Peer Review File

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Round 1

Reviewer A

The authors provide a narrative review on workup and management of carcinoid tumours and diffuse idiopathic neuroendocrine cell hyperplasia in a multidisciplinary setting.

The manuscript is overall well written. The objective as stated by the authors is to provide a summary of published literature and provide evidence-based algorithms for workup and treatment. The authors successfully provide a summary of the published literature however they have not been equally successful in providing algorithms for diagnosis and management.

Thank you for your review.

Some more specific comments:

Abstract:
Line 59: The authors conclude 'Clinical trials should be considered for each patient if available'. I find this a very generalised and abstract statement often included at the end of almost every abstract/manuscript without appropriate backup information. Throughout the manuscript the authors have emphasised that trial results have been mostly underwhelming when it comes to management of carcinoids and also the rarity of the disease and long term follow up requirements do not allow for trials to be easily planned and executed. If the authors would like to conclude that patients should participate in relevant trials it is important to specifically highlight in the main body of the text at least the most important trials (completed, in progress or upcoming) and discuss the advantages and disadvantages of participating in them.

Thank you for your comment. We have revised the abstract and also the manuscript to direct reader to some of the ongoing clinical trials for pulmonary carcinoid tumors.

Introduction:

Lines 70-72: Consider referencing your statements.

Thank you. We have included the reference from Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine tumors of the lung: current challenges and advances in the diagnosis and management of well-differentiated disease. Journal of thoracic oncology 2017;12(3):425-436.

Methods:
The strategy for conducting this review is presented however there is no mention of the strategy followed to provide algorithms for workup and management, which has been a highlighted objective. In fact, other than figure 4, no algorithms have been provided.

Thank you for this comment. We have revised the algorithms for work up and management to include overall work up, endobronchial therapy and medical considerations for the management of advanced disease. Most of this guidance on management comes from extrapolation from expert guidelines from The National Comprehensive Cancer Network, Commonwealth Neuroendocrine Tumour Research

Collaboration/North American Neuroendocrine Tumor Society and The European Neuroendocrine Tumor Society. Some of the guidance is based on our clinical practice at Vanderbilt University Medical Center where we have a high volume neuroendocrine tertiary care center where we have weekly thoracic and neuroendocrine tumor boards and conduct many clinical trials.

Workup, Diagnosis and Management of PCs.

Diagnosis:
Line 136: consider rephrasing to 'evaluation of PCs' instead of 'evaluation for PCs'.

Thank you. We have rephrased this statement.

Lines 136-148: You specifically mention that the yield of washings is 26%, the risk of bleeding is low and the risk for pneumothorax is 20%. But you haven't provided the diagnostic accuracy of bronchoscopy/navigational bronchoscopy/CT biopsy for central and peripheral carcinoids. What is the evidence to support different strategies for biopsies and how much tissue should be obtained to provide an accurate diagnosis and characterisation of the tumour?

We appreciate your comments and questions.
Unfortunately, we do not have studies that reports the diagnostic yield or accuracy of either modality (bronchoscopy or CT guided biopsy) for nodules that are suspicious for carcinoid. What we understand and know is that overall, the yield for navigation bronchoscopy for peripheral pulmonary lesions ranges from 47% to 94% with conventional navigation bronchoscopy (1-6) and 69% to 86% for robotic assisted bronchoscopy (7-10), and CT guided biopsy has a diagnostic yield of 92% (11). We do not have the direct comparative data of the yields for these two modalities at this time due to many confounding factors hindering the comparison.
Presently, we also do not have data to suggest that amount of tissue that should be obtain during any of the two biopsy techniques to provide a diagnosis and characterization of the tumor.

