TRANSLATIONAL LUNG CANCER RESEARCH

Peer Review File

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Reviewer A

This study evaluates the safety of sleeve lobectomy after chimioimmunotherapy.

This a study with few cases (10 cases only) and retrospective series.

The percentage shoud be adapted (10 instead of 10.00). Table 1 and 3, the percentage of operation are wrong (middle lobe, etc...), please control the numbers...

Reply: Thank you very much for your review and suggestion. We have change all percentage in manuscript as XX in stead of XX.00. We also checked all numbers again and fixed the error in Table 1 and 3.

Change: Please refer in manuscript (Abstract and Result) and Tables. We have checked and fixed all numbers.

Why do you consider that the surgery was more difficult? No data can show a difference (operative time, bleeding, etc..) this is just a feeling, isn't it right?

Reply: Thank you for your question. We found that compared with neoadjuvant chemotherapy alone, the surgery is more difficult after chemoimmunotherapy from the following aspects: first, the space between vessels and bronchus is very narrow, thus the division is more difficult; second, the hilar and mediastinal lymph node are tougher and more difficult to dissect from the bronchus; third, the visceral pleura becomes tighter, which is more difficult to cut with electrosurgical or ultrasound scalpel. We can observe that although no statistically significant (probably owing to the sample size), the operation time (291.88 vs 287.50 min) was longer and the intraoperative bleeding volume (365.00 vs 347.50 ml) was more in chemoimmunotherapy group when the lymph node dissection number was significantly less in chemoimmunotherapy group. Besides, from the results of the NEOSTAR study, 40% of operations after immunotherapy was judged to be "more difficult" than usual cases, we have the reason to believe that operation after chemoimmunotherapy is more difficult than that after immunotherapy alone. However, we must acknowledge that the systematic objective evaluation of the difficulty should be prospectively applied to confirm this preliminary subjective perception.

Change: We have added these comments in Discussion.

"During the operation, first, the space between vessels and bronchus is very narrow and the majority of cases in IO+C group presented more severe tissue edema and increased vascular fragility, thus surgeons noted the space between vessels and tissue were difficult to divide; second, the hilar and mediastinal lymph node are tougher and more difficult to dissect from the bronchus; third, the visceral pleura becomes tighter, which is more difficult to cut with electrosurgical or ultrasound scalpel. All these factors contributed to a potentially higher risk of bleeding. The fact that we observed more severe tissue

degeneration in histological paraffin sections of the neoadjuvant IO+C group than the neoadjuvant chemotherapy group lends some credence to this hypothesis. However, this opinion also needs prospective data to support. The subjective difficulty of surgery after IO+C should be evaluated by a scoring system to facilitate quantification of apparent surgical complications in future studies.

We can observe that although no statistically significant (probably owing to the sample size), the operation time (291.88 vs 287.50 min) was longer and the intraoperative bleeding volume (365.00 vs 347.50 ml) was more in chemoimmunotherapy group when the lymph node dissection number was significantly less in chemoimmunotherapy group. Besides, from the results of the NEOSTAR study, 40% of operations after immunotherapy was judged to be "more difficult" than usual cases, we have the reason to believe that operation after chemoimmunotherapy is more difficult than that after immunotherapy alone. However, we must acknowledge that the systematic objective evaluation of the difficulty should be prospectively applied to confirm this preliminary subjective perception."

How do you explain the difference in term of number of harvested lymph nodes? There is a potential biais in term of downstaging, but also in term of post-op complications (less dissection and devascularisatzion of bronchus). This point should be discussed.

Otherwise, congratulations for your results

Reply: Thank you for your question. As mentioned above, the hilar and mediastinal lymph node are tougher and more difficult to dissect from the bronchus after neoadjuvant IO+C, thus the number of harvested lymph nodes was less in IO+C group than C group. We admit your comments that this could be a potential bias in term of downstaging and post-op complications. We added this in the limitation.

Change: Discussion: "Last, the hilar and mediastinal lymph node are tougher and more difficult to dissect from the bronchus after neoadjuvant IO+C, thus the number of harvested lymph nodes was less in IO+C group than C group, and this could be a potential bias in term of downstaging rate and post-operative complications."

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Reviewer B

You describe an important topic regarding the sleeve resections in locally advanced NSCLC after neoadjuvant immunochemotherapy. Here are my comments/questions on your manuscript:

1. How was the pathologic reponse detected in the primary tumor and also in lymph nodes? Are there any differeces in the assessment process of pathologic response after IO-C and chemotherapy? A table with pathological finding comparing both groups would be helpful to better analyse and compare the results.

