Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-23-1669

Reviewer A

• Overall:

Comment 1: o This is a single-center, retrospective analysis looking at perioperative outcomes following thoracic surgery for lung cancer in lung transplant recipients. This is an interesting question for which there is limited previous data. However, there are some inherent limitations in the analysis because the number of patients that received cancer surgery is so low. I think this could be more interesting if the authors talked in more detail about some of the more granular details for the management of these patients like managing immune suppression perioperatively etc and including more detail about transplant outcomes in these patients.
Reply 1: Thank you for pointing out the importance of immunosuppression. Indeed, under the first paragraph of the result section, we only stated the immunosuppressive therapy following LT. For the perioperative management of TS, mycophenolate was discontinued until wound healing was completed. Prednisolone and tacrolimus or ciclosporine were continued perioperatively. In LT patient #2, everolimus was added at the time of lung cancer diagnosis. For the other 5 LT patients, postoperative immunosuppression remained unchanged compared to the preoperative immunosuppression (Table 1).
We reported transplant outcome by describing 4 cases in detail under paragraph 3 of the result section (pathologic characteristics of LT patients) and by showing data on in-hospital and 1-year survival (Figure 2, Table 3). Moreover, ranked postoperative complication according to the Clavien-Dindo classification (Figure 4, Table 3). For a more detailed report about transplant outcome, we added overall survival: All 7 LT patients, who underwent TS for the diagnosis or treatment of lung cancer, of which 6 turned out to have lung cancer, have died after median 10.5 months (range 0.4 to 76.7).
Changes in the text: We added a comment on immunosuppressive therapy in paragraph 1 of the result section (page 7, line 196 to 202) and in paragraph 3 on pathologic characteristics on LT patients for patient #2 (page 8 line 51).

• Abstract:

Comment 2: o For the sentence starting on line 36, “averagely” is an odd word choice. I could consider saying something like “…after 4.2 years on average…” instead.
Reply 2: Wording is corrected to “…after 4.2 years on average…”
Changes in the text: We have corrected the wording on Page 2, line 38-39

Comment 3: o For the sentence starting on line 44, “derived” could be excluded and just say cancer and postoperative complications were more likely after SLT.
Reply 3: Wording is corrected to "were" instead of "derived"
Changes in the text: We have corrected the wording on Page 2, line 48

• Introduction:

Comment 4: o Fine as written

Reply 4: Not necessary.
Changes in the text: No changes.

• Material and methods:

Comment 5: o How often were pulmonary function tests performed on recipients? At every follow up visit?
Reply 5: Thank you for your comment. After lung transplantation (LT), patients were followed up surgically and medically at the outpatient clinic, where they were seen every three months. The visit interval depended on the clinical condition of the patient. At every follow up visit, pulmonary function test (PFT) was performed since PFT is a crucial part of respiratory workup in patients following LT. Besides the assessment of the present pulmonary function, PFT serves essentially to diagnosing any form of chronic lung allograft dysfunction (CLAD).
Changes in the text: Page 5, line 117-125: the chapter "clinical assessment" was changed.

• Results:

