

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Observational cross-sectional study of 5279 bronchoscopy results for the practical effectiveness of various biopsy techniques in the diagnosis of lung diseases with particular emphasis on lung cancer
AUTHORS	Błach, Justyna; Frąk, Małgorzata; Krawczyk, Pawel; Pankowski, Juliusz; Pankowski, Adam; Buczkowski, Jarosław; Szlubowski, Artur; Siwiec, Jan; Krudyś, Piotr; Michnar, Marek; Kieszko, Robert; Milanowski, Janusz

VERSION 1 – REVIEW

REVIEWER	Christina MacRosty University of North Carolina System, Division of Pulmonary and Critical Care Medicine
REVIEW RETURNED	26-Sep-2020

GENERAL COMMENTS	<p>The authors present a retrospective study evaluating 5279 bronchoscopies performed between 2016 and 2018 in three pulmonary centers with eight different bronchoscopists in Poland with the aim to assess the yield of bronchoscopy in the diagnosis of various respiratory diseases with a focus on diagnostic yield for varying types of lung cancer. I commend the authors for including over 5000 subjects in the study.</p> <p>Overall comments: The paper focuses on analysis of lung cancer in their cohort with very little information in the results or discussion about non-malignant lung diseases. Perhaps the study question should be reframed to focus on lung cancer with a separate evaluation of other lung diseases, if the authors' goal is to focus on lung cancer. If their goal is to evaluate their diagnostic yield for all lung diseases, recommend expanding the discussion to include more thoughts on the diagnoses of non-malignant lung diseases within this cohort.</p> <p>Specific comments:</p> <ul style="list-style-type: none">- Recommend avoiding use of abbreviations in the abstract without defining them as some of these abbreviations are not universally used.- The article summary subtitle is "Strengths and limitations of this study." Items #2-5 are results of your study, not strengths and limitations. Please add separate subheadings such as "Results, Conclusions" or list the limitations and strengths as described later in your paper.- Page 4, third paragraph of the introduction - The authors state that it is difficult to obtain accurate epidemiological data on the occurrence of individual pathomorphological types of lung cancer in advanced stages. Please specify in which patient population and why. Is this because there is no registry for patients diagnosed bronchoscopically (versus the surgical registry mentioned)?- On page 5, second to last sentence of the paragraph at the top of page states that "In addition, LCC should be diagnosed only in the
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	<p>surgical material." Expanding on this statement with appropriate literature support would be helpful for context.</p> <ul style="list-style-type: none"> - Page 5, first full paragraph. The authors describe the need for varied approaches to lung cancer in "different compartments of the lung or metastatic lymph nodes." Please clarify what is meant by lung compartments and what approaches are used in which situations. - Recommend discussing guidelines for bronchoscopic staging and diagnosis of lung cancer within the context of your study. A comment on whether the centers included in the study use these guidelines would be helpful. - In the second-to-last sentence of the first full paragraph on page 5, the authors describe a meta analysis by Micames et al of 18 studies "with LC diagnosed by ultrasound-guided fine needle aspiration" showing a sensitivity of 83%... This study was looking at mediastinal staging for lung cancer so a discussion of EBUS-TBNA for staging would provide some context for this statement. - Under the Materials and methods section on page 6, please briefly explain what "pathomorphological examination" entails, particularly for diagnoses of lung cancer. - Please describe how large cell carcinomas of the lung were diagnosed histologically. Were immunohistochemical stains performed to evaluate for adenocarcinoma, squamous cell carcinoma, and neuroendocrine tumors? - In the second full paragraph on page 6 the authors state that "EBUS-TBNA and EUS-FNA was performed and cytological material archived in a cytoblock was obtained." Please comment on whether EUS-FNA was a transesophageal approach. - Under the Statistical Analysis section on page 6 the authors state the sensitivity of different procedures could not be done because the final diagnosis of analyzed patients could not be verified. Does this statement reference final diagnosis for non-malignant lung diseases? Please provide clarification. - In the last paragraph on page 7 the authors mention that squamous cell carcinoma was significantly more often diagnosed in material obtained from forceps biopsy. Knowing more about the procedural details and imaging findings would be helpful as biopsies obtained from an endobronchial tumor usually contain more tissue for pathologic analysis than transbronchial needle aspirations from lymph nodes or peripheral tumors (with some exceptions such as in necrotic endobronchial tumor that does not contain a lot of viable cells). - Page 8, second full paragraph, the authors use the term "USG-guides transbronchial biopsy" which may be a typo. If not, please define this term. - On page 8 in the second paragraph the authors state that endobronchial biopsy is more effective for diagnosis of squamous cell carcinoma because patients often had a centrally located tumor. It is more accurate to say that patients in this cohort with squamous cell carcinoma were more likely to have endobronchial disease accessible by forceps rather than stating that endobronchial biopsy is more effective for diagnosis of squamous cell lung cancer as there was no comparison to EBUS-TBNA for those patients. - The authors mention a study by Schmid-Bindert et al in the last paragraph of page 8. This study was powered to look at adequacy for RNA extraction for molecular analysis and not diagnostic yield of the procedure. Please clarify how this study relates to your results. - Please comment on how the studies cited in the first two paragraphs (references 10, 11, 13, 14) on page 9 relate to your findings.
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	<p>- In the conclusion, the authors state "our study proved that 41% bronchoscopy material was insufficient to perform reliable pathomorphological examination." Recommend against using concrete terms such as "proved.". Consider using the terms "showed" or "demonstrated." Please review this sentence for grammatical clarity.</p> <p>- In the conclusion, the authors say there is a problem in the diagnosis of advanced lung tumors using bronchoscopy if it is the only procedure performed. Please clarify what specific sole bronchoscopic procedures you are discussing and what other procedures are recommended in addition to bronchoscopy. Multiple procedures are often performed during a single bronchoscopy (for example, EBUS-TBNA plus needle aspiration and transbronchial biopsy of a lung nodule or FNA and endobronchial biopsy of an endobronchial mass) so clarification of the specific practice patterns at the centers in this study would be helpful.</p> <p>In summary, I again commend the authors for the large sample size and for the significant amount of effort to collect and analyze these data. Clarification of the stated question and more specific information about the procedural approach and imaging would provide more context for the results and discussion. More discussion of the results of non-malignant lung diseases is indicated as this is part of the stated aim of the study. Recommend some editing for optimizing grammar and spelling as well.</p>
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REVIEWER	Anne Gonzalez Research Institute of the McGill University Health Center, Respiratory Division
REVIEW RETURNED	24-Nov-2020

