

Peer review file

Article Information: <http://dx.doi.org/10.21037/tlcr-20-677>

Reviewer A: *The review entitled "LUNG CANCER SCREENING: WHO PAYS? WHO RECEIVES? THE EUROPEAN PERSPECTIVES" focused the attention on the current status of lung cancer screening from a European point of view. It is a comprehensive review on the different screening methods for lung cancer patients, with a particular attention for novel future possibilities for these patients (e.g. liquid biopsy).*

REVIEWER A COMMENT: in the abstract section, the Authors should provide the extensive form for the acronym "ICER".

AUTHOR RESPONSE: Thank you for the suggestion. We changed it in “incremental cost-effectiveness ratio (ICER)”. (Line 37)

REVIEWER A COMMENT: Page 11 lines 261-262 "According to this model blood microRNA + LDCT would allow optimal screening intensity and reduce unnecessary LDCT repeats, thus improving the efficacy of screening." The Authors should add a reference for this statement.

AUTHOR RESPONSE: Thank you for the comment. This passage is referring to the paper by Pastorino et al. “Blood MicroRNA and LDCT Reduce Unnecessary LDCT Repeats in Lung Cancer Screening: Results of Prospective BioMILD Trial”. We added the reference as suggested. (reference 82)

Reviewer B: *The authors are presenting a comprehensive review on lung cancer screening. The topic is of interest, especially for European countries, because of the feasibility of the screening by National Health Systems.*

REVIEWER B COMMENT: the introduction section is longer compared to subsequent sections: I suggest to shorten it, or to define one additional section within it.

AUTHOR RESPONSE: Thank you very much for your suggestion, this is absolutely right. In order not to remove passages that we think are necessary for the completeness of the paper, we decided to define an additional section covering the potential downsides of LCS. The section is entitled: “Potential Drawbacks”. (Line 88)

REVIEWER B COMMENT: the unpublished data that the authors are mentioning, are not reference for a review. Please consider to delete any consideration on unpublished data, unless able to provide a valid reference.

AUTHOR RESPONSE: Thank you for your comment. Not being able to provide a

reference, in the wake of your observation we decided to eliminate unpublished data.

REVIEWER B COMMENT: The future prospective section is very long and covers many different aspects. Please consider to organize this section with subheadings.

AUTHOR RESPONSE: This is a very useful remark. We thus divided the future perspectives section in four sub-chapters, as follows: 1) Prevention and detection of cardiovascular diseases; 2) Increase in minimally invasive surgical procedures; 3) Artificial intelligence for radiological analysis; 4) Liquid biopsies for pre-operative diagnosis.

Reviewer C: *Authors reported an analysis about the screening impact in Lung cancer. This is a relevant issue and Authors explored deeply its role.*

REVIEWER C COMMENT: Please specified ICER.

AUTHOR RESPONSE: Thank you for the suggestion. We changed it in “incremental cost-effectiveness ratio (ICER)”. (Line 37)

REVIEWER C COMMENT: I would suggest to add a sentence about the important in smoke interruption, that is still the correct behavior to prevent Lung cancer.

AUTHOR RESPONSE: Thank you for your advice, this is of course a key point in lung cancer prevention and screening. We therefore added the following statement: “Therefore, the first crucial step in lung cancer prevention should be smoking interruption, a point that is discussed with every single patient enrolled in lung cancer screening protocols.” (Lines 60)

REVIEWER C COMMENT: Line 60: please remove "s" to stages

AUTHOR RESPONSE: Thank you, we changed it as suggested. (Lines 63)

REVIEWER C COMMENT: Line 64: change small with early

AUTHOR RESPONSE: Thank you, we changed it as suggested. (Lines 67)

REVIEWER C COMMENT: Line 65: move "published in 2011" at the beginning or at the end of the sentence

AUTHOR RESPONSE: Thank you, we changed it as follows: “Published in 2011, the US large randomized National Lung Screening Trial (NLST) demonstrated that LDCT performed in high-risk patients reduces lung cancer mortality by more than 20% compared with the group screened by chest X-ray”. (Lines 68)

REVIEWER C COMMENT: Line 69: by using what? X-Ray? CT scan? Both? Other?