References:

1. Aboudara M, Roller L, Rickman O, et al. Improved diagnostic yield for lung nodules with digital tomosynthesis-corrected navigational bronchoscopy: Initial experience with a novel adjunct. *Respirology*. Feb 2020;25(2):206-213. doi:10.1111/resp.13609
2. Katsis J, Roller L, Aboudara M, et al. Diagnostic Yield of Digital Tomosynthesis-assisted Navigational Bronchoscopy for Indeterminate Lung Nodules. *J Bronchology Interv Pulmonol*. Oct 01 2021;28(4):255-261. doi:10.1097/LBR.0000000000000766
3. Avasarala SK, Roller L, Katsis J, et al. Sight Unseen: Diagnostic Yield and Safety Outcomes of a Novel Multimodality Navigation Bronchoscopy Platform with Real-Time Target Acquisition. *Respiration*. 2022;101(2):166-173. doi:10.1159/000518009
4. Khandhar SJ, Bowling MR, Flandes J, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. *BMC Pulm Med*. Apr 11 2017;17(1):59. doi:10.1186/s12890-017-0403-9
5. Folch EE, Bowling MR, Pritchett MA, et al. NAVIGATE 24-Month Results: Electromagnetic Navigation Bronchoscopy for Pulmonary Lesions at 37 Centers in Europe and the United States. *J Thorac Oncol*. Apr 2022;17(4):519-531. doi:10.1016/j.jtho.2021.12.008
6. Folch EE, Bowling MR, Gildea TR, et al. Design of a prospective, multicenter, global, cohort study of electromagnetic navigation bronchoscopy. *BMC Pulm Med*. Apr 26 2016;16(1):60. doi:10.1186/s12890-016-0228-y
7. Kalchiem-Dekel O, Connolly JG, Lin IH, et al. Shape-Sensing Robotic-Assisted Bronchoscopy in the Diagnosis of Pulmonary Parenchymal Lesions. *Chest*. 02 2022;161(2):572-582. doi:10.1016/j.chest.2021.07.2169
8. Benn BS, Romero AO, Lum M, Krishna G. Robotic-Assisted Navigation Bronchoscopy as a Paradigm Shift in Peripheral Lung Access. *Lung*. 04 2021;199(2):177-186. doi:10.1007/s00408-021-00421-1

9. Chaddha U, Kovacs SP, Manley C, et al. Robot-assisted bronchoscopy for pulmonary lesion diagnosis: results from the initial multicenter experience. *BMC Pulm Med*. Dec 11 2019;19(1):243. doi:10.1186/s12890-019-1010-8
10. Chen AC, Pastis NJ, Jr., Mahajan AK, et al. Robotic Bronchoscopy for Peripheral Pulmonary Lesions: A Multicenter Pilot and Feasibility Study (BENEFIT). *Chest*. Feb 2021;159(2):845-852. doi:10.1016/j.chest.2020.08.2047
11. DiBardino DM, Yarmus LB, Semaan RW. Transthoracic needle biopsy of the lung. *J Thorac Dis*. Dec 2015;7(Suppl 4):S304-16. doi:10.3978/j.issn.2072-1439.2015.12.16

Surgery:
Lines 174-176: You mention that 'smokers should be counselled to stop'. Would you recommend postponing their operation until they have stopped smoking, if they are for example diagnosed with typical carcinoids? Would you recommend to proceed with an operation at earliest possible with the patient still smoking as carcinoids need to be treated as any other lung cancer? What is the algorithm you propose for workup and management for current smokers diagnosed with carcinoid tumours?

This is a very controversial topic with data supporting both sides of the argument contemporarily in the literature. Surgical practices around the world vary dramatically with regards to desire for smoking cessation. Within our own practice, there is significant variability. We have added a statement supporting smoking cessation counseling, but caveating that this should not prevent the ultimate performance of surgery affording a patient a high cure rate.