GENERAL COMMENTS	<p>This manuscript presents an analysis of the pathological results of 5279 bronchoscopies performed in 2016-2018 in three Polish hospitals. There is strength in having access to the results of such a large number of procedures. Most of the analysis focuses on approximately a third of procedures in which a diagnosis of lung cancer was established. The study findings are significantly limited by the lack final diagnosis in patients who had a diagnostic procedure. As a result, the authors recognize the inability to evaluate sensitivity or diagnostic yield, yet the title of the paper is yield of bronchoscopy in lung diseases and the author discuss "effectiveness" of bronchoscopy in various types of lung cancer.</p> <p>The paper ends up being a descriptive analysis of the pathological results of bronchoscopy, and the authors make epidemiological extrapolations: they discuss "incidence" yet the study groups is only patients who underwent bronchoscopy, and who had a diagnosis of lung cancer established by bronchoscopy vs. all patients diagnosed with lung cancer over the study period. There is discussion of the specific lung cancer diagnosis established by various procedures –it is not surprising that squamous cell carcinoma is established more frequently by forceps biopsy, given more frequent central location, but there is no mention of the fact that EBUS-TBNA has an essential role in invasive staging. Without due recognition of this essential role of EBUS-TBNA in the investigation of lung cancer, the authors need to be cautious in discussing its role in daily clinical practice.</p> <p>Overall, the paper would benefit from significant revision and restructuring, including clarifying the study question(s), and ensuring the intent of each section is respected (e.g. some results are presented in methods; certain limitations are discussed in statistical</p>
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	analysis session). Proof-reading by a native English speaker would also enhance the manuscript. The use of “transbronchial biopsy” is confusing, I think it is used by the authors to indicate TBNA however it could easily be interpreted as transbronchial forceps biopsy of a peripheral lesion. This also contributes to confusion when reading the abstract. Some references are outdated (the authors quote the 1st and 2nd edition of the ACCP lung cancer diagnosis guideline – the most recent one is the 3rd edition published in 2013).
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VERSION 1 – AUTHOR RESPONSE

Reviewers:

Reviewer 1

The authors present a retrospective study evaluating 5279 bronchoscopies performed between 2016 and 2018 in three pulmonary centers with eight different bronchoscopists in Poland with the aim to assess the yield of bronchoscopy in the diagnosis of various respiratory diseases with a focus on diagnostic yield for varying types of lung cancer. I commend the authors for including over 5000 subjects in the study.

