Peer Review File

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Reviewer A

the manuscript entitled "Prognostic factors of recurrence and disease-free survival in radically resected pulmonary carcinoids" is well written and focused in the fields. Methods are full explanatory.

I suggest to accept your manuscript.

Reply 1: Thank you for your appreciative comment.

Changes in the text: Not applicable

Reviewer B

Liu et al analyzed long term prognosis and prognostic factor in 82 pulmonary carcinoid patients undergoing curative resection. However, the data are insufficient to draw conclusions.

・The sample size is small

Reply 1: Thank you for your valuable comments. We agree that the absolute sample size is small. However, since this is a single center study from the largest thoracic surgical center in Austria, with all consecutive patients included, this is only a relative limitation. Moreover, the published references with more included patients are either multicentric studies, or are based on large population databases, like SEER or similar. Thus, our study retains its value in comparison with other published studies.

Changes in the text: The attribution ‘consecutive’ had been added for the sake of a clearer description of the study cohort (line 105). Moreover, for the same reason the title of the study had been amended as follows: ‘a real-world analysis’ (line 3).

・Since typical and atypical carcinoid have different malignant potential, the analysis should not be performed for both together.

Reply 2: We agree that typical and atypical carcinoids do have different malignant potential and thus a different prognosis. However, from a statistical point of view, it cannot make any difference, whether they are analyzed separately, or if typical and atypical carcinoids are treated as concurrent prognostic variables in a multivariate model, as we did. Therefore, we insist on the chosen statistical approach.

Changes in the text: Not applicable.

Reviewer C

I think that this study included several problems although some readers may be interested in this study.

・This study was a retrospective and single institutional study.
・Cases were few, especially atypical carcinoids.

Reply 1: Thank you for your valuable comments. We agree that the cohort is small in absolute numbers. However, since this is a single center study from the largest thoracic surgical center in Austria, with all consecutive patients included, this is only a relative limitation. Moreover, the published references with more included patients are either multicentric studies, or are based on large population databases, like SEER or similar. Thus, our study retains its value in comparison with other published studies.

Changes in the text: The attribution 'consecutive' had been added for the sake of a clearer description of the study cohort (line 105). Moreover, for the same reason the title of the study had been amended as follows: 'a real-world analysis' (line 3).

・Compared to previous study, the prognosis of patients with atypical carcinoids was better. Why?

Reply 2: We observed a 5-year overall survival of 87.5% and 84.7% for TCs and ACs, respectively. This is in complete agreement with prior studies reporting a 5-year overall survival for TCs to be between 86% to 93%, and between 80% to 87% for ACs. Therefore, our results are in line with the literature.

Changes in the text: For the sake of clarity, the relevant paragraph in the discussion (lines 281-288) has been redrafted.

・They could not refer to necrosis in pathological findings of atypical carcinoids.
Reply 3: Absence/presence of necrosis is one of the diagnostic criteria for atypical carcinoids, especially if the mitotic count is below 2%. However, since the absence/presence of necrosis was not relevant for our research question, we did not show it in this paper.

Changes in the text: Not applicable.

Reviewer D

The authors present a single-center retrospective analysis of resected lung carcinoids. The aim is to evaluate factors associated with DFS and recurrence, which, according to their review, are scarce in the literature. I believe that this matter has already been investigated and reported over the last decades. Moreover, multicentric studies have emphasized the importance of multiple prognostic factors, especially nodal involvement, which are already associated with OS, DFS, recurrence, etc. (find below a list of references regarding this matter).
Reply 1: Thank you for your valuable comments. We agree that the cohort is small in

absolute numbers. However, since this is a single center study from the largest thoracic surgical center in Austria, with all consecutive patients included, this is only a relative limitation. Moreover, the published references with more included patients are either multicentric studies, or are based on large population databases, like SEER or similar (see below). In the proposed references, only one refers to a larger single center study, but from 2004, and therefore not up to date.