Lines 177-189: You mention that patients undergoing pulmonary resections commonly have other co-morbidities which is true. However, patients with carcinoid tumours may be younger with no other co-morbidities. You highlight the importance of spirometry which is also correct however patients with central carcinoids may have impaired lung function because their tumours are occluding their airways and a limited bronchial resection or sleeve resection could improve their breathing post-op. You reference a paper which describes how 'Thoracoscopic lobectomy facilitates the delivery of chemotherapy after resection for lung cancer'. How is that relevant to management of carcinoids? I would suggest the entire paragraph is rewritten to apply specifically to surgical management of patients with carcinoid tumours and not to patients undergoing lung resections for any lung malignancy.

Carcinoid patients, like all NSCLC patients, present at all ages and thus attention to appropriate testing for co-morbid conditions remains important. Further, being young does not guarantee health. A statement has been added to both address the pulmonary impact of DIPNECH as well as obstructing tumors.
The offending references has been removed and replaced.

Pulmonary carcinoids make up the minority of pulmonary resections and thus large studies often lump carcinoids in under “NSCLC” thereby making studies isolated to carcinoids more limited. Surgical considerations such as PFTs and basic workup are pretty standardized across resections regardless of histology as all tumors can present centrally, peripherally, invade into surrounding structures or be well contained within lung parenchyma.

Lines 191-192: Consider referencing 'Lobectomy remains the most commonly performed surgery for PCs'. Also consider discussing this further. Why is lobectomy still the most common? Is it because of evidence to support the practice or because of lack of evidence to support another approach? Is it because surgeons select to perform a less technically challenging operation when they should be considering parenchymal sparing resections instead which can be technically more challenging but with comparable oncological outcomes when for example it comes to typical carcinoids?

Reference provided for lobectomy being most common approach.
We stated in the write up that degree of resection remains controversial but added additional sentences to expound upon this statement.
Resections are often dictated by anatomy and it is quite common for cancers to involve multiple pulmonary segments thereby rendering a sublobar resection non-ideal. Data to support sublobar resection at this time for carcinoid tumors specifically is very poor. Comment added to address this.

Lines 198-199: You mention that 'many PCs are centrally located and pneumonectomy may be required'. Would a lower bilobectomy be an acceptable procedure for a 45 year old with tumour in the bronchus intermedius? Should a left pneumonectomy be performed for a patient with tumour in the left main bronchus? How should a decision for a parenchymal sparing operation be made? What is the role of the MDT in that? You propose endobronchial treatment, what would be the indication, the duration, the outcome that should be considered successful or unsuccessful to guide further intervention? Which is the algorithm for surgical management you propose based on the evidence collected from your literature review?

A tumor within the bronchus intermedius is standardly treated with a bilobectomy, this is not an indication for pneumonectomy.
With regards to endobronchial therapy, there is an entire section dedicated to this below with type of therapy, number of treatments and surveillance. This will not be described in the same detail within the surgical section to avoid redundancy.
At this time there is no data to support that EBT ultimately results in a lesser degree of parenchymal resection. We all have anecdotal experience but this is not sufficient to create a protocol at this time. A comment has been added to state this.

Lines 205-210: Lymph node dissection should indeed be performed as for any other lung cancer. However, what is the significance of lymph node involvement for carcinoid tumours? How do they impact survival? How should a patient with N1, N2 disease be managed post-op? What is the evidence in the current literature specifically for carcinoid tumours? If lymph node dissection is important, does that mean that every patient managed with bronchoscopic treatment is receiving suboptimal management since lymph nodes are not sampled? Should all patients undergoing bronchoscopic management have EBUS? Your literature review is incomplete if the reader of this article cannot be informed on the precise outcomes of surgical management, which you have already mentioned is the treatment of choice.

Lymphadenectomy/pathologic nodal assists with formal pathologic staging which informs treatment decisions, clinical trial enrollment and prognostication which is important for patients.

Endobronchial treatment for carcinoid tumours:

Good summary of the literature but again you don't provide an algorithm for workup and management.

A algorithm for work up and management, figure 4, has been revised.