Overall comments: The paper focuses on analysis of lung cancer in their cohort with very little information in the results or discussion about non-malignant lung diseases. Perhaps the study question should be reframed to focus on lung cancer with a separate evaluation of other lung diseases, if the authors' goal is to focus on lung cancer. If their goal is to evaluate their diagnostic yield for all lung diseases, recommend expanding the discussion to include more thoughts on the diagnoses of non-malignant lung diseases within this cohort.

We thank the reviewer for the suggestion. The aim of the study was more detailed, which made it possible to highlight those elements of the analysis related to the effectiveness of bronchoscopy in the diagnosis of lung cancer. The title of the article was also changed, which indicates that the main research problem was lung cancer diagnostics. The introduction and discussion have been significantly supplemented.

Specific comments:

Recommend avoiding use of abbreviations in the abstract without defining them as some of these abbreviations are not universally used.

We thank the reviewer for the suggestion. Abbreviations that are not commonly used are explained in the abstract.

The article summary subtitle is "Strengths and limitations of this study." Items #2-5 are results of your study, not strengths and limitations. Please add separate subheadings such as "Results, Conclusions" or list the limitations and strengths as described later in your paper.

We thank the reviewer for the advice. The „Strength and limitation” section was added.

Page 4, third paragraph of the introduction - The authors state that it is difficult to obtain accurate epidemiological data on the occurrence of individual pathomorphological types of lung cancer in advanced stages. Please specify in which patient population and why. Is this because there is no registry for patients diagnosed bronchoscopically (versus the surgical registry mentioned)?

We thank the reviewer for the advice. The registry we relied on in our analysis was identified and discussed.

On page 5, second to last sentence of the paragraph at the top of page states that "In addition, LCC should be diagnosed only in the surgical material." Expanding on this statement with appropriate literature support would be helpful for context.

Suitable extensions to the statement on the diagnosis of large cell carcinoma have been added.

Page 5, first full paragraph. The authors describe the need for varied approaches to lung cancer in "different compartments of the lung or metastatic lymph nodes." Please clarify what is meant by lung compartments and what approaches are used in which situations.

We thank the reviewer for the suggestion. Appropriate guidelines for the diagnosis of different groups of lymph nodes and the primary tumor depending on its location have been added to the text.

- Recommend discussing guidelines for bronchoscopic staging and diagnosis of lung cancer within the context of your study. A comment on whether the centers included in the study use these guidelines would be helpful.

Principles were applied in our study, in all the centers that participated in the study. Similarly, the principles of pathomorphological and predictive factors examination described in the materials and methods were applied in the same manner at all participating sites. All the centers participating in the study used these same procedures described above.

In the second-to-last sentence of the first full paragraph on page 5, the authors describe a meta analysis by Micames et al of 18 studies "with LC diagnosed by ultrasound-guided fine needle aspiration" showing a sensitivity of 83%... This study was looking at mediastinal staging for lung cancer so a discussion of EBUS-TBNA for staging would provide some context for this statement.

We thank the reviewer for the suggestion. Appropriate information has been added to the Introduction.

Under the Materials and methods section on page 6, please briefly explain what "pathomorphological examination" entails, particularly for diagnoses of lung cancer.

The principles of pathomorphological and predictive factors examination in the case of suspected lung cancer were additionally described in the materials and methods.

Please describe how large cell carcinomas of the lung were diagnosed histologically. Were immunohistochemical stains performed to evaluate for adenocarcinoma, squamous cell carcinoma, and neuroendocrine tumors?

Large cell carcinoma (LCC) of the lung according to The 2015 World Health Organization (WHO) Classification of Tumors of the Lung, Pleura, Thymus and Heart cannot be diagnosed in small specimens and aspiration biopsy materials. The diagnosis of LCC can only be made in the postoperative material. Therefore, there were no patients diagnosed with LCC in our study. Such patients were included in the group of patients diagnosed with NSCLC NOS. Other principles of pathomorphological and predictive factors examination in the case of suspected lung cancer were additionally described in the materials and methods.

In the second full paragraph on page 6 the authors state that "EBUS-TBNA and EUS-FNA was performed and cytological material archived in a cytoblock was obtained." Please comment on whether EUS-FNA was a transesophageal approach.

The materials and methods state that EUS-FNA was a transesophageal procedure.

Under the Statistical Analysis section on page 6 the authors state the sensitivity of different procedures could not be done because the final diagnosis of analyzed patients could not be verified. Does this statement reference final diagnosis for non-malignant lung diseases? Please provide clarification.