Comment 6: o For the pulmonary function data in section 4: how soon post-operatively was the after assessment? Were patients having multiple assessments in subsequent follow up visits? If you have the data, it would be interesting to see if it these were long standing deficits or if the patients recovered at all further out.
Reply 6: Thank you for your comment. As shown in Supplementary table S1 "Median change in respiratory characteristics following LT", the median preoperative, postoperative, and perioperative times between PFT, BGA and 6MWD testing and TS were 25, 17, or 33 days, respectively. As stated in comment 5, LT patients were regularly seen in the outpatient clinic. Following the valuable comment 6, we investigated the course of PFT of each study participant. We added a second supplementary table showing individual respiratory characteristics of 4 LT patients following TS (Supplementary table S2). For patient #6 and 7, no postoperative PFT was available since they were in no condition for PFT and died during the hospital stay following TS. Patient #2 underwent PFT once after TS but have not been able to show up for further clinical follow up visits in the outpatient clinic.
For the data available, all 5 patients underwent PFT within the first 3 months following TS (0.3 to 2.3 months). The last PFT was performed after for 2 individuals within the first postoperative year (11.0 and 7.3 months) and for another 2 individuals more than 5 years after TS (61.9 and 73.1 months). PFT parameters of the short-term group (#1 and 3) who underwent pneumonectomy showed the following development: FVC: -0.19 L and -0.06 L; FEV_1: -0.16 L and +0.30 L; TLC: +1.3% and -4.1%; RV: -9.6% and +16.1%; and DLCO/VA: -15.6%.
For those LT patients following pneumonectomy, dynamic and static lung volumes showed rather decreased relative values.
PFT parameters of the long-term group (#4 and 5) who underwent segmentectomy showed the following development: FVC: +0.61 L and -0.26 L; FEV_1: +0.56 L and -0.38 L; TLC: -7.9% and -21.0%; RV: -17.3% and -36.0%; and DLCO/VA: +14.8% and +19.5%.
For those LT patients following segmentectomy, static lung volumes and CO diffusion seemed to improve (normalized RV, TLC, DLCO/VA).
Changes in the text: On page 9, line 259 to 279, we added the paragraph shown in reply 6.

Comment 7: o Also, I realize it was a small cohort, but for these patients were there any complications from a transplant standpoint? Like episodes of rejection? It would be helpful to know this information to better contextualize the pulmonary function changes.
Reply 7: Thank you for your comment. In Table 1, we already showed that 5/7 LT patients were diagnosed with CLAD. In Supplementary table S2, we assigned CLAD to the respective LT patient and listed the established treatment regimens (e.g. azithromycin thrice a week, pulse corticosteroid therapy, or extracorporeal photopheresis).
Patient #2 suffered from CLAD grade 3, for which he was treated with azithromycin thrice a week, pulse corticosteroid therapy, and regular extracorporeal photopheresis. He deceased within the first year following TS for lung cancer.
Changes in the text: We added the paragraph above on page 7, line 215 to 220.

Comment 8: o For section 5: if this data is available, it might be useful to look at matched historical controls that were not transplant patients but had similar operations for comparable malignancies. It would be useful to context to understand how these outcomes differ based on these being transplant recipient versus complications due to the surgery itself.
Reply 8: We do fully agree with the reviewer's suggestion that a comparison of surgical outcome between patients with lung cancer with or without prior LT should be drawn in order to estimate the effect of transplantation on TS. We added to the result section survival rates from our local lung cancer center stemming from an in-hospital lung cancer registry. We extracted lung cancer patient's demographics, pathologic tumor stage, and histology. Of 2,856 lung cancer patients, 83 lung cancer patients matched to tumor stage (IA, IIB, IIIB and IVA) and histopathology (small cell lung cancer, squamous cell carcinoma, adenocarcinoma) of those lung cancer patients who had underwent prior LT (shown in the Supplementary table S3). The 1-year survival rate of LT patients who were diagnosed with lung cancer was 50 % (3/6) with a median overall survival of 17.6 months, while the 1-year survival rate in the match register cohort was 53% (44/83) with a median overall survival of 13.9 months. Taken together, given the limitation of small sample size, 1-year survival rate (50% versus 53%) and median overall survival (17.6 versus 13.9 months) between LT cohort with lung cancer and the historical lung cancer cohort were comparable.
Changes in the text: We added information on how the historical cohort was established in the method section (page 5, line 117 to 120 and page 6 line 153 to 156) as well as to the ethical statement section (page 14, line 443). Data is presented in Supplementary table S3 and on page 10 to 11, line 316 to 328.

• Discussion:

Comment 9: o For the sentencing starting on 251, I'm not sure if you actually showed this since the PFTs were reduced across the board and it wasn't clear that the extent of subsequent pulmonary dysfunction correlated with other complications from your data.
Reply 9: Correct, we did not show the association of PFT and postoperative complications. Now, we summarized the results from the PFT analysis.
Changes in the text: We replaced the phrase on Page 9 line 277 to 279.

