AMJ AME MEDICAL JOURNAL
AN OPEN ACCESS GENERAL MEDICAL JOURNAL

Peer Review File

Article information: https://dx.doi.org/10.21037/amj-22-19

Reviewer A

The authors non-systematically reviewed the topic of the influence of the lung resections to the postoperative lung function. They found that the existing guidelines should be adhered in the everyday practice. Some evidence gaps and specific situations given in the review should be taken into consideration as well.

I have the following concerns:
Abstract
Comment 1
The purpose is unclear in the background.
I recommend moving the opening statement in the Methods section to the background.
Answer: done as suggested in the revised version
Changes in the text: …
Abstract; *Background and objectives*
As the reliable prediction of postoperative complications, especially in patients at risk, may be challenging, a non-systematic review of the literature on the topic of the influence of the lung resections to the postoperative lung function was done".
Accordingly, the opening statements was removed from the "Methods" section

Comment 2
The following statement is not clear in meaning, please clarify its content.
(Line20-22)
The prediction of the postoperative lung function after lobectomy is reliable in many aspects, but the influence of the particular type of the lobectomy requires further analysis.
Answer: the term "particular type of the lobectomy" refers to upper/lower and left/right lobectomy. It is clarified in the revised version.
Changes in the text: … but the influence of the upper vs. lower lobectomy either independently, or depending of the side of the operation, requires further analysis.

Introduction
Comment 3
Please provide references in the following sentence.
(Line37-38)

After the lung resection, the lung function recovers till some point, but it may take 1- 2 weeks to more than 2 months to reach the desired/predicted value.

Answer: done as suggested in the revised version

Changes in the text: After the lung resection, the lung function recovers till some point, but it may take 1- 2 weeks to more than 2 months to reach the desired/predicted value (1, 2).

Comment 4

The purpose is unclear in the introduction.

I recommend moving the opening statement in the Methods section to the introduction.

Answer: done as suggested

Changes in the text (in the revised version from the line 6 till the end of the "Introduction" section):

"A non-systematic review of the literature on the topic of the influence of the lung resections to the postoperative lung function is performed with the following aims: first, to avoid unjustified upfront rejection from surgery of some patients that at first sight may seem as unfit for surgery; second, to avoid offering surgery to patients, who are under the functional limit for safe surgery according to the existing evidence."

The preexisting text was deleted; ~~"That is why the awareness of the pattern of the lung function change after the lung resection and available methods for its prediction, with related limitations and pitfalls, is of utmost importance for the appropriate preoperative patient selection for two reasons":~~

Methods

Comment 5

The formula used (with descriptors) should be included in the search for the articles included in this review.

Answer: done as suggested, the combination of terms is included within the "methods" section of the revised version

Results

Late postoperative lung function recovery

Comment 6

It is very interesting that COPD differentially affects postoperative lung function.

The authors cite only one paper. Please cite other papers and provide additional results, as the impact of COPD on postoperative lung function is one of the main findings of this review.

Answer: the reviewer's comment 6 relates to the paragraph "Late postoperative lung function recovery", where only differences in the postoperative lung function recovery

between COPD and non-COPD patients were reported and supported by one reference specifically addressing that aspect. Other aspects of the influence of COPD on postoperative lung function are given in the particular paragraph "COPD patients", after the paragraph VATS vs. thoracotomy and supported by additional five references.

However, as suggested by the reviewer, to strengthen the evidence (and in the same time to challenge the widespread attitude that "almost all patients can tolerate a lobectomy"), in the revised version we included data from additional two studies specifically focused on differences in postoperative lung function between COPD- and non-COPD patients after lobectomy.

Changes in the text (from the line 4 of the 4th paragraph till the end of that paragraph): Rare studies specifically addressing differences in postoperative lung function changes between COPD and non-COPD patients help to avoid this pitfall. *The average loss of FEV1 was about 8.6%–19.0% after lobectomy for non-COPD patients, whilst the postoperative change of FEV1 in patients with COPD was between −18.3% and 5%. COPD (new ref. 10). Such an interval of values can be explained by the quality of the resected lung tissue. Indeed, patients with a low preoperative FEV1 and COPD index > 1.2 may have restrictive diseases and can be expected to sustain a 5% to 20% loss of function (FEV1) after lobectomy. Unlike them, patients with a COPD index <1.0, in whom the nonfunctioning lobe has remaind, seem to lose higher percentage of their FEV1 with resection of a functioning lobe (new ref. 11). It was also demonstrated that the reduction in FEV1 was lower in COPD vs non-COPD patients (6% vs 13%, p = 0.0002), but residual postoperative FEV1 values were lower in COPD patients as well (62% vs 74%, p < 0.0001), despite much lower FEV1 loss compared with preoperative values (new ref. 12). The presented date clearly confirm the need to take all these elements into account during the preoperative patient selection.

