

Peer Review File

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Reviewer A

In introduction

Comment 1: Pneumonectomy is treatment option not only for the cancer but also other various disease (for example massive hemoptysis due to fungal disease, bronchiectasis, intractable tuberculosis etc). It is not the only indication for oncological problem.

It need to include more benign disease indications and add references.

So I recommend remove the “oncological” in 1st sentence.

Reply 1: We agree. The word "oncological" has been removed. The references were added in the Introduction.

In Methods

Comment 2: Did you obtain those informed consent from all participants, really?

You enrolled patients since 2006 and presented that this study is cross sectional study from medical records. (retrospective study)

Reply 2: Thank you, we fully agree. The syntax used was confusing. The Bioethics Committee of the Poznan University of Medical Sciences requires ethics approval and the need to obtain consent to collect, analyze, and publish the retrospectively obtained and anonymized data even for this non-interventional study. Our department applied for ethics approval. Appropriate consent for the analysis and publication of anonymized data has been obtained (No. 948/21). This part was changed in the manuscript text, in the Methods section

Comment 3: If you enrolled only lung cancer patients as you describe in methods, you should add this in title, abstract and so on.

Reply 3: This has been changed in the appropriate sections.

Comment 4: If right pneumoectomy has the higher risk of BPF than left side, additional subanalysis of Rt. pneumonectomy will be meaningful.

Reply 4: Thank you, we agree. We thought so too. We did this analysis, but we did not get any significant results. We also thought that the propensity score match could partially explain this difference. We send the results of this analysis in the attachment. Overall, we obtained similar results to those previously presented in the manuscript.

Reviewer B

This is an interesting and important topic addressed by the authors of this manuscript. The morbidity and mortality of pneumonectomy including postop BPF remains significant and is largely responsible for more and more patients who would otherwise require pneumonectomy for NSCLC being treated non surgically. This is a very large experience, so the authors are to be congratulated on this effort. The high risk of BPF after right pneumonectomy has been well established in multiple publications, however. Additionally, there are several issues which are not addressed and would strengthen the manuscript significantly including variables such as induction chemoradiation therapy and the need/length of postoperative ventilation, both of which have been cited in previous publications to be significant risk factors for postoperative BPF. From a statistical standpoint, the authors admit multivariable analysis could not be applied to these data which is a limitation.

Comment 1: How many patients needed reoperation for BPF?

Reply 1: Out of 34 patients with a fistula, 6 were reoperated. The purpose of the reoperation was resuturing of the bronchial stump. In 2 patients, an unsuccessful attempt was made to fix the stump with tissue glue. Most patients required fenestration and, after the fistula had healed - myoplasty.

Comment 2: What type of operations were used for BPF repair?

Reply 2: At the early stages of BPF we tried to close the micro-BPF with tissue glue during bronchoscopy. Alternatively, a re-thoracotomy was performed with revision of the bronchial stump and resuturing. At advanced stages, we performed the three stages treatment:

-stage I - pleural drainage and antibiotic therapy,

-stage II - fenestration,

-stage III - myoplasty, after the BPF healed (from 6 to 9 months).

Comment 3: How many patients died from BPF and what was the BPF non-fatal morbidity?

Reply 3: 7 people died in hospital, 22 died later, including 7 (20.0%) within 30 days of surgery, and another 5 within 90 days of surgery - total 90-day mortality at the level of 12 people (35.3%).

Comment 4: Although comparing different closure and buttress techniques, there were no apparent differences in BPF incidence but did any closure technics suture/sewn or buttress material that reduced the morbidity or mortality of BPF?

Reply 4: Unfortunately not. It was analyzed in long-term follow-up and the possible effect on 30- and 90-day mortality was assessed. The differences were not statistically significant.

Comment 5: Some of the syntax is a bit confusing, for example beginning on line 114 the sentence states that all patients had diffusing capacity measured but the following

sentence gives the reader the sense that diffusing capacity was obtained selectively. In addition, pulmonary function tests, diffusing capacity of the lung for carbon monoxide, and capillary blood gas screening were all employed to assess respiratory efficiency. If indicated, echocardiography, exercise testing, and diffusing capacity for carbon monoxide were performed.

Reply 5: there has been a mistake. Diffusing capacity of the lung for carbon monoxide is routinely performed on admission at our department to each patient prior to the planned pneumonectomy. This has been corrected in the Methods section.

Comment 6: In Table 1. MI and History MI seems redundant and confusing

Reply 6: This has been corrected.

Comment 7: Whether the stage of NSCLC was clinical or pathologic was not provided in the manuscript or table legends.

Reply 7: We meant pathological stages, from grade I to IV. The numbers of patients in each stage of pathological advancement are presented in Table 1.

Reviewer C

Skrzypczak and colleagues present an original manuscript entitled “The technique of stump closure has no impact on post-pneumonectomy bronchopleural fistula- a cross-sectional study”. In this single-institutional retrospective study, the authors accessed the risk factors for BPF and the impact of bronchial stump closure technique on the occurrence of BPF in 455 post pneumonectomy patients. Although surgical devices and techniques have been improved recently, BPF after pneumonectomy remains a crucial issue for thoracic surgeons. This paper would be of interest to the readers of this journal.