Reply: Thank you very much for your comments and valuable suggestion. We performed the pathological analysis according to the criteria of CheckMate-159 study **(1)**: pathological analyses were performed on available biospecimens of surgical groups by two senior pathologists. MPR rate was defined as 10% or less viable tumor remaining on postoperative pathologic review, which was identified on routine hematoxylin and eosin staining **(2, 3)**. No residual tumor cells found in dissected tissues and lymph nodes was defined as complete pathological response (CPR) **(4)**. We described this in methods, please kindly check. The IO + C group have the same pathological evaluation procedure with the chemotherapy group. We conducted a Table to summarize the characteristic of pathological changes as your suggestion.

Change: Pathological analyses were performed on available biospecimens of surgical groups by two senior pathologists. MPR rate was defined as 10% or less viable tumor remaining on postoperative pathologic review, which was identified on routine hematoxylin and eosin staining. No residual tumor cells found in dissected tissues and lymph nodes was defined as complete pathological response (CPR). The IO+C group have the same pathological evaluation procedure with the chemotherapy group. The pathological evaluation for lymph node is also the same wit that of primary tumor. Please refer Table 4 for the pathological response evaluation.

Reference:

[1] Hellmann MD, Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhor N, Pataer A, Travis WD, Swisher SG, Kris MG; University of Texas MD Anderson Lung Cancer Collaborative Group. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol. 2014 Jan;15(1):e42-50. doi: 10.1016/S1470-2045(13)70334-6. PMID: 24384493; PMCID: PMC4734624.

[2] Pataer A, Kalhor N, Correa AM, et al. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol. 2012;7(5):825-32. Epub 2012/04/07.

[3] Hellmann MD, Chaft JE, William WN, Jr., et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol. 2014;15(1):e42-50. Epub 2014/01/05.

[4] Mouillet G, Monnet E, Milleron B, et al. Pathologic complete response to preoperative chemotherapy predicts cure in early-stage non-small-cell lung cancer: combined analysis of two IFCT randomized trials. J Thorac Oncol. 2012;7(5):841-9. Epub 2012/06/23.

2. Did you perform a preoperative PET scan in all patients routinelly? Were there some differences in the SUV- uptake in primary tumor and lymph nodes after IO-C and chemotherapy detectable?

Reply: PET scan is not a routine practice for all patients. Besides, a CT scan was used to re-evaluate the lesion every 2 cycles of neoadjuvant therapy, PET is not used at this time point. Thus, we are unable to report the difference in SUV- uptake between IO+C and chemotherapy group. However, the main topic of this study is to prove the hypothesis that sleeve lobectomy is feasible after neoadjuvant IO+C. The oncological results were secondary outcomes, and the SUV-uptakes should be a more appropriate and interesting topic in first-line therapy of PD-1/L1 for metastatic NSCLC.

Change: We have added these comments in methods, please kindly refer: “Brain magnetic resonance imaging (MRI), bone scan or positron emission tomography (PET) examination were performed to exclude distant metastasis. Preoperative lymph node status was assessed via one of following techniques:

contrast-enhanced CT, PET, endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) or mediastinoscopy. Not all patients underwent PET examination or invasive mediastinal staging pre-operatively. Except for necessary CT scan and physical examination, all other evaluation strategies would be discussed and decided together with patients and his/her family members. ”

3. Unfortunately, the prognostic impact of major and complete pathologic response is not clearly described in your manuscript. In my opinion, it appears as relevant.

Reply: Thank you very much for your constructive comments. We followed up these patients, and only 1 patient in neoadjuvant chemotherapy group were lost. All patients in neoadjuvant IO+C are alive and no one suffers from recurrence or death. However, 4 patients in neoajuvant chemotherapy group dead after recurrence or metastasis. We draw a K-M plot and added these new outcomes in manuscript (Results). In the meanwhile, we have to acknowledge that limiting the insufficient follow up time, the outcomes of PFS and OS were premature. We also added this in discussion.

Change: We added these outcomes in result and discussion, please kindly refer.

In method: “Patients were followed up by Oct. 1st, 2020. Progression press survival (PFS) and overall survival (OS) were calculated. Kaplan-Meier (K-M) method was used to evaluate the survival status between two groups and compared with the log-rank test. Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs).”

In results: “Patients were followed up by Oct. 1st, 2020, and only 1 patient in neoadjuvant chemotherapy group was lost in contact. The median follow-up time were 406 and 623 days in neoadjuvant IO+C and neoadjuvant chemotherapy, respectively. All patients in neoadjuvant IO+C were alive, and no one suffered from recurrence or death. However, 4 patients in neoajuvant chemotherapy group dead after recurrence or metastasis.”

In discussion: “Second, all patients underwent neoadjuvant IO+C in 2018 or 2019, limiting the insufficient follow up time, the outcomes of PFS and OS were premature and the prognostic impact of major and complete pathological response is not clearly, either.”