COPD patients

Comment 7

The meaning of lung hernia is ambiguous. Please clarify with references.

Answer: In the revised version this point was clarified with reference.

Changes in the text: In patients with a pneumonectomy, a definitive remodeling of the chest exists, with mediastinal shift towards the operated side. ~~and sometimes a major lung hernia towards the operated side as main features~~. Overdistension of the remaining lung occurs as an adaptive response. It was demonstrated that patients with a low body mass index (BMI) (< 20 kg/m^2) showed a significantly greater degree of lung herniation towards the operated side than those with a high BMI (≥ 20 kg/m^2) (**new ref.** Fujimoto et al. Thorac Cardiovasc Surg 2002; 50(5): 292-295). Although COPD itself has no effect on lung herniation, in COPD patients this can cause a lung volume reduction effect, …

Site of lobectomy and postoperative lung function

Comment 9

Please cite references in the following sentence.

(Line 193) Despite sufficient amount of evidence…

Answer: as suggested, in the revised version some references were included supporting this statement. In fact, the subsequent literature search showed that the term "certain amount of evidence" appears to be more appropriate than "sufficient amount",,, In the revised version, the term "sufficient" was replaced by "certain" and supported by references.

Changes in the text: Despite ~~sufficient~~ certain amount of evidence (20, 26, 27)

Comment 10

(Line 199) analysed→analyzed

Answer: corrected as suggested

Changes in the text: Another study analyzed the duration…

Prediction of the postoperative lung function

Comment 11

Please cite references in the following sentence.

(Line 212) Several methods of the postoperative lung function prediction have been confirmed as reliable in terms of the FEV1 prediction 3-6 months after surgery.

Answer: in the original version, in the paragraphs appearing after the aforementioned sentence, these methods were listed with references (listed below). If we included them immediately after the aforementioned statement, each of them would have to be re-cited once again upon mentioning each method. It would be embarrassing for the reader. That is why we did not change the text, we only listed these references here for the reviewer's insight.

35. Juhl B, Frost N. A comparison between measured and calculated changes in the lung function after operation for pulmonary cancer. Acta Anaesthesiol Scand Suppl 1975; 57: 39-45.

36. Nakahara K, Monden Y, Ohno K, Miyoshi S, Maeda H, Kawashima Y. A method for predicting postoperative lung function and its relation to postoperative complications in patients with lung cancer. Ann Thorac Surg 1985; 39:260-5.

37. Wu MT, Pan HB, Chiang AA, Hsu HK, Chang HC, Peng NJ et al. Prediction of postoperative lung function in patients with lung cancer: comparison of quntitative CT, with perfusion scintigraphy. Am J Roentgenol. 2002; 178: 667-672.

38. Eslick EM, Bailey DL, Harris B, Kipritidis J, Stivens M, Li BT et al. Measurement of preoperative lobar lung function with computed tomography ventilation imaging:

progress towards rapid stratification of lung cancer lobectomy patients with abnormal lung function. Eur J Cardiothorac Surg 2016; 49:1075-82.
39. Pai DB, Quagliatto R Jr, Toro I, Kunha Neto C, Etcbehere E, Camargo E. The use of SPECT in preoperative assessment of patients with lung cancer. Eur Respir J 2004; 24: 258-62.
40. Ohno Y, Koyama H, Nogami M, Takenaka D, Matsumoto S, Yoshimura M et al. Postoperative lung function in lung cancer patients: comparative analysis of predictive capability of MRI, CT and SPECT. Am J Roentgenol 2007; 189: 400-8.
41. Brunelli A, Xiume F, Refai M, Salati M, Marasco R, Sciarra v et al. Evaluation of expiratory volume, diffusion capacity and exercise tolerance following major lung resection: a prospective follow up analysis. Chest 2007: 131: 141-7.

Comment 12

Please cite references in the following sentence.

(Line 213) However, it was demonstrated that the FEV1 can be overestimated during the first postoperative days, when, in fact, the most of the severe complications may occur.

Answer: in the sentence following the one cited by the reviewer ("…it was clearly demonstrated that on post-operative day 1 after lobectomy, the actual FEV_1 was 30% lower than predicted (1).), the above mentioned statement is supported by the corresponding reference. That is why we did not include this reference after the first sentence.

