Peer Review File

Article Information: https://dx.doi.org/10.21037/tlcr-22-540

Reviewer A

This article is an important study to understand the proper method of postoperative follow-up testing. The paper is of interest to many researchers. There are several issues that need to be corrected.

Comment 1: Is there evidence that chest x-rays are useful in stages I and II? I am wondering to what extent chest x-rays are useful in postoperative follow-up.

Reply 1: In response to the reviewer´s comment, there is no evidence on the usefulness of chest x-ray in stages I-II.

Comment 2: Are blood tests referring to tumor markers? If tumor markers, how many items are tested at what time? Please describe. Many thoracic surgeons measure tumor markers as the most economical and convenient method.

Reply 2: Blood tests are complete tests, not referred to tumour biomarkers. There are no validated tests or biomarkers.

Comment 3: What is the status of the EGFR mutation? Many papers indicate that patients with driver gene mutations are at high risk of recurrence. Do I need to change my follow-up in patients with harboring driver oncogene ? Please describe the authors' thoughts.

Reply 3: EGFR mutation determination remains out of protocol. Published results imply that genetic variants in the early cancer stage have higher probabilities of cancer recurrence, but all these findings need to be confirmed by data from larger cohorts.

Comment 4: EGFR mutation-positive patients are at higher risk of brain metastasis recurrence. Does screening methods for recurrent brain metastases need to be changed in these patients? Please provide data and specify the authors' thoughts.

Reply 4: Molecular targeted therapies have significantly improved the treatment outcome of patients with non-small cell lung cancer harboring driver gene mutations such as EGFR. However, the brain is a frequent site of recurrence, and it significantly deteriorates the prognosis of these patients (Nishino M, Soejima K, Mitsudomi T. Brain metastases in oncogene-driven non-small cell lung cancer. Transl Lung Cancer Res. 2019 Nov;8(Suppl 3):S298-S307. doi: 10.21037/tlcr.2019.05.15. PMID: 31857953; PMCID: PMC6894990).

Several studies have tried to identify the predictive factors for brain metastasis in patients with NSCLC. Carcinoembryonic antigen, size of primary tumor, nodal stage, and presence of bone metastases have been proposed as predictive factors for the presence of brain metastasis in patients with NSCLC. A histopathology of nonsquamous cell carcinoma is also known to be a

predictive factor, which means that pulmonary adenocarcinoma has a higher tendency to metastasize to the brain than squamous cell carcinoma. However, the clinical implications of EGFR mutation status in terms of brain metastasis in patients with pulmonary adenocarcinoma have not yet been examined (Shin DY, Na II, Kim CH, Park S, Baek H, Yang SH. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. J Thorac Oncol. 2014 Feb;9(2):195-9. doi: 10.1097/JTO.0000000000000069. PMID: 24419416).

Comment 5: If you suspect recurrence, PET/CT is excellent. However, economically, I think CT is more effective. How do you use these two measurement methods? Or do you measure both?

Reply 5: We use them upon demand and based on the clinical judgement of the oncologist.

Reviewer B

Comment 1: I miss a quantification of the number of diagnosed early stage lung cancer patients in the introduction, as well as an estimation of the amount of money that is associated with the treatment for these early stage patients. As far as I know is the treatment for the advanced stage lung cancer patients a high burden to society. To get an impression of the burden associated with the treatment and follow-up of early stage lung cancer patients, it might be useful to get a quantification of the treatment for these patients.

Reply 1: Early stage diagnosis of lung cancer patients in Spain is approximately 20-30%. We do not have any real figures or estimations on the cost of treatment for these patients, due to the lack of cost-effectiveness studies. Advanced stages have a higher cost for healthcare systems given the duration of the treatments and the high number of tests performed throughout the disease. Early stages are considered cured after surgery, some undergo adjuvant chemotherapy or radiotherapy, and receive a follow-up for tumour recurrence.

Comment 2: I'm somewhat astonished that for lung cancer stage 3a, surgical treatment is the preferred strategy, as there are also metastases.

Reply 2: IIIA stages do not have metastasis at diagnosis.

Comment 3: Regarding the hypothesis, this seems a rational hypothesis, though the intended (not explicit mentioned aim) of the follow-up seems related to an early detection of an in principle treatable cancer.

