Peer review file

Article information: https://dx.doi.org/10.21037/jtd-21-1195

Reviewer A

Comment 1:

I would like to thank the authors for the opportunity of reviewing this manuscript by sending it to this journal.

Neoadjuvant immunotherapy (ICIs) plus chemotherapy or ICIs alone followed by surgical resection seems to have change the natural history of locally-advanced lung cancer. This paper is focused in the impact of ICIs on the feasibility and radicality of the surgery in a subset of patients defined as surgically-challenging lung squamous cell cancer. In my opinion, this manuscript is pertinent. However, I do have some comments/suggestions:

- Introduction: I would change the last paragraph for a more common formula: "the aim of this study is...", plus "the secondary endpoint is to assess the accuracy of CT scans to predict pathological reponses. I think the current paragraph is a mix of material and methods and discussion/conclusion, sounds confusing in the Introduction section.

Reply 1: Thanks for your suggestion. We have modified our text as advised.

Changes in the text: see Page 5, line 108-111.

Comment 2:

- Patient and Methods:

*Treatment response assessment: in my opinion, PET/CT offers interesting information about the potential response or inflammatory component after neoadjuvant ICIs. Would be possible to add the correlation with SUVmax in PET study and pathological response in the same way the authors show the CT correlation?

I consider this is a very interesting issue because we can see in the future many patients with ICIs as neodjuvant therapy with inflammatory changes rather than residual tumor. PET scan can give contradictory information and prevent the multidisciplinary tumor boards to offer surgery for that particular patient.

Reply 2: We appreciated the reviewer`s comments. In this retrospective study with a small sample size, PET-CT was only performed in a few cases (n=5) after neoadjuvant

immunotherapy. For the rest, 7 patients had PET-CT before the neoadjuvant immunotherapy only. As a result, we were not able to access the relevant data to investigate the correlation with SUVmax in PET-CT and pathological response. However, it is certainly interesting to study this point. Despite that, one recent study showed that there was a significant relationship between the SUVmax reduction and pathologic response after neoadjuvant sintilimab treatment in patients with NSCLC, suggesting that SUVmax reduction after neoadjuvant treatment could be predictive of response to neoadjuvant PD-1 blockade (PMID: 32036071). We will focus on this issue in our future studies.

Comment 3:

*Clinical characteristics: would it be possible to add the reason for being staged as IIIA?

Reply 3: Thanks for your suggestion. Stage IIIA includes T4 N0 M0 and T3/4 N1 M0 tumors as well as T1/2 N2 M0 tumors according to AJCC (The American Joint Committee on Cancer) Lung Cancer Staging (8th edition), which is mentioned in the Operation part of Patient and methods section

Changes in the text: see Page 8, line 179-181.

Comment 4:

*Surgical resection and postoperative course: the % of minimal invasive resections shows the expertise of the surgeons, I think is a motive to be proud of. Did you have any conversion to thoracotomy? If so, please, state the rate.

In this section I would add a more detailed information about the the positive margin patients: parenchyma? bronchial or vascular margin?

Also, I would include the complications after surgery according to Clavien-Dindo classification, an international validated scale. The 30-day mortality rate should be included.

Reply 4: We appreciated the reviewer`s comments. We have added the rate of conversion to thoracotomy and detailed information about the positive margin in the surgical resection part. In addition, we added the Clavien-Dindo Classification (PMID: 19638912) as the complement for the traditional classification methods and the 30-day mortality rate was also included in our manuscript.

Changes in the text:

Conversion to thoracotomy (see Page 12-13, line 275-276).
Detailed information about the positive margin (see Page 13, line 276-278).
The Clavien-Dindo classification (see Page 8, line 184-185 & see Page 13, line 283-285).
The 30-day mortality rate (see Page 13, line 292).

Comment 5:
*Survival: 2 year OS is 94.1%. However, the graph showed in figure 2 seems to me to be lower than that. Could it be further explained?
Reply 5: Thanks for. We have checked our data in figure 2 again, the two-year RFS and OS were 84.40% and 94.1%, respectively, which are consistent with the data in our manuscript.
Changes in the text: see Page 14, line 309-310.

Comment 6:
- Discussion:
This section is very well written. I would add some information to limitations section:
*This study includes a very heterogeneous some of patients regarding the given neoadjuvant treatment.
*Also, the definition of surgically-challeging patients is very very heterogeneuos.
It is clear than is very difficult to sub-divide this already limited serie, but I think this should be at least aknowledge as a limitation of the study.
Reply 6: Thank you for your suggestion. We have modified the limitation part as advised.
Changes in the text: See Page 17, line 387-392.

Comment 7:
Minor revisions:
- Please, change 'LSQCC' for 'LSqCC'.
Reply 7: Thank you. We have changed 'LSQCC' for 'LSqCC'
Changes in the text: see Page 4, line 77.

Reviewer B

Yang et al report about their retrospective analysis of 23 patients with locally advanced squamous cell carcinoma that underwent surgery after receiving immochemotherapy. All patients were initially challenging for surgical resection due to invasion of adjacent essential structures, N3-lymph node- involvement, or, pericardial or pleural effusion. Finally, radical resection could be achieved in 20 of 23 patients and 14 patients showed at least major pathologic response. The authors present an interesting selected group of patients showing that surgery can be safe and feasible after immunotherapy and that even patients with initially technical of functional inoperable tumors can be candidates for complete resection. The manuscript adds a selected retrospective cohort to the rapidly developing field of immunotherapy for locally advanced lung cancer.

Comment 8:
I have several comments and questions:
- Abstract lines 46 and 58: locally-advanced is written twice
Reply 8: Thank you. We have deleted the unnecessary text
Changes in the text: Delete one of “locally-advanced” (see Page 4, line 68).