We thank the reviewer for the suggestion. This statement applies to all patients who underwent bronchoscopy, including patients with suspected lung cancer (tumor in the lung, lung cavity lymphadenopathy) in whom a definitive diagnosis was not achieved. A relevant explanation has been added to the text and to "Strengths and limitations of this study".

In the last paragraph on page 7 the authors mention that squamous cell carcinoma was significantly more often diagnosed in material obtained from forceps biopsy. Knowing more about the procedural details and imaging findings would be helpful as biopsies obtained from an endobronchial tumor usually contain more tissue for pathologic analysis than

transbronchial needle aspirations from lymph nodes or peripheral tumors (with some exceptions such as in necrotic endobronchial tumor that does not contain a lot of viable cells).

We thank the reviewer for the suggestion. Appropriate information has been added to the Results.

Page 8, second full paragraph, the authors use the term "USG-guides transbronchial biopsy" which may be a typo. If not, please define this term.

We apologize for the error. The typo has been removed.

On page 8 in the second paragraph the authors state that endobronchial biopsy is more effective for diagnosis of squamous cell carcinoma because patients often had a centrally located tumor. It is more accurate to say that patients in this cohort with squamous cell carcinoma were more likely to have endobronchial disease accessible by forceps rather than stating that endobronchial biopsy is more effective for diagnosis of squamous cell lung cancer as there was no comparison to EBUS-TBNA for those patients.

The paragraph has been amended as suggested by the reviewer.

The authors mention a study by Schmid-Bindert et al in the last paragraph of page 8. This study was powered to look at adequacy for RNA extraction for molecular analysis and not diagnostic yield of the procedure. Please clarify how this study relates to your results.

We thank the reviewer for the suggestion. Appropriate information has been added to the Discussion.

Please comment on how the studies cited in the first two paragraphs (references 10, 11, 13, 14) on page 9 relate to your findings.

We apologize for the mistake. These items should not be cited in these paragraphs and have been removed.

In the conclusion, the authors state "our study proved that 41% bronchoscopy material was insufficient to perform reliable pathomorphological examination." Recommend against using concrete terms such as "proved.". Consider using the terms "showed" or "demonstrated." Please review this sentence for grammatical clarity.

We thank the reviewer for the suggestion. The word "proved" was replaced by the word "showed".

- In the conclusion, the authors say there is a problem in the diagnosis of advanced lung tumors using bronchoscopy if it is the only procedure performed. Please clarify what specific sole bronchoscopic procedures you are discussing and what other procedures are recommended in addition to bronchoscopy. Multiple procedures are often performed during a single bronchoscopy (for example, EBUS-TBNA plus needle aspiration and transbronchial biopsy of a lung nodule or FNA and endobronchial biopsy of an endobronchial mass) so clarification of the specific practice patterns at the centers in this study would be helpful.

We thank the reviewer for the suggestion. The relevant procedures are listed.

In summary, I again commend the authors for the large sample size and for the significant amount of effort to collect and analyze these data. Clarification of the stated question and more specific information about the procedural approach and imaging would provide more context for the results and discussion. More discussion of the results of non-malignant lung diseases is indicated as this is part of the stated aim of the study. Recommend some editing for optimizing grammar and spelling as well.

The content of the article was adapted to the main goal of this work, which was to test the efficiency of bronchoscopy in the diagnosis of various types of lung cancer. Spelling and grammar errors have also been removed.

Reviewer 2

This manuscript presents an analysis of the pathological results of 5279 bronchoscopies performed in 2016-2018 in three Polish hospitals. There is strength in having access to the

results of such a large number of procedures. Most of the analysis focuses on approximately a third of procedures in which a diagnosis of lung cancer was established. The study findings are significantly limited by the lack final diagnosis in patients who had a diagnostic procedure. As a result, the authors recognize the inability to evaluate sensitivity or diagnostic yield, yet the title of the paper is yield of bronchoscopy in lung diseases and the author discuss “effectiveness” of bronchoscopy in various types of lung cancer.

Thank you for review and all comments. We point out the weakness of our article in 'Strengths and limitations'. The title of the article and its content have been changed in numerous places to adapt to the main topic, which is the efficiency of bronchoscopy in the diagnosis of various types of lung cancer.

