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DIPARTIMENTO DI MEDICINA (DIMED)
Sezione di Anatomia Patologica Generale

To Lian-Sheng Ma, Company Editor-in-Chief,

June, 8th 2020

Dear Editor,

Thank you for giving us the opportunity to re-submit our manuscript entitled "The histopathological landscape of rare oesophageal neoplasms" for your consideration for publication as an original research article in the *World Journal of Gastroenterology*.

We have carefully considered the editorial criticisms and revised the manuscript accordingly. Below is a point-by-point response.

Reviewer 1

1 Please note that the reviewing time is short (1 week) for this 64-pages manuscript. The reviewing comments are with regard to the first 20 pages. The authors report a review of rare histological type of esophageal tumors. The topic is of interest, the manuscript requires revision before publishing. Minor revision is required, however extensive. Long and complex sentences should be simplified: 1 idea/1 sentence.

Thank you for your comment. We modified the sentences as requested. We asked to an English editing service (i.e., SpringerNature author services) to shorten most of the long and complex sentences.

2 ex: page 7 "Glomus tumours //".

The sentence was modified as "Glomus tumours are mesenchymal neoplasms composed of cells resembling the modified smooth muscle cells of the normal glomus body. They account for less than 2% of soft tissue tumours [12].".

3 p8 ""OSs are unencapsulated //".

The sentence was modified as "OSs are unencapsulated but well-circumscribed tumours that are characterized by spindle cells with microtrabecular architecture. OSs can also present focal cellular pleomorphism with nuclear atypia, rare mitotic figures and a lymphoid infiltrate, also containing germinal centres [8,21]."

4 p8 "This neoplasm may develop //".

The sentence was modified as "These neoplasms may develop in many different anatomic sites (gastric location being the most common), but oesophageal calcifying fibrous tumours (OCFTs) are extremely rare, with fewer than ten cases described in the medical literature [23-25]."



5 p9 "Immunohistochemically, tumour cells //".

The sentence was modified as "On immunohistochemistry, tumour cells are positive for CD34 and, in a minor subset, SMA. Immunohistochemistry for AE1/AE3, desmin, CD117, DOG-1, S100 and ALK1 is negative."

6 p11 "The most common symptom //"

The sentence was modified as "The most common symptom of OIFPs is dysphagia, but patients can also present with bleeding and gastro-oesophageal reflux disease. Occasionally, OIFPs can be asymptomatic [34, 35]."

7 p13 "IMTs are typically //"

The sentence was modified as "On immunohistochemistry, IMTs are typically positive for SMA. More than 50% of paediatric cases are positive for ALK, indicating the presence of ALK gene rearrangement. Furthermore, CD117, CD34 and EMA are consistently negative [43]."

8 p14 "OASC is rare, //"

The sentence was modified as "Oesophageal adenosquamous carcinomas (OASCs) are rare, with only a few dozen cases reported in the medical literature. OASCs are more common in male patients, with a median age of onset of 60 years [8,52], and the most common location is the middle third of the thoracic oesophagus [52]."

9 The authors should revise the use of cap letters (ex chapter titles).

The use of cap letters has been revised as requested.

10 Examples of