I have the following questions for the authors, which should be addressed in a revision.

Comment 1: 1. How many in-hospital deaths after BPF were recorded?

Reply 1: 7 people died in hospital, 22 died later, including 7 (20.0%) within 30 days of surgery, and another 5 within 90 days of surgery - total 90-day mortality at the level of 12 people (35.3%).

Comment 2: 2. The bronchial stump was closed by the staplers in 204 patients and by the manual suturing in 251 patients. In addition, the stump was covered in 198 patients and not covered in 257 patients. How did surgeons make a decision for bronchial closing method?

Reply 2: The closure of the bronchial stump (stapler vs. manual suture) or tissue buttressing was an individual decision of the surgeon. Closing the bronchus with a stapler requires more space, especially on the right side. In a situation when there was

not much of a bronchial fragment free from neoplastic infiltration, the bronchus was often closed through the manual suture.

Comment 3: 3. And the several types of tissues were used for buttressing the stump. How did surgeons select the tissue from IMF, pericardial fat pad, or pleural flap.

Reply 3: The selection of the tissue buttressing material was also an individual decision of the surgeon.

Comment 4: 4. Is there any association between the mortality after BPF and the method used for stump closure? For example, in my opinion, the mortality in patients whose stump was covered may be lower than that in patients whose stump was not covered. It is because covering tissue may prevent bronchial stump from a direct contact with pulmonary artery. I mean that the incidence of the broncho-arterial fistula should be decreased in such patients even if BPF occurred.

Reply 4: There was no association between the in-hospital, 30-day, and 90-days mortality and the method used for stump closure.

Reviewer D

The authors' study reported the risk factors of BPF after pneumonectomy. The presented data included multiple cases that were well analysed; however, there are some concerns regarding this study, as noted below.

Comment 1: 1. Based on your data, pneumonectomy was performed for many patients in your institute. Currently, in other countries, the number of pneumonectomies has been decreasing because of the developments in chemotherapies, surgical techniques, decrease in the incidence of advanced lung cancer, and so on. Please describe the reasons for the need to perform pneumonectomy on these patients.

Reply 1: We agree. We are also limiting the number of pneumonectomies performed annually in our center - we attach the revised Figure 1. It is, of course, influenced by the possibility of neoadjuvant therapy and minimally invasive techniques, including sleeve-lobectomy, the annual frequency of which increases every year. However, it should be remembered that for approximately 10% of people with centrally located NSCLC, pneumonectomy is still an effective treatment.

Comment 2: 2. Looking at the data, stage I and II cases constitute 43% of the total pool. In general, pneumonectomy should not be necessary for such patients. Please state the reasons for performing pneumonectomy on the patients, including those at stages III and IV.

Reply 2: According to TNM8, grade I NSCLC contains stages up to T2aN0M0, so tumors that can be up to 4 centimeters in size. The tumor may infiltrate the hilum of the lung or the main bronchi, which could require even a pneumonectomy in some patients. Similarly, grade II can include grades up to T3N0M0 or T2BN0M0 - that is, large tumors that may require pneumonectomy due to their central location. Stage III - of course, patients with N2 features should not be operated on, but stage III patients may also include N1 features - T3N1M0, T4N0M0 and T4N1M0. If there is N1 feature, the metastases could be located in the lung's hilum and we can not avoid the pneumonectomy. In our database, stages IV are single cases - most often they were patients with a lung tumor and a single metastasis in the brain that was successfully treated surgically.

Comment 3: 3. To confirm your criteria and technical aspects for the pneumonectomy cases, please describe the cases where bronchoplasty was performed in your institute.

Reply 3: We limit the number of pneumonectomies performed annually in our center (revised Figure 1). If only anatomical conditions allow, we always try to consider vascular and bronchial resections and perform less extensive resections. Because of this, the annual percentage of pneumonectomies is declining and sleeve-lobectomies are increasing. For example: in 2013, we performed 55 pneumonectomies and 26 sleeve-lobectomies, in 2016 - 39 pneumonectomies and 30 sleeve-lobectomies, and 2020 - 26 pneumonectomies and 25 sleeve-lobectomies.

Comment 4: Please consider propensity score matching for statistical analysis. Please do share your thoughts on this aspect.

Reply 4: We also thought that the propensity score match could partially explain this difference. Unfortunately, we did not have all the data mentioned by you, so we adopted a slightly different model. We send the results in the attachment. Overall, we obtained very similar results to those presented in the manuscript.

Comment 5: 5. There is no mention of the criteria for diagnosis of BPF after pneumonectomy. Please describe on this point.

Reply 5: The diagnosis of BPF was made based on clinical symptoms followed by endoscopy. This has been added in the Methods section.

Comment 6: 6. I understand the difficulties in grading BPF; however, there could be differences in the grading of BPF with or without tissue buttressing. Please elaborate on this aspect.