The paper ends up being a descriptive analysis of the pathological results of bronchoscopy, and the authors make epidemiological extrapolations: they discuss “incidence” yet the study groups is only patients who underwent bronchoscopy, and who had a diagnosis of lung cancer established by bronchoscopy vs. all patients diagnosed with lung cancer over the study period. There is discussion of the specific lung cancer diagnosis established by various procedures –it is not surprising that squamous cell carcinoma is established more frequently by forceps biopsy, given more frequent central location, but there is no mention of the fact that EBUS-TBNA has an essential role in invasive staging. Without due recognition of this essential role of EBUS-TBNA in the investigation of lung cancer, the authors need to be cautious in discussing its role in daily clinical practice.

Thank you very much for this valuable suggestion. Information on the EBUS-TBNA value in lung cancer staging has been included in Conclusion.

Overall, the paper would benefit from significant revision and restructuring, including clarifying the study question(s), and ensuring the intent of each section is respected (e.g. some results are presented in methods; certain limitations are discussed in statistical analysis session). Proof-reading by a native English speaker would also enhance the manuscript. The use of “transbronchial biopsy” is confusing, I think it is used by the authors to indicate TBNA however it could easily be interpreted as transbronchial forceps biopsy of a peripheral lesion. This also contributes to confusion when reading the abstract. Some references are outdated (the authors quote the 1st and 2nd edition of the ACCP lung cancer diagnosis guideline – the most recent one is the 3rd edition published in 2013).

The article has been restructured. A fragment of the results from the Material and Method section has been moved to the Result section. The section on statistical analysis has been kept to a minimum and fragments that might have pertained to the results have been removed from it. The article was also significantly revised to emphasize the main goal of the study - to analyze the effectiveness of bronchoscopy in the diagnosis of lung cancer. The word transbronchial biopsy has been replaced by the abbreviation TBNA to avoid confusion. Spelling, punctuation and grammar errors have been corrected. Obsolete article with ACCP guidelines has been deleted. The literature was updated with article published in 2020.

VERSION 2 – REVIEW

REVIEWER	Anne Gonzalez Research Institute of the McGill University Health Center, Respiratory Division
REVIEW RETURNED	19-Mar-2021

GENERAL COMMENTS	<p>Thank you for the opportunity to review this revised version of the manuscript.</p> <p>The title remains somewhat misleading, given that only a subgroup of the 5279 bronchoscopy procedures examined were in patients with suspected lung cancer. The descriptive analysis largely focuses on the third of patients in whom bronchoscopy yielded a diagnosis of lung cancer. The authors go on to describe the frequency of lung</p>
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	<p>cancer subtypes, according to various diagnostic procedures performed.</p> <p>The introduction has been modified to address reviewer comments and concerns, however it is excessively long and the main research question becomes buried. The title of the article has been modified but the stated aim remains to assess the “yield” of bronchoscopy. (Yield is also mentioned at start of the discussion). However, if the starting point of the study is all bronchoscopic procedures performed for various indications, and no final diagnosis in the patients who had a non-diagnostic procedure, than yield cannot be assessed. Rather, this is a descriptive analysis of lung cancer diagnoses established by various bronchoscopic procedures.</p> <p>The authors state that squamous cell lung cancer is diagnosed more often by forceps biopsy than EBUS (and adenocarcinoma more often by EBUS). But in fact, more diagnoses of squamous cell cancer were established by EBUS of nodes (209) or tumor (135) than by forceps (270) based on Table 1. (This table is still labelled “effectiveness” of various techniques). I believe to phrase their observation more accurately, the authors could conclude that of all patients who underwent bronchoscopic forceps biopsy and were diagnosed with lung cancer, squamous cell carcinoma was the most common type. Of note, it is also unclear how many patients had more than one type of bronchoscopic samples examined e.g. both EBUS-TBNA and forceps biopsy.</p> <p>In their description of subtypes of lung cancer observed in patients with lung cancer (page 30), the authors need to state again that this relates to patients in whom lung cancer was established by a bronchoscopic procedure (i.e. not a broader population of patients with lung cancer, diagnosed through a range of procedures including thoracentesis, TTNA, etc).</p> <p>In the results, there is still mention of TBNA or FNA compared to endobronchial biopsies being similarly “effective” (page 30) but again, this is a comparison of the types of pathological diagnoses established by various procedures, not a comparison of two procedures in a given set of patients being investigated for suspected lung cancer. This concern about “efficiency” of various bronchoscopic techniques arises again in the discussion: the authors note that EBUS and biopsy have similar “efficiency” in SCLC detection. They go on to (correctly) state that whether biopsy is more effective than EBUS-TBNA for dx of squamous cannot be ascertained.</p> <p>The discussion and conclusions have also been modified to address reviewer comments, but could benefit from being shortened/more focused on the key research findings presented in this series. The authors may be missing on an opportunity to emphasize what proportion of all bronchoscopies performed yield specific diagnostic information e.g. 60% of all bronchoscopies (figure 1) and approximately 50% of those performed in patients with suspected lung cancer. But again, without final diagnosis and limited clinical data, the conclusions need to be cautious.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