Comment 9:
- Introduction line 67 LSQCC or LSqCC
Reply 9: Thank you. We have changed 'LSQCC' for 'LSqCC'
Changes in the text: see Page 4, line 77.

Comment 10:
- I recommend to remove lines 96 to 101 as they anticipate the results
Reply 10: Thank you for your suggestion. We have modified the last paragraph of Introduction as advised.
Changes in the text: see Page 5, line 108-111.

Comment 11:
- Line 114 did the authors include patients with pericardial or pleural effusion (stage IV) or limited cardiopulmonary function?

Reply 11: Yes, these patients were included. In this study, we focused on surgically-challenging lung cancer cases, which were defined as 1) NSCLC tumors of any size which have spread to the contralateral lymph nodes, or have invaded other essential structures or organs in the chest such as the large vessels (e.g., superior vena cava, aorta), heart, trachea, esophagus or vertebral body; 2) involvement of multiple mediastinal lymph nodes (N2); 3) the presence of malignant pleural or pericardial effusion; 4) patients who were potentially intolerable to extensive resections due to the limited cardiopulmonary function reserve and/or comorbidities.
Changes in the text: See Page 6, line 122-129.

Comment 12:
- Histological diagnosis was confirmed by EBUS/Mediastinoscopy, however, only 2 patients received EBUS and none mediastinoscopy for staging?
What were the cN and pN stages in the patients?
Reply 12: The pathological confirmation was based on tumor biopsies. For most cases, the diagnosis was based on transbronchial biopsy. In our center, PET-CT or invasive mediastinoscopy (or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)) was used to evaluate mediastinal nodal status for clinical staging. Nowadays, we preferred to using PET-CT or EBUS-TBNA given their less invasiveness compared with traditional mediastinoscopy. To make our statement more accurately, we modified the statement by deleting mediastinoscopy
Changes in the text: Delete “mediastinoscopy” (see Page 7, line 144-146).

Comment 13:
- Were there only VATS procedures and posterolateral thoracotomies?
Reply 13: Thank you. We were sorry for the inaccurate statement. There were 23 patients included in our study and 8 received posterolateral thoracotomies and 14 received VATS procedures. One patient required conversion to thoracotomy due to the adhesions. We have corrected the relevant content in both article and table.
Changes in the text: See page12-13 line 275-276 & Table 1 “Surgical approach”.

Comment 14:
- What were the reasons for incomplete resections? What means “mainly” due to (line

255)

Reply 14: Thank you. We were sorry for the inaccurate statement. Actually, these incomplete resections were all due to the limited lung function reserve.

Changes in the text: Delete the “mainly” (see Page 13, line 278-280).

Comment 15:

- Only 9 patients occurred irAEs, what were “others”?

Reply 15: Thank you. We were sorry for the inaccurate statement. One patient developed nausea and vomiting after treatment. We modified the statement and changed “others” to “nausea/vomiting”.

Changes in the text: Change “others” to “nausea/vomiting” (see Page 12, line 264).

Comment 16:

- On what basis decided the authors for 2, 3, 4 or 5 dosages of neoadjuvant therapy?

Reply 16: Thank you. In CheckMate 816 (NCT02998528) study, patients were designed to receive three cycles of neoadjuvant therapy, then underwent radiologic staging and surgery within 6 weeks of neoadjuvant therapy. In our center, patients underwent routine preoperative examinations to assess the surgical resectability and safety after neoadjuvant therapy. We found that most patients met the criteria (showed partial response or stable disease in post-treatment CT) for surgery after 2 or 3 cycles of neoadjuvant therapy. In addition, patients who received 4 or 5 cycles of neoadjuvant therapy and met the criteria for surgery were also able to undergo surgery and have good outcomes. Besides, the median interval between the last cycle of therapy and surgery was 36 days (range, 25–93 days), without treatment-related delay in surgery. The detailed basis has mentioned in “Preoperative examinations” section.

Changes in the text: See Page 7, line 140-146.

Comment 17:

- Line 252; resection extend percentages do not equal 100%

Reply 17: Thank you. The proportion of patients receiving different types of resection was divided by the total number of patients which is 23. The sum of percentages does not equal 100 because of rounding.

Comment 18:

- Line 262 a death due to bronchopleural fistula after 29 days is not usual, please comment with a few sentences.

Reply 18: Thanks for your suggestion. BPF that occurs after seven days postoperatively is usually due to ischemia or necrosis secondary to residual tumor, the extension of an empyema, or inadequate vascular supply of the bronchial stump. We hypothesized that the extensive dissection required for a proximal tumor and preoperative chemotherapy may be the risk factors for BPF (PMID: 29027099). This patient suffered life-threatening complications secondary to the BPF including pneumonia and respiratory failure which attributed to the poor outcome. We have added the comment about this case in the article.

Changes in the text: See Page 13, line 288-292.

- Table 1:

Comment 19:

o smoking history does not equal 100%

Reply 19: Thank you. Same as mentioned above, the error comes from rounding.

Comment 20:

o LD and RD is not abbreviated, do you mean RL and LL?

Reply 20: Thank you. We have modified the correct abbreviations in Table 1.

Changes in the text: Change LD and RD to LL and RL (see Table 1, Location).

Comment 21:

- Why were there 56.5% of patients with unknown PD-L1 expression?

Reply 21: Thank you. Because most cases were treated with chemo-immunotherapy, for which PD-L1 expression test was not necessary before the neoadjuvant treatment. The previous phase 3 randomized clinical trial provided the evidence that adding immunotherapy to chemotherapy was associated with significantly prolonged survival in patients with advanced sq-NSCLC, regardless of PD-L1 expression (PMID: 33792623)