Comment 13

(Line 221) analysed→analyzed

Answer: corrected as suggested

Changes in the text: "… meta analysis of 17 studies analyzed…"

Comment 14

This section contains the central results of the paper.

Please provide a table of the papers cited in the following statement. In that table, please summarize the author, year, number of cases, and method of respiratory function assessment.

(Line 221-)

A recent meta analysis of 17 studies analysed the accuracy of the postoperative FEV1 prediction of different techniques: segment counting, subsegment counting, perfusion

scintigraphy, ventilation scintigraphy, single photon-emission computer tomography (SPECT), CT volume and density and CT volume and partial density.

Answer: done as suggested in the revised version. A table was created with requested data.

Changes in the text: a completely new table (table 1) is created

Comment 15

The example of predictive respiratory function is unnecessary.

Answer: in the revised version, the example is removed

Changes in the text: ~~In order to express the obtained values in percent of predicted values, the following eqution is to be used (example):~~

~~$_{preop}FEV_1$ = 1450 ml (50%); calculated ppoFEV_1 is 1150 ml~~
~~ppoFEV_1(%) = (50x1150)/1450 = 57500/1450 = **39,6%**~~

Some specific considerations:

Comment 16

(Line 314) The parenthesis after "purely" is a misnomer.

Answer: the parenthesis is deleted in the revised version, typing mistake

Changes in the text: severe mixed or purely ~~)~~restrictive disorders

Comment 17

Please cite references in the following sentence.

(Line 298-300)

This is a known phenomenon, attributed to transitory decrease of the small airways' tonus under this type of therapy, so that these patients should be carefully monitored, rather than being upfront rejected from surgery.

Answer: in the revised version the requested references are included with additional two sentences additionally clarifying this phenomenon.

Changes in the text: This is a phenomenon known as paradoxical response to bronchodilation (new ref. 56)~~.~~ Although it is attributed to transitory decrease of the small airways' wall tonus and subsequent collapse during the forced expiration under this type of therapy, the exact mechanisms are not clear. They include incorrect inhaler use, bronchospasm from the propellant or the benzalkonium chloride, chlorofluorocarbons, and oleic acid contained in inhalers were suggested as possible causes. (new ref. 57-59). Airway thickness is significantly increased in the paradoxical BDR group, and may reduce the response to bronchodilators (new ref. 60). Paradoxical bronchoconstriction after short-acting beta-agonists was suggested as a possible mechanism as well (new ref. 61). These patients should be carefully monitored, rather

than being upfront rejected from surgery.

Comment 18

Please cite references in the following sentence.

(Line 321-322)

Furthermore, the preservation vs. scarifying of the phrenic nerve during surgery has for a long time been considered as non-relevant for the postoperative lung function.

Answer: The reference for this statement is the same as the existing reference (40) in the sentence following the one the reviewer addresses (P. Ugalde et al. Ann Thorac Surg 2008; 86: 1745-1752. The original statement from the "discussion" section of the cited source is: *"In persons with only one lung, however, it is a common belief that loss of diaphragmatic motion due to phrenic nerve injury has little or no effect on respiratory function because there is no underlying lung."*

Conclusions

Comment 19

The following statement is not clear in meaning, please clarify its content.

(Line20-22)

The prediction of the postoperative lung function after lobectomy is reliable in many aspects, but the influence of the particular type of the lobectomy requires further analysis.

Answer: as clarified in the answer to "comment 2", the term "particular type of the lobectomy" refers to upper/lower and left/right lobectomy. In the revised version, we modified the conclusion accordingly.

Changes in the text: "… but the influence of the upper vs. lower lobectomy either independently, or depending of the side of the operation, requires further analysis"

Others

Comment 20

Throughout the text, please supplement abbreviations with their full names.

VATS, COPD, FEV, FVC, VC, DLco, LVR, LF, Tiff, p.op. d, and Kco.

Answer: done as suggested throughout the text with all the abbreviations except for FEV1 and COPD, given the frequency of their appearance. Besides, each abbreviation was preceded by the full name upon the first appearance in the text.

Comment 21

Lighting is visible in Figures 2 and 4, and the figures are distorted.

Answer: that is true, several attempts to eliminate it by using available PC-tools failed.

Comment 22

Change the units of arterial blood gas analysis in Figure 3 to mmHg or Torr.

Answer: the units in Figure 3 are changed into mmHg in the revised version

Reviewer B

In this manuscript, the author performed non-systematic review of the literature on the topic of the influence of the lung resections to the postoperative lung resection.