Reply 6: Yes, fistula grading is complicated to pin down. However, we do not use a special BPF grading at our department. Regardless of the stage of advancement, BPF treatment in our center is similar.

Comment 7: 7. Please describe the treatment for BPF, which should be similar to the grading of BPF, with potential investigation of the effects of tissue buttressing.

Reply 7: At the early stages of BPF we tried to close the micro-BPF with tissue glue

during bronchoscopy. Alternatively, a re-thoracotomy was performed with revision of the bronchial stump and resuturing. At advanced stages, we performed the three stages treatment:

- stage I - pleural drainage and antibiotic therapy,
- stage II - fenestration,
- stage III - myoplasty, after the BPF healed (from 6 to 9 months).

Out of 34 patients with a fistula, 6 were reoperated. The purpose of the reoperation was resuturing of the bronchial stump. In 2 patients, an unsuccessful attempt was made to fix the stump with tissue glue. Most patients required fenestration and, after the fistula had healed - myoplasty. Tissue buttressing did not significantly affect the treatment outcomes and 30 and 90 days of survival.

Reviewer E

The authors have performed an excellent review of their experience of pneumonectomies and BPFs over a period of 11 years. It is impressive that they performed 455 pneumonectomies over this short period at a single institution (as pneumonectomies should be decreasing in number in this era). Interestingly, they found that neither the technique nor the buttressing makes a difference in leak rate, but indeed the side of surgery (right vs. left) does. I only have a few minor questions/comments:

Comment 1: 1. Can the authors include neoadjuvant therapy used in their analysis as that can significantly impact BPF rate, esp radiation in the field.

Reply 1: There were no patients in the study group who underwent neoadjuvant therapy, but we know of course, that, according to the literature, it is an essential risk factor for BPF.

Comment 2: 2. Page 9, line 171 has a typo "steadily diminished om2006-2012 compared to that from 2013-2017" should read as "steadily diminished from 2006-2012 compared to that from 2013-2017".

Reply 2: The typo has been corrected.

Comment 3: 3. Table 1 - smoking and date when smoking was quit prior to surgery is extremely important for this study as well as prior radiation or steroid use. This information must be included.

Reply 3: In our group, 66% of patients smoked before the surgery and 34% had never smoked or quit smoking before the surgery. Unfortunately, we do not have data on the exact number of days before the procedure that patients quit smoking for the entire period from 2006 to 2017.

Comment 4: 4. Can the authors include "Days when BPF developed from date of surgery" in Table 2?

Reply 4: Unfortunately, due to the very long follow-up time, we do not have detailed data on days when BPF developed from the surgery date. We have indirect information - on what day after the pneumonectomy the reoperation/endoscopy/fenestration took place, but this does not fully answer the question asked.

Comment 5: 5. Finally, perhaps a propensity match of right vs left pneumonectomies based on some common risk factors in both groups (neoadjuvant therapy, radiation, smoking, diabetes) can elucidate what predisposes a right pneumonectomy to BPF vs. the left.

Reply 5: We also thought that the propensity score match could partially explain this difference. Unfortunately, we did not have all the data mentioned by you, so we adopted a slightly different model. We send the results in the attachment. Overall, we obtained very similar results to those presented in the manuscript.

Reviewer F

First of all, I would like to show my appreciation to all contributing authors for analyzing large number of patients underwent pneumonectomy. As you described, pneumonectomy is rather challenging surgical procedure, still, to date. I, as a thoracic surgeon, would make every effort to avoid pneumonectomy.

The data you have provided were indeed consistent with what we have experienced and there is no argue. However, the message you brought might give us rather biased impression that we might not need stump closure any longer.

Comment 1: Closure of the stump does not prevent incidence of BPF, because it would not supply blood flow especially in immediately after surgical resection. However, when BPF occurred due to ischemia at anastomosis, for example, the stump covering would enclose the area not to spread infected or necrotic tissues into the pleural cavity, which might eventually lead to empyema. Stump closure and incidence of BPF may not correlate, however, we still do not know if covering is beneficial in postoperative patients care. I would like you to evaluate intraoperative procedures which correlate to the incidence of BFP in your future study.

Reply 1: We agree, so we conducted a study using indocyanine green in our department, which was published in 2013. The results of these studies led to a change in the surgical technique in our department - the less frequent buttressing of the bronchial stump. However, our results still do not clarify that bronchial stump buttressing is the wrong technique and should be avoided. Thank you, we would like to evaluate the intraoperative procedures to the incidence of the BFP.

Reviewer G

Congratulations to the authors for showing a big experience on pneumonectomies. Their study shows no differences in the appearance of BPF according to the technique.

Some questions:

Comment 1: The pericardial fat pad had a pedicle or was free fat?

Reply 1: It was always a pedicle fat pad.

Comment 2: All the manual sutures were continuous? Have you ever done single stitches and compared the two manual techniques?

Reply 2: Yes, we have always used a continuous manual suture on bronchial stumps. Only a few cases were the additional single sutures used when, for example, the tightness of the stump was not sure.