https://doi.org/10.1159/000480015: 62 patients, multicenter
https://doi.org/10.1007/s00408-017-0056-8: 195 patients, multicenter
10.3892/ol.2023.13666: 404 patients, multiple subsidiaries (Mayo Clinic)
10.1016/j.atssr.2023.07.016: 8257 patients, National Cancer Database
https://www.mdpi.com/2072-6694/14/11/2601: 283 patients, multicenter
10.1002/jso.26912: 283 patients, multicenter
10.1093/icvts/ivaa114: 293 patients, multicenter
10.1016/j.jtho.2018.10.166: 4645 patients, SEER
10.1016/j.athoracsur.2018.05.044: 3335 patients, National Cancer Database
10.1093/ejcts/ezt470: 247 patients, multicenter
10.1016/j.athoracsur.2003.10.089: 163 patients, single center (from 2004)

Thus, our study evaluating a cohort of 82 consecutive patients in a real-world single center setting retains its value in comparison with other published studies.

Changes in the text: The attribution ‘consecutive’ had been added for the sake of a clearer description of the study cohort (line 105). In addition, for the same reason the title of the study had been amended as follows: ‘a real-world analysis’ (line 3). Moreover, the limitation part of the discussion (lines 324-330) has been amended by the above reasoning.

Additionally, the statistical analysis may have some issues considering that the authors had only 6 cases of recurrence among their sample. Although this is stated by the authors at the end of the manuscript, it hinders the main objective of the paper. The multivariable analysis has serious issues considering this fact (e.g., 4 variables were considered in the logistic regression for 6 cases of recurrence).

Reply 2: We agree completely with you. A small number of events significantly reduces the statistical power, but due to the expectedly low mortality and recurrence risk of lung carcinoids, a much larger sample size would be needed. This is, however, not achievable in our local institutional setting. We acknowledged this limitation, though.

Changes in the text: Not applicable.

While the findings are in accordance with the literature, I believe the authors would need a larger sample size to draw new insights into the topic. Thank you for the opportunity to review the following manuscript.

Reply 3: As already stated, a larger sample size is not achievable in our local institutional setting. However, that the findings from our small cohort are nonetheless

in accordance with much larger samples from the literature, proves that we could we were able to show the principle.

Changes in the text: Not applicable.

References
https://doi.org/10.1159/000480015: 62 patients, multicentre
https://doi.org/10.1007/s00408-017-0056-8: 195 patients, multicentre
10.3892/ol.2023.13666: 404 patients, multiple subsidiaries (Mayo)
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10.1002/jso.26912 : 283 patients, multicentre
10.1093/icvts/ivaa114: 293 patients, multicentre
10.1016/j.jtho.2018.10.166 : 4645 patients, SEER
10.1016/j.athoracsur.2018.05.044: 3,335 patients, National Cancer Database
10.1093/ejcts/ezt470 : 247 patients, multicentre
10.1016/j.athoracsur.2003.10.089: 163 patients, single centre (from 2004)

Reviewer E

Thank you for the opportunity to review this interesting manuscript entitled "Prognostic factors of recurrence and disease-free survival in radically resected pulmonary carcinoids". A couple of comments are listed below for the authors' consideration.
1. This study included 82 patients who underwent surgical resection for pulmonary carcinoid tumors between 2010 and 2019, but the median follow-up period was only 22 months, which seems to be too short to me. Were there any reasons?

Reply 1: Thank you for your valuable comments. We agree that the median follow-up period is with 22 months relatively short. This is due to the circumstance, that according to our previous institutional custom, patients with primary lung carcinoids had not been committed to adhere to a long-term follow-up program. They came back on a voluntary basis, and due to the perceived 'benign' character of the disease, many patients chose not to.

Changes in the text: Not applicable.

2. How many patients had preoperative diagnosis of carcinoid? Did preoperative diagnosis affect the surgical procedures? In addition, details on lymph node dissection and adjuvant therapies should be provided.