AUTHOR RESPONSE: Thank you for your comment, this is another important remark. The studies we were referring to compared chest X-Ray and CT scan. We added the clarification and modified the sentence as follows: “In Europe, several randomized screening trials comparing low-dose CT scan versus chest X-Ray were released but had insufficient statistical power to demonstrate any mortality benefit”. (Lines 71)

REVIEWER C COMMENT: Line 71: please change as the 10 years as the 10-year

AUTHOR RESPONSE: Thank you, we changed it as suggested. (Lines 74)

REVIEWER C COMMENT: Line 74: reformulate the sentence, just to be more readable

AUTHOR RESPONSE: Thank you for your suggestion. In order to make the statement more readable and straightforward we modified the passage as follows: “Recently, however, the large European Randomized Controlled Trial (The Dutch-Belgian Randomized Lung Cancer Screening Trial – NELSON study) showed that the 10-year lung cancer mortality in the LDCT screening group was 2.5 deaths per 1000 person-years, while in the control group it was 3.30. The screening arm therefore showed 24% lung cancer mortality reduction (cumulative rate ratio for death from lung cancer of 0.76, $p=0.01$). It must be also stressed that in the screening arm about 77.6% of diagnosed cancers were early stages (IA to II), while in the control arm 71.6% of cancers were stage III-IV at diagnosis.” (Lines 73)

REVIEWER C COMMENT: Line 76: If you decide to use the current sentence "This means that LDCT screening saves lives" please add more data about OS probability.

AUTHOR RESPONSE: This is a very useful comment. We decided to remove this “catch phrase” underlining the fact that screening is related to early diagnosis. We substituted the sentence as follows: “Being related to early-stage diagnosis, screening thus leads to a reduction in mortality”. (Lines 79)

REVIEWER C COMMENT: Do you have any data about the radiological screening time suggested in high risk patients?

AUTHOR RESPONSE: thanks for the question that anticipates the reflection of the next comments: we prefer to talk about subjects and not about patients in those who are candidates for screening. Subsequently, as also highlighted by your questions, we will talk the different risk models and screening interval.

REVIEWER C COMMENT: Are there any international study focused on CT and circulating tumors cells?

AUTHOR RESPONSE: This an interesting remark. We tried to improve the paragraph regarding circulating tumor cells by adding a reference to the work by Ilie et al. entitled: “Sentinel” Circulating Tumor Cells Allow Early Diagnosis of Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease”. We modified the paragraph as follows: “Migration of CTCs in the bloodstream is an early event in carcinogenesis: they are released by cancer tissue as single or clusters of cells that can be isolated in peripheral blood in different ways. Ilie et al. examined the presence of ‘sentinel’ CTCs in COPD patients without radiologically detectable lung cancer and screened them annually with LDCT. CTCs were detected in 3% of COPD patients; in 1 to 4 years these patients developed a radiologically detectable lung nodule, leading to prompt surgical intervention of an early stage tumor. In the setting of LCS, these results support the use of liquid biopsies as a tool for non-invasive pre-operative diagnosis of lung cancers, reducing the number of invasive diagnostic procedures such as EBUS-TBNA, CT-guided biopsies and diagnostic surgeries and improving the effectiveness of the treatment by reducing the time required for pre-operative invasive diagnostic procedures.” (Lines 354)

REVIEWER C COMMENT: In the paragraph SELECTION OF TARGET POPULATION AND SCREENING INTERVAL: RISK MODELS, it is interesting a table that compared the different studies and the results. This is the crucial part of the article!

AUTHOR RESPONSE: thank you very much for this interesting suggestion. In this regard, a table (table 1) has been inserted in the manuscript.

REVIEWER C COMMENT: Another table about what patients could benefit from a lung cancer screening is useful for readers

AUTHOR RESPONSE: thanks also for this precious suggestion. Considering that the two habits that smoking and age are the two principal risk factors used in lung cancer screening, it was a bit difficult to insert a dedicated table, so the age were included in the previous table. However, we created a second table where we listed the elements of the PLCO and Maisonneuve risk-model, which quickly helps the reader to focus on the salient elements.

REVIEWER C COMMENT: A native speaker revision is necessary

AUTHOR RESPONSE: Thank you for your advice. The whole manuscript was revised, checking grammar and syntax.