When we think on the benefits of follow-up, we can come up with the following points:

1. Early detection of an in principle treatable cancer

2. Early detection of complications for which early detection by a doctor has clear health benefits compared to self-report of the patient.

3. Reassurance (of patient and doctor)

4. Quality assessment of the offered treatment.

This way of reasoning is well known in the field of breast cancer and colorectal cancer follow-up.

The authors should add this way of thinking to the discussion, to put there results in context.

Reply 3: We appreciate the reviewer's insights, we have modified the discussion accordingly.

Comment 4: Regarding the results: there should be a Table 1, including the patient characteristics. I miss the description of the treatment provided at baseline. All patients were treated with surgery, however, I guess that some also had other treatment, like radiotherapy and/or chemotherapy. That should be added.

Reply 4: We thank the reviewer for this comment. The table was indeed missing, so we have produced one with the patient's characteristics and it has been included in the results section, line 122-123.

Comment 5: Then there should be a table with data regarding the outcomes. For follow-up times, please also add the ranges (min-max of IQR, what is preferred). The current percentages are raw percentages. Given the right censoring of the data (not all patients are followed for the same amount of time), the raw percentages will be misleading and should be replaced by the Kaplan Meier percentages (also available in SPSS). Even in a descriptive analysis, you have to provide the correct percentages.

Reply 5: Table 2 has been added with data regarding the survival outcomes, ranges and percentages (line 134) and Kaplan Meier curves showing probability of DFS and OS have been added to the results (Figure 1) (line 139).

Comment 6: Is it true that only patients who came to the Emergency Room, are unscheduled patients? Is there no other way to go to the hospital in case of symptoms before the fixed appointment? In line 164 it is stated that: …. 45 (100%) were informative. Most of the latter correspond to patients who went to the Emergency Room. I would say that all of the 45 were from patients that went to the Emergency Room. If not, please clarify the text.

Reply 6: In response to the first and questions, the answer is yes, patients that go to ER do not have a fixed appointment and come upon symptom occurrence, as it is the only way to see them if they do not have an appointment. And answering the last question, yes, the 45 were patients that went to the Emergency Room.

Comment 7: The results section regarding pet-CT and chest CT scans is not readable. Please add a table and focus in the text on the highlights.

Reply 7: You can already find the results regarding PET-TC and chest TC in Table 3. I have referenced Table 3 in this part of the text in the results section, focusing only the highlights in the text, so it can be more readable.

Comment 8: Table 3 is difficult to understand, as there is no dimension of time. Please add the numbers per year.

Reply 8: Table 3 has been modified according to the reviewer´s suggestion.

Comment 9: The main message of this work is the low amount of informative tests performed. The discussion should start with summarizing the main findings regarding the main message. The current text is not adequate as a start of the discussion.

Reply 9: The discussion has been modified according to the reviewer´s comments.

Comment 10: There should not be new results in the discussion, e.g. line 241.

Reply 10: Results have been removed from the discussion as suggested by the reviewer.

Comment 11: I miss a discussion on the point whether the guidelines have been followed or not. I guess that the guidelines changed over time, so this might be an interesting point. When the doctors just followed the guidelines, this might be an important notification. Maybe the guidelines should be updated. This point should be stressed in the discussion. It might be a suggestion to perform CT after 1 year, then after 3 years, then after 5 years. I do not know how many patients had a complete follow-up time for these amount of years. It would be great to have these data stratified by tumour stage (can be an extension of table 2). How many informative tests would have been missed with this scenario? The data are relevant, the discussion should highlight the relevance of the data and start a discussion on the optimal follow-up scheme for patients diagnosed with lung cancer with an in principle curative treatment.

Reply 11: The following discussion has been included in the manuscript´s discussion, in response to the reviewer´s questions (lines 204-214).

NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of early and locally advanced NSCLC recommend on surveillance every 6 months for 2 years with a visit including history, physical examination and—preferably contrast enhanced—volume chest CT scan at least at 12 and 24 months, and thereafter an annual visit including history, physical examination

and chest CT scan in order to detect second primary tumours. For patients who are suitable for salvage treatment (e.g. surgery, local ablative therapy), follow-up with six-monthly CT scans for 3 years is recommended, but there is no recommendations other than a personalized tailoring of the follow-up for those not suitable for salvage treatment, based on the oncologist´s criteria.