I consider that there are some important issues to improve.

First, the most concern is the conclusions of this review article are unclear. What does author want to conclude in this article? What did the author want to clarify? The author mentioned the adherence of guidelines in conclusion paragraph, what is guidelines? What and how does author want to change?

Answer: the aim of the review article is not that the author should conclude something himself, but rather to present the evidence and uncertainties in a way that reader should be able to use these data in the daily praxis. The current evidence gaps are clearly pointed out. However, although it is not possible to draw a single conclusion from the evidence of many different aspects of the problem, in line with the reviewer's comment and in order to make the "conclusion" more clear, we included an additional sentence in the conclusion, stating that the preoperative lung function assessment is a dynamic process and that the published data should be used cautiously, with the awareness of the presented evidence gaps, uncertainties and controversial data as well.

Related to guidelines, the "ERS/ESTS guidelines on fitness for radical therapy in lung cancer patients", published in 2009. is mentioned, because this text summarizes a comprehensive evidence overview and several practical issues that can facilitate decisions in the everyday practice.

Changes in the text:

Conclusion:

The prediction of the postoperative lung function after the lung resection is currently the standard in most of the centers. Both the postoperative lung function loss and recovery are well documented and both should be taken into account during the lung function prediction. In COPD patients the predicted postoperative lung function parameters may be initially underestimated vs. non COPD patients, but COPD patients have the limited capacity of later lung function improvement. The prediction of the postoperative lung function after lobectomy is reliable in many aspects, but the influence of the upper vs. lower lobectomy either independently, or depending of the

side of the operation, requires further analysis. Issues related to pneumonectomy are sufficiently evidence-based and combining of lung function analysis and cardiorespiratory risk assessment is now an accepted standard. The cut-off values for safe surgery given in the existing guidelines should be adhered, taking into account the above mentioned evidence gaps and issues given under ”specific considerations” of this text. In brief, the preoperative lung function assessment is a dynamic process and the published data should be used cautiously, with the awareness of the presented evidence gaps, uncertainties and controversial data as well.

Second, the author mentioned only about lobectomy and pneumonectomy, not included segmentectomy. From recent studies, pulmonary segmentectomy for early-stage lung cancer has been increased in worldwide. The assessment of segmentectomy should be done.

Answer: done as suggested, a new text was included before the section “Specific considerations”

Changes in the text:

Functional aspects of anatomical segmentectomy

Before presenting the evidence about functional effects of anatomical segmentectomy, it should be mentioned that, since the publication of the Lung Cancer Study Group Trial, dealing primarily with oncological aspects of segmentectomy vs. lobectomy, it has been suggested that segmentectomy brings nonsignificant, if any, functional advantage over lobectomy (45). In fact, in that trial there were no significant differences only in postoperative FVC between patients with lobectomies vs. limited resections, whilst a significant benefit of limited resection in preserving FEV_1 was demonstrated. Despite this, the authors’ conclusion that there was no functional advantage of limited resection compared with lobectomy, continued to be widely accepted. A similar conclusion appeared after the study of Takizawa and coworkers who compared patients with segmentectomy and lobectomy and found that the choice of the procedure had no effect on postoperative forced vital capacity at 12 months, although a significant impact on postoperative FEV_1 was demonstrated (46). Both of these studies have suggested that lobectomy should remain the procedure of choice despite the slight functional advantage in favor of limited resection.

During the past 20 years anatomical segmentectomy is in the widespread use for stage one lung cancer smaller than 2 cm in diameter and is considered as advantageous vs. lobectomy because it preserves the lung function, and allows patients to benefit from eventual future resection in case of metachronous lung cancer as well (47). The pool of evidence about functional effects of segmentectomy increases and in general supports such a statement, although some conflicting and opposite results were

also reported,

In the study of Tane and co-workers with well matched groups (74 VATS segmentectomies and 74 VATS lobectomies), the postoperative lung function was significantly better preserved in the segmentectomy than in the lobectomy group (48). The same study demonstrated that after both segmentectomy and lobectomy, the regional forced expiratory volume in 1 second of the ipsilateral non-affected lobe was increased in comparison with the preoperative value, whereas that of the residual lobe rescued by segmentectomy was decreased. Interestingly, the preservation rate of the residual lobe inversely correlated with the extent of the resected segment, possibly because of inflation of the unaffected ipsilateral lobe causing limited expansion of the residual lobe. Conversly, the preservation rate of the unaffected lobe directly correlated with the extent of the resected segment. In other words, the larger the extent of resection of the segment, the greater the increase in the lung function of the ipsilateral nonaffected lobe.