Reply 2: All patients had preoperative diagnosis of carcinoid. The surgical procedure was customized according to the preoperative lung function, not according to the preoperative diagnosis. As a matter of fact, a curative anatomical resection was always pursued, except for three cases, in whom the preoperative lung function allowed only a wedge resection. However, even in these cases, as in all other cases, a complete

mediastinal lymph node resection was performed. Of the six patients with recurrence, two underwent adjuvant radiotherapy (alone or in combination), four underwent radionuclide therapy, and one underwent complex abdominal metastasectomy.

Changes in the text: The results section was amended by the adjuvant treatment modalities of the six patients with recurrences (lines 170-172).

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3. This study aims to identify risk factors for recurrence, but only six cases developed recurrence, which was also stated in the limitation. In addition, study population was heterogeneous, including typical carcinoids and atypical carcinoids with various stages. Therefore, results of this study should be interpreted with full caution.

Reply 3: We agree partially with you. The number of cases is relatively small, and the number of recurrences even smaller. Thus, this limitation has been already acknowledged. As for the heterogeneity of study population, our statistical analysis addressed this circumstance satisfactorily.

Changes in the text: Not applicable.

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4. What surgical resection and lymph node dissection did six cases with recurrence receive?

Reply 4: Of the six cases with recurrence, three underwent a lobectomy, one a bilobectomy, one a bronchial sleeve lobectomy, and one a lobectomy with a partial vascular sleeve resection. Moreover, all patients underwent also a complete mediastinal lymph node dissection, and all cases were a R0 resection.

Changes in the text: The surgical details of the patients with recurrences had been added to the results section (lines 158-162).

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5. Why did authors select “tumor size” instead of “T stage” for a prognostic factor in univariate and multivariate analyses?

Reply 5: It is true, that ‘T stage’ would have been a more obvious choice as prognostic factor than ‘tumor size’. However, as you certainly noticed, almost 80% of our patients had pT1 tumors. Thus, analyzing the data only by adoption of ‘T stage’, would underestimate the essential relationship between tumor size and outcome. Thus, we elected to choose ‘tumor size in cm’ as a more relevant size parameter.

Changes in the text: To avoid misunderstandings, the results section has been amended by this clarification (lines 180-182).

Reviewer F

This retrospective study was performed to identify risk factors for recurrence and reduced DFS, and to assess the differences between typical and atypical carcinoids in patients who underwent curative intent surgery.

I have included several comments and questions below that will express some of my concerns generated by my reading of this manuscript.

Major Comments:
The authors presented a relatively large number of lung carcinoids in a series of accumulated data over 10 years. From their outcomes, the authors demonstrated statistically that tumor size and nodal involvement are the most important prognostic factors for recurrence and reduced DFS.
This manuscript was well written; however, I find the result quite natural because tumor size and nodal involvement are equal to the T and N factors in the TNM classification of lung cancer—the stage increases with tumor size and lymph node metastasis. Therefore, we could not obtain new knowledge in this manuscript and the results are not interesting.

Reply 1: Thank you for your valuable comment. We agree, that in a certain way our results seem quite natural. However, please consider that almost 80% of our cases had pT1 tumors, and 85% were in a pN0 situation. Thus, focusing on T and N factors alone would therefore not have captured the essential prognostic relevance of tumor size and lymph node involvement. Thus, for pulmonary carcinoids the adoption of 'tumor size in cm' seems to be a more relevant prognostic parameter. We believe, this insight is a new knowledge.
Moreover, since this is a single center study from the largest thoracic surgical center in Austria, with all consecutive patients included, we believe our results are still of interest.

Changes in the text: The discussion section has been broadened by the above argument (lines 254-261).

Although statistical studies are performed for many parameters in many Tables, the number of each parameter is so small that it makes no sense to perform statistical studies for comparison in typical and atypical carcinoids.

Reply 2: We agree completely. A small number of parameters significantly reduces the statistical power, but due to the expectedly low mortality and recurrence risk of lung carcinoids, a much larger sample size would be needed. This is, however, not achievable in our local institutional setting. We acknowledged this limitation, though.

Changes in the text: Not applicable.