Medical treatments for advanced disease, Radionuclide Therapy, Radiation therapy.

All these sections are better written and structured compared to surgery and bronchoscopy and evidence is better presented. Again however, the reader is left to piece information together and the role of a multidisciplinary team to guide treatment is not described. An algorithm for workup and management is not provided.

Thank you. We have included additional algorithms for the work up and management.

Lines 383-385 are the same as Lines 390-392, consider deleting one of the two identical statements.

Thank you. We have deleted line 383-385.

Follow-up and surveillance:
Lines 442-444. What is the evidence?

While the surveillance guidelines from NCCN for NSCLC following curative intent resection consist of CT chest at 6 month intervals for 5 years. The NCCN guidelines for neuroendocrine tumors of the lung differ. These guidelines state surveillance should continue for up to 10 years and consider surveillance as clinically indicted beyond 10 years. This is because of the known risk of late recurrence. Additionally, dotatate PET is not recommended.

Shah MH, Goldner WS, Benson AB, et al. Neuroendocrine and adrenal tumors, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network 2021;19(7):839-868.

Ciment A, Gil, J, Teirstein. Late recurrent pulmonary typical carcinoid tumor: case report and review of the literature. Mt. Sinai J Med. 2006 Oct;73(6):884-6

Lamarca, A, Clouston, H, Barriuso, J et al. Follow-up recommendations after curative resection of well-differentiated neuroendocrine tumours: Review of current evidence and clinical practice. J Clin Med. 2019, 8, 1630; doi:10.3390/jcm8101630

Ferolla, P, Daddi, N, Urbani, M et al. Tumorlets, multicentric carcinoids, lymph node metastases, and long-term behavior in bronchial carcinoids. J Thorac Oncol. 2009;4: 383-387

DIPNECH
This whole section reads like a second manuscript. Either consider reducing its size to 1-2 paragraphs with only most important information or incorporate with previous sections of the manuscript.

Thank you. While we appreciate this comment, we feel this separate section adds to the manuscript. Since DIPNECH can occur in the presence of pulmonary carcinoid tumors, we felt it would be best that the reader be aware of both entities. Additionally, due to the rarity of DIPNECH it often goes misdiagnosed and many clinicians are unaware that it exists or how to manage this. By combining these two (sometimes co-occurring) entities in a single manuscript, we feel that the reader will have gain the knowledge on how to work up and manage both conditions. That said, we have reduced the size of this section.

Reviewer B

In this work, the authors performed a review of the literature on the management of pulmonary carcinoid tumors and DIPNECH.
The interest is strong, as the management of these tumors is regularly updated in national and international guidelines, but is also based on expert opinions due to their singularity within the bronchopulmonary tumors.
This work is very interesting and well written, and represents an excellent synthesis of the literature while providing a definite educational value.

Thanks for your review.

Some points deserve to be developed to optimize the manuscript.

i. Summary:
The abstract could be reworked to be more clear-cut.
line 34: the syntax would benefit from optimization, avoiding unharmonious repetitions of certain words ("these"). Perhaps more "straight to the point" sentences would be more appropriate for the abstract in general.
The conclusion of the abstract is vague, and would benefit from being more precise.

Thank you. We have reworded the abstract to be more to the point.

ii. Introduction:
Each disease entity should be exhaustively detailed, explaining what each corresponds to.
Thank you. We have re-worded the introduction.

Line 73 to 75: the authors explain that the incidence of neuroendocrine tumors is increasing over time, giving figures ex abrupto. These figures should also be given in relation to the data for all bronchopulmonary tumours, in order to normalize them, which will make them more interpretable.

Thank you. We have added to this section to state that the incidence of all malignancies is decreasing including lung cancers.

In line 79, the different survivals attributed to these diseases could perhaps be shown in a figure, if this is of interest in terms of the presentation of this data.

