher than that in patients with lung cancer without COPD. In

Reply: We have revised the wording and added relevant citations.