1. The title remains somewhat misleading, given that only a subgroup of the 5279 bronchoscopy procedures examined were in patients with suspected lung cancer. The descriptive analysis largely focuses on the third of patients in whom bronchoscopy yielded a diagnosis of lung cancer. The authors go on to describe the frequency of lung cancer subtypes, according to various diagnostic procedures performed.

We thank the reviewer for the suggestion. We corrected the title of the manuscript: “Observational cross-sectional study of 5279 bronchoscopy results for the practical effectiveness of various biopsy techniques in the diagnosis of lung diseases with particular emphasis on lung cancer”.

2. The introduction has been modified to address reviewer comments and concerns, however it is excessively long and the main research question becomes buried. The title of the article has been modified but the stated aim remains to assess the “yield” of bronchoscopy. (Yield is also mentioned at start of the discussion). However, if the starting point of the study is all bronchoscopic procedures performed for various indications, and no final diagnosis in the patients who had a non-diagnostic procedure, than yield cannot be assessed. Rather, this is a descriptive analysis of lung cancer diagnoses established by various bronchoscopic procedures.

The introduction has been shortened. The aim of the study was changed as suggested by the reviewer.

3. The authors state that squamous cell lung cancer is diagnosed more often by forceps biopsy than EBUS (and adenocarcinoma more often by EBUS). But in fact, more diagnoses of squamous cell cancer were established by EBUS of nodes (209) or tumor (135) than by forceps (270) based on Table 1. (This table is still labelled “effectiveness” of various techniques). I believe to phrase their observation more accurately, the authors could conclude that of all patients who underwent bronchoscopic forceps biopsy and were diagnosed with lung cancer, squamous cell carcinoma was the most common type. Of note, it is also unclear how many patients had more than one type of bronchoscopic samples examined e.g. both EBUS-TBNA and forceps biopsy.

We thank the reviewer for their comment. We corrected the title of the table. We made a change in the text to emphasize that of all patients who underwent bronchoscopic forceps biopsy and were diagnosed with lung cancer, squamous cell carcinoma was the most common type. Unfortunately, the weakness of our study is the fact that we do not know how many lung cancer patients were diagnosed only in the material from EBUS-TBNA or only in the material from EUS-FNA or in both types of these materials. We also do not know the number of biopsies performed during one bronchoscopy. These data are missing from the results of the pathomorphological examination that we analyzed. We included this information in the discussion.

4. In their description of subtypes of lung cancer observed in patients with lung cancer (page 30), the authors need to state again that this relates to patients in whom lung cancer was established by a bronchoscopic procedure (i.e. not a broader population of patients with lung cancer, diagnosed through a range of procedures including thoracentesis, TTNA, etc).

This note has been added to the text (Material and Methods section).

5. In the results, there is still mention of TBNA or FNA compared to endobronchial biopsies being similarly “effective” (page 30) but again, this is a comparison of the types of pathological diagnoses established by various procedures, not a comparison of two procedures in a given set of patients being investigated for suspected lung cancer. This concern about “efficiency” of various bronchoscopic techniques arises again in the discussion: the authors note that EBUS and biopsy

have similar “efficiency” in SCLC detection. They go on to (correctly) state that whether biopsy is more effective than EBUS-TBNA for dx of squamous cannot be ascertained.

Thank you to the reviewer for this remark. Corresponding corrections have been made in the Results section. The words "efficacy" or "effectiveness" of bronchoscopy were deleted and replaced with synonyms for the words "bronchoscopy results".

6. The discussion and conclusions have also been modified to address reviewer comments, but could benefit from being shortened/more focused on the key research findings presented in this series. The authors may be missing on an opportunity to emphasize what proportion of all bronchoscopies performed yield specific diagnostic information e.g. 60% of all bronchoscopies (figure 1) and approximately 50% of those performed in patients with suspected lung cancer. But again, without final diagnosis and limited clinical data, the conclusions need to be cautious.

We thank the reviewer for this remark. The discussion has been shortened. The conclusions were closely related to the results of our study, they are very concise and cautiously formulated.