The similar functional advantage of segmentectomy was demonstrated in the study on 147 patients with lobectomy and 54 patients with segmentectomy for stage I non–small cell lung cancer, where the preoperative lung function being significantly worse in the segmentectomy group (FEV_1 75.1% versus 55.3%; $p < 0.001$) (49). After one year, in the lobectomy group, significant drops in forced vital capacity (85.5% to 81.1%), forced expiratory volume in 1 second (75.1% to 66.7%), maximum voluntary ventilation (72.8% to 65.2%), and diffusing capacity (79.3% to 69.6%) existed, whilst in the segmentectomy group, the only significant change was a decline in diffusing capacity.

Some other reports are in line with the aforementioned results. In one study, the suitability of segmentectomy for <2 cm peripheral T1 N0 M0 lung cancers was suggested based on the small postoperative decline in lung function - only 11.3% in forced vital capacity and 13.4% in FEV_1 (50). Another study on 103 patients with segmentectomy and the same number with lobectomy showed that the lung function was significantly better preserved after segmentectomy, because the operated lobe retained 48 ± 21% of the preoperative function. Furthermore, the function of the ipsilateral non-operated lobe increased only after segmentectomy (51).

Some reports, although not denying the functional effects of segmentectomy, express some concerns. Firstly, according to the available evidence, the mean decrease in FEV_1 seems to range from -9% to -24% of the preoperative value after two months and -3 to -12% 12 months after segmentectomy. Despite the significantly lower lung function reduction than after lobectomy, segmentectomy saves only a few percents of the preoperative FEV1 value, so that the question arises about the real benefit of this procedure. Moreover, the published data do not clearly confirm the functional benefit

of segmentectomy in patients with poor lung function (52). Secondly, it was also demonstrated that, although the lung function was better after segmental resection than after lobectomy after 6 months, the actual lung function did not reach the predicted-postoperative value at 1 month after surgery (53). It means that after segmentectomy, the early postoperative pulmonary function may be significantly less than the expected value.

In some studies no functional advantage for segmentectomy could be demonstrated, like in the study on 37 patients with segmentectomy and 33 patients with lobectomy for T1aN0M0 non-small cell lung cancer. In this study, no statistically significant difference was demonstrated neither for recovery ratios of the forced vital capacity nor of the FEV1 (54). Similarly, the recovery ratios for radiologic lung volume and weight followed the similar pattern in both groups (P = 0.46 and P = 0.22).

Unlike lobectomy, anatomicel segmentectomy has some technical points that may cause differences between predicted und actual lung function of the residual lobe and these points are addressed in the literature as well. (48). Developing the intersegmental plane by using electrocautery and stapler may cause the restricted the reexpansion of the preserved segments. Similarly, in order to achieve tumor-free margins, dissection of the parenchyma is directed towards the residual segment, thus additionally restricting its function. Finally, because of the segmental anatomy, resection of the 6th segment, as technically less complicated (well defined, only one intersegmental surface), is more likely to cause better preservation of the residual lobe's function, compared with posterior-basal segmentectomy, requiring dissection at multiple surfaces at an acute angle and with deeply located point of divergence of the bronchus and vessels.

Finally, by considering these functional effects of segmentectomy, it should be rememberd that preservation of lung function makes sense only if these patients will not be exposed to an increased risk of local or regional recurrence. In only one report both aspects were synchronously analyzed (49). Segmentectomy was also reported as associated with longer mean operative time (270 ± 70 min vs. 202 ± 67 min) and more frequent postoperative complications (19.6% vs. 6.5%, p = 0.03) compared with lobectomy (55) and it should be kept in mind in preoperative patient selection.

Third, the fonts of main text and figure were not unified. There were some spelling mistakes.

Answer: in the revised version, the font was corrected.

After the careful re-reading, spelling mistakes were corrected.

In addition, the explanations of figure were insufficient and unclear. Why used X-ray instead of CT scan? Unfortunately, I did not understand the meaning of figures.

Answer: Related to figure explanations, the figure 1 illustrates the true "lung volume reduction effect", because a big bulla was removed with the tumor-bearing upper lobe. The radiographies in figures 2, 3 and 4 served only to illustrate the location of the main tumor and dynamic of the lung function parameters and blood gas analyses, whilst the problem itself was explained within the main text.

The chest X-ray instead of CT scan was used in order to better present the overall chest configuration and diaphragm position in a single figure and because the local pathology was not so much in the focus.