Thank you. Since there is only one line discussing survival, we have opted not to present this in table format.

iii. Methods:
The principles of the "SEER" analysis should be explained in this section.

Thank you. There are multiple facets to a SEER analysis. While we agree all large database analyses have their benefits and limitations, we think that a detailed explanation is beyond the scope of this manuscript. Additionally we are at our word limit so we would not want to detract from other pertinent information to include this.

iv. Workup, Diagnosis and Management of PCs:
The imaging section should be more detailed, the suggestive CT signs of these pathological entities should be presented. An illustration by a table for example, could be of interest.

Thank you. We have added to the imaging section to describe some characteristics seen on CT and also added to the discussion of functional imaging.

Line 118: "The majority of PCs overexpress somatostatin receptors (SSTR) by immunohistochemistry." The syntax should be revised: "the expression of SSTRs, using immunohistochemistry techniques". It should also be clarified which tools are used in immunohistochemistry (recommended antibody(s) and clone(s)?)

We recognize that immunohistochemistry techniques can detect SSTRs. That said, most centers do not assess SSTR positivity with these but rather assess SSTR positivity by functional imaging with either indium 111 SPECT/CT or gallium 68/copper 64 dotatate PET. Therefore, we have removed the words “by immunohistochemistry”.

Line 122: "Variations in the somatostatin analogue, chelator, and choice of isotope can alter the affinity to SSTRs". This very important information should be detailed and supported.

Limitations related to the use of octreotide radiotracers should appear somewhere (e.g. limited accessibility, cost..)

Thank you. We agree that there are multiple limitations to each isotope. Clinically speaking, some of the techniques that are available are determined by the institution and where they are located geographically. Not all centers may have access to Gallium 68 dotatate but may have access to Copper 64 dotatate. Some may not have access to dotatate and only use indium based SPECT/CT. We have tried to point out that regardless of technique functional imaging is required. Furthermore, we have stated that dotatate PET/CT is superior to SPECT/CT and also more cost effective. A detailed analysis of comparisons between dotatate, dotatoc and dotanoc is beyond the scope of this manuscript.

v. Pathology:
The histological architecture and cytological features of these pathological entities should be detailed precisely, as well as the limitations of these diagnostic techniques.

The pathology section has been modified to include detailed morphology, immunohistochemical features, and differential diagnosis. These changes are as follows:
Line 162-166: Morphologically, carcinoid tumors may have organoid, trabecular, rosette, insular, pseudoglandular, or solid growth patterns. Oncocytic, clear cell, and melanin-laden carcinoids, although rare, can occur. Tumor cells are uniform, featuring round to oval or spindled nuclei with finely granular nuclear chromatin, moderate to abundant eosinophilic cytoplasm, and inconspicuous nucleoli.
Line 171-173: By immunohistochemistry, carcinoid tumors are positive for low-molecular-weight cytokeratins. They are strongly reactive for neuroendocrine markers such as chromogranin A, synaptophysin, CD56, and INSM1. TTF1 tends to be positive in peripheral but negative in central tumors.
Line 185-189: The differential diagnosis of pulmonary carcinoids includes metastatic carcinoids from elsewhere, especially those originating in the gastrointestinal tract. Glandular structures are unusual in pulmonary carcinoids but a frequent finding in those arising from the gastrointestinal tract. Gastrointestinal and pancreatic carcinoids are usually negative for TTF1 but frequently express CDX2 or PAX8.

vi. Treatment for Pulmonary Carcinoids
Lines 190-197: The principle of infralobar resection (wedge resection versus infralobar segmentectomy resection?) should be detailed more precisely. More precision would be desirable, with reference to the literature, especially since the principle of parenchymal sparing surgery appears next. This principle should be briefly described.

Thank you. We added definitions for sublobar to comprehend wedge and anatomic segmentectomy.

Lines 230 to 232: the reference should be added.