Reviewer B
Comment 1. In the result, LT patient was diagnosed of cancer as early as 0.4 years after lung

transplantation. Did the cancer occur at the native lung or the donor lung? Could you explain the lung allocation system of your clinic?

Reply 1: Patients with end-stage lung disease are evaluated at the department of respiratory medicine and jointly discussed in a LT conference on a regular basis. FDG-PET/CT imaging is a major contributor the initial work up in terms of tumor assessment. Lung cancer was found in the transplant lung 0.4 years after LT, which presumably developed rapidly under immunosuppression.

Changes in the text: No changes.

Comment 2. Lung cancer was diagnosed stage IV at 1.5years after lung transplantation. The stage of lung cancer was very advanced at the time of diagnosis. What is the follow up protocol after lung transplantation? Was there a chance to detect lung cancer earlier?

Reply 2: Since we report on surgical outcome, we present pathologic tumor stage. For patient #3, the initial clinical tumor stage was IIB (cT2 cN0 cM0) during the oncologic workup. But as described under paragraph 3 of the result section "pathologic characteristics of LT patients", histopathologic examination reported a 5.5 cm large tumor mass that showed local invasion of the mediastinum, the great venous vessels and the left atrial wall resulting in a R1 situation, which had not been appreciated by means of the radiological investigation. In the end, a single metastasis of the visceral pleura was identified leading to an unforeseen pathologic stage IVA (PLE, pT4 pN1 pM1a).

Currently, there is no established cancer surveillance screening program for lung cancer in LT patients evidenced by international guidelines. However, we do perform chest radiographs twice a year of all LT patients. For those at higher risk for malignancy (single LT due to COPD or lung fibrosis), we additionally initiate a CT thorax studies on an annual basis.

Changes in the text: No changes.

Comment 3. What is the preoperative and postoperative immunosuppressant protocol for TS patients? What precautious treatments were applied to the TS candidates in order to prevent infections including pneumonia?

Reply 3: All patients presented in this report received immunosuppressive combination therapy (Table 1) as well as prophylactic oral fungal and viral treatment. The specifics of the regimens also depend on whether SLT or BLT was performed.

For the perioperative management of TS, mycophenolate was discontinued until wound healing was completed. Prednisolone and tacrolimus or ciclosporine were continued perioperatively. In LT patient #2, everolimus was added at the time of lung cancer diagnosis. For the other 5 LT patients, postoperative immunosuppression remained unchanged compared to the preoperative immunosuppression (Table 1).

We added a Supplementary table S2, in which we assigned chronic lung allograft dysfunction (CLAD) to the respective LT patient and listed the established treatment regimens (e.g. azithromycin thrice a week, pulse corticosteroid therapy, or extracorporeal photopheresis).

Patient #2 suffered from CLAD grade 3, for which he was treated with azithromycin thrice a week, pulse corticosteroid therapy, and regular extracorporeal photopheresis. He deceased within the first year following TS for lung cancer.

Changes in the text: We added a comment on immunosuppressive therapy in paragraph 1 of

the result section (page 7, line 196 to 202).

Comment 4. 1year survival after lung resection was only 50% in six patients. Then could it be suggested that lung resection profits the lung cancer patients after lung transplantation? Could chemotherapy or radiotherapy be more beneficial for the patients?
Reply 4: Thank you for the comment. In paragraph 3 of the result section, we presented several courses of lung cancer in LT patients. For example, the LT patient who was diagnosed with small cell lung cancer, did receive two courses of platinum-based chemotherapy prior to TS. Chemotherapy exerts additional immunosuppressive effects in LT patients that may increase risk for infections (e.g. neutropenic fever), thus add harm to the patient as well. On the other hand, wound infection and would healing is hampered by immunosuppressive therapy. As describe in reply 3, immunosuppressive therapy was adapted to surgical procedure.
Changes in the text: We added a comment to patient #1 on page 8, line 241 to 242.