Thank you. We have added the references:
Amoils SP. The Joule Thomson Cryoprobe. *Arch Ophthalmol.* 1967;78(2):201–207. doi:10.1001/archopht.1967.00980030203014

DiBardino DM, Lanfranco AR, Haas AR. Bronchoscopic Cryotherapy. Clinical Applications of the Cryoprobe, Cryospray, and Cryoadhesion. *Ann Am Thorac Soc*. 2016;13(8):1405-1415. doi:10.1513/AnnalsATS.201601-062FR

Concerning the endoscopic techniques from the studies cited, the average number of therapeutic endoscopy sessions required for the patients in these studies should be specified.

We appreciate your comment.
As each study have utilized different endobronchial treatment modalities, there have not been a consensus for average number of therapeutic bronchoscopies or number of surveillance bronchoscopy that may be required. In the study by Perikleous (49), median number of cryotherapy was three, and average of five in an older study by Luckraz (50). This is mentioned in line 254 and 255 under endobronchial treatment for carcinoid tumors.

The sentence is as following:
"The median number of cryotherapy applications performed was three (49), compared to an average of five in an older study (50)."

The detail of the endoscopic techniques is quite appreciable and legitimate, but it must be balanced with the surgical techniques, so that the reader does not find an "opposition" between these two techniques which are complementary. The gold standard for the management of these tumors should also be recalled in this section, as it is very clearly explained in the "conclusion" chapter.

Thank you. We agree that surgical resection remains the gold standard for treatment of pulmonary carcinoid tumors. We have indicated this in the first sentence of this section. We have also added a statement reflecting these techniques can be complementary to surgery.

vii. Radiation therapy:
The type of SBRT technique used in the studies cited, should be precised.

Thank you. We understand that SBRT techniques vary between institutions. We have outlined the number of fractions and the total doses for each study. The Wegner et al study was an NCDB review which did not list techniques. Thomas et al and Singh et al list a linear accelerator technique. Colaco et al used a non-coplanar static beam technique. Since these techniques vary and no studies compare the various techniques, we felt it was more important to emphasize SBRT can be an option (regardless of technique) for patients with pulmonary carcinoid tumors.

Reviewer C

This manuscript is providing the newest multidisciplinary overview to approaching patients with PCs and DIPNECH. This is an important review paper and I have no hesitation in recommending it for publication.

Thank you for your review and comments.

Minor comments:
1. In line 71, ---they represent approximately 25% of all NETs. The author should cite references.

Thank you. We have included the reference from Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine tumors of the lung: current challenges and advances in the diagnosis and management of well-differentiated disease. Journal of thoracic oncology 2017;12(3):425-436.

2. In line 229, ---these multiple complex pathways resulting in inhibition of cell cycle arrest. This should be --resulting in cell cycle arrest--.

Thank you. We have made the change. This causes regulation of these multiple complex pathways resulting in cell cycle arrest, inhibition of growth factors, and cell apoptosis.

This is an important review paper. and I have no hesitation in recommending it for publication

Reviewer D

In this present Review, the author Robert A. Ramirez and cols did good work, which should be mentioned, in studying the current scientific literature covering the carcinoid tumors of the lung, approaching from its origin to its clinical management.
However, there are some minor points that could be addressed in order to improve the content of this work.

Thank you for your review.

1) In the Introduction section: the sentence "Neuroendocrine tumors (NETs) of the lung represent a spectrum of disease. These range from pre-malignant diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) to malignant pulmonary carcinoid (PC) tumors (typical and atypical), aggressive large cell neuroendocrine carcinoma (LCNEC), and small cell lung cancer (SCLC)". NETs of the lung comprise the carcinoid tumors (typical and atypical) and the high-grade NE carcinomas (LCNEC and SCLC) as the authors describe properly. However, even though the WHO recognizes DIPNECH as a precursor lesion of carcinoid tumors, not all carcinoid tumors have a DIPNECH as a precursor lesion. Thus, DIPNECH should not be considered a component of the four major neuroendocrine entities of the lung. Once that carcinoid tumor can be presented without a DIPNECH lesion, I suggest that in this sentence the neuroendocrine variants should be defined in the four groups raging from carcinoid tumors (TC and AC) to high-grade neuroendocrine carcinomas (LCNEC and SCLC).

Thank you. We agree that DIPNECH sometimes represents a precursor lesion and that not all DIPNECH patients progress. Likewise, not all pulmonary carcinoid patients have DIPNECH. We have changed the wording in the introduction to reflect this.

2) In the introduction section, the sentence: "Survival of PCs vary by stage and mitotic index - whether they are typical carcinoid (TC) or atypical carcinoid (AC), with the median survival of all distant stage PCs being 24 months (1)". Please check this information, it does not seem correct. In the article that the author referred to, in the Survival section, Arvind Dasari and cols described as follows: " NETs in the rectum (24.6 years) and appendix (>30.0 years) had the best median OS among site groups, while NETs in the pancreas (3.6 years) and lung (5.5 years) had the worst median OS. (...) For distant NETs, those in the small intestine had the best median OS (5.83 years); NETs in the lung (6 months) and colon (4 months) had the worst median OS". Please, fix it, if necessary.

Thank you for your comment. We have reviewed the original paper by Desari et al and found that indeed the survival for distant lung NETs of all grades (1-4) was 6 months (presumably this included small cell lung cancer and large cell neuroendocrine carcinoma). There is also a supplement from the same article describing the median survival for distant stage G1/G2 NETs indicating that the median survival for lung is 24 months.

eTable 3. Median Survival of Distant Stage G1/G2 NETs Diagnosed From 2000-2012

Primary Tumor Site	Median Survival (months)	Survival Rate (%)	
		3-year	5-year
Appendix	NA	NA	NA
Cecum	98	70	61
Colon	14	33	29
Lung	24	39	32
Pancreas	60	62	50
Rectum	33	48	28
Small Intestine	103	80	69
Stomach	29	45	32

*NA = not assessed due to small numbers

3) In the section Medical Treatments for Advanced Disease: Please check this information and fix it, if necessary. "In the 44 patients with PCs in RADIANT-2, the PFS was 13.6 months in the everolimus plus octreotide arm and 5.6 months in the placebo plus octreotide arm (63)."

Thank you. We have confirmed that the PFS for the lung population (n=44) in RADIANT-2 was 13.6 months versus 5.6 months favoring the everolimus arm.

Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. The Lancet 2011;378(9808):2005-2012.

4) As a suggestion, it would be important to mention, if it is possible, to describe something about the ongoing trials in this field, such as the open-label phase II trial utilizing nivolumab and ipilimumab in patients with advanced NETs (NCT03420521).

Thank you for this suggestion. We have added this trial and also NCT04579757 to the medical managment section discussing immunotherapy.

Reviewer E

The authors review the diagnosis and multidisciplinary approach to pulmonary neuroendocrine tumors and DIPNECH. That is overall a well written and very informative review.

Thank you for your review.

A few comments and suggestions:

In line 297 “Direct anti-tumor effects of SSAs require SSTR expression on tumor cells and direct binding to multiple SSTR subtypes. This causes regulation of these multiple complex pathways resulting in inhibition of cell cycle arrest, inhibition of growth factors, and cell apoptosis.” Please clarify whether SSAs really inhibit cell cycle arrest or whether their engagement with SSR receptors actually lead to cell cycle arrest.

Thank you. We have revised this statement for more clarity.

Direct anti-tumor effects of SSAs require SSTR expression on tumor cells and direct binding to multiple SSTR subtypes. This causes regulation of these multiple complex pathways resulting in cell cycle arrest, inhibition of growth factors, and cell apoptosis.

Figure 6B shows a carcinoid tumorlet.