Reviewer C
This is an institutional study to aim at investigating the impacts of surgical resection for lung cancer after lung transplantation on outcomes.
The study includes a total of 6 patients who underwent surgical resection for lung cancer after lung transplantation between 2000 and 2020 while 248 patients underwent lung transplantation during the study period for twenty years. They conclude that surgical resection for lung cancer after lung transplantation is feasible but carries a high risk of postoperative complications.

In line with a very small number of the patients enrolled in the study, essentially, the report is a case series of those who underwent lung resection for lung cancer after lung transplantation. Of note, half of them (3/6) underwent pneumonectomy, which I believe contributed to their high mortality.

Given all together, it is difficult to make any conclusive statements aside from the experiences with ‘a case series’ while the current discussion appears to be redundant and somewhat difficult to follow.
Reply 1: We agree with the reviewer's comment that the sample size is rather small to draw any robust conclusion from the analysis. The small sample size is also rather due to the rare event of TS. We hope to present some new insights into TS for lung cancer in LT patients.
To compared outcome of LT patients who underwent TS for lung cancer with lung cancer patients without LT, survival indices were collected from a matched retrospective cohort stemming from the same thoracic surgery department which performed TS for lung cancer in LT patients. Therefore, we added to the result section survival rates from our local lung cancer center stemming from an in-hospital lung cancer registry. We extracted lung cancer patient's demographics, pathologic tumor stage, and histology. Of 2,856 lung cancer patients, 83 lung cancer patients matched to tumor stage (IA, IIB, IIIB and IVA) and histopathology (small cell lung cancer, squamous cell carcinoma, adenocarcinoma) of those lung cancer patients who had underwent prior LT (shown in the Supplementary table S3). The 1-year survival rate of LT patients who were diagnosed with lung cancer was 50 % (3/6) with a median overall survival of 17.6 months, while the 1-year survival rate in the match register cohort was 53% (44/83)

with a median overall survival of 13.9 months. Taken together, given the limitation of small sample size, 1-year survival rate (50% versus 53%) and median overall survival (17.6 versus 13.9 months) between LT cohort with lung cancer and the historical lung cancer cohort were comparable.

Changes in the text: We added information on how the historical cohort was established in the method section (page 5, line 117 to 120 and page 6 line 153 to 156) as well as to the ethical statement section (page 14, line 443). Data is presented in Supplementary table S3 and on page 10 to 11, line 316 to 328.

Reviewer D

Frille et al present an excellent and comprehensive series of 7 individuals who underwent surgical resection after lung transplant surgery for lung cancer (NSCLC, and one SCLC). They did a wonderful job putting together the information, staging, data, and characteristics of these patients. Yes, the case series is small. However, there is a paucity of patients who develop lung cancer after lung transplantation. While their data is not overwhelmingly novel in this population of patients, the more data we have in the literature will continue to help build knowledge on this population. More importantly, they address lung transplant recipients who undergo oncological resections for lung cancer. Most of the literature in this area demonstrates that lung transplant recipients do not typically receive guideline directed oncological treatment for their lung cancer due to multitude of reasons, but this demonstrates the significant risks and benefits of pursuing oncological resection in this population. I have no major concerns with the manuscript. The data is clearly presented, the figures are clear and highlight the results well, and the tables are easy to read. Given these reasons, I recommend the publication of this manuscript without any reservations.

Reply: Thank for your comment, no changes to the manuscript.

Reviewer E

The authors are congratulated for their manuscript dealing with thoracic surgery following lung transplantation. Most of the indications occurred in patients undergoing single lung transplantation, and developed in the native lung. As currently nearly 80% of the procedures are double lung transplantations, it's expected that the incidence may decrease. Going to the paper, it's well written and the authors have made an updated review of the problem. I have 2 minor comments:

-How was the patients managed with regard to immunossupression treatment after surgery for NSCLC? The authors should comment on this, as there is the problem with how to manage immunossupression and chemotherapy...

-References are quite old, some of them. I know that not many papers have been published dealing with this issue, but I wonder if they could update them.

Again, congratulations for the paper. It's really important for the transplant community.

Reply: Thank for your comment, no changes to the manuscript.