We agree that 6B is a carcinoid tumorlet in a patient with DIPNECH. The figure 6 caption has been modified to reflect that.
Line 1009 and 1010: Figure 6: Light microscopy representing neuroendocrine cell hyperplasia and carcinoid tumorlet in a patient with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Recommend also a table for the medical treatment

Thank you for this suggestion. We have added a table describing several clinical presentations in patients with advanced pulmonary carcinoid tumors and considerations for the medical management of each.

Round 2

Review Comments

The authors have answered all the questions addressed.

The manuscript is clearly improved and of high quality.

However, there are still some spelling mistakes that have crept into the text, and some syntax imperfections.

A proofreading by a native English speaker would be desirable.

We appreciate the reviewers time and comments and have addressed all the remarks. We're happy you find this improved.

Minor remarks:

Line 78-80:

"Despite lack of regulatory approvals for advanced disease, multiple options are available for advanced disease but should be sequenced according to the clinical status and disease biology."

Maybe the repetition of "advanced disease" could be avoided, to improve the sentence syntax.

We have changed to "Despite lack of regulatory approvals for advanced disease, multiple options are available but should be sequenced according to the clinical status and disease biology"

Line 101-102:

"PCs represent only 2% of all lung cancers, however, represent approximately 25% of NETs."

The repetition of the word "represent" could be avoided.

We have changed to " . PCs represent only 2% of all lung cancers, however, embody approximately 25% of NETs."

Line 116-118:

“Studies have questions this staging system owning that it may not reflect the biologic behavior of PCs and alternatives have been offered”

Orthograph should be controlled, i.e. “studies have questioned”

We have made this change

Line 145-146:

“While the presentation, work up, diagnosis and treatment overlap with NSCLC, PCs have several nuances require different methods and modalities”

Orthograph should be controlled, i.e. “several nuances that require”

We have added the word “that”.

Line 282: “The primary concern with this approach is pneumothorax, which occurs in approximately 20%”

Nonclear-cut terms should be avoided (“approximately” could be replaced by a clear-cut term: median? Mean?)

We have changed to: “The primary concern with this approach is pneumothorax, which occurs with an average of 20% of cases.”

Line 299: the reference should appear only as a number

Corrected

Line 319-320: The ref does not appear properly as recommended by the Authors guidelines. Please control all the ref to make them appear as the Authors guidelines.

This has been corrected. All titles of journals should be abbreviated according to the style used in Index Medicus

Line 348-349: “Underlying DIPNECH commonly manifests with shortness of breath with the majority of patients demonstrating an obstructive pattern on spirometry”

Please use a most concise term than “commonly” and precise the % of patients presenting shortness of breath according to the literature.

We have change this to say: Underlying DIPNECH commonly manifests with shortness of breath in a third of patients with the majority of patients demonstrating an obstructive pattern on spirometry.

Added in reference: (57) Almquist DR, Sonbol MB, Ross HJ, Kosiorek H, Jaroszewski D, Halfdanarson T. Clinical characteristics of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: a retrospective analysis. Chest 2021;159(1):432-434.

Line 354: there is a Ref duplicate

Line 354 cites the reference (58) Cavaliere S, al., as required. This is not a duplicate.

Line 498: the terme “REF” appear

We have deleted REF

Line 585: Please control the orthograph: “Figure 4 shows”

We have made this change

Line 757-758: “Another ongoing trial is NCT04579757 which surufatinib in combination with tislelizumab”

A word is missing: “which […word missing] surugatinib”

We have changed this to: Another ongoing trial is NCT04579757 which surufatinib in combination with tislelizumab in patients with advanced solid tumors including a NET cohort

Line 1180-1181: A word is missing.

“Wherever possible, we recommend that patients are assessed in a multidisciplinary setting at a high-volume NET centre.”

We have changed this to: Wherever possible, we recommend that patients be evaluated in a multidisciplinary setting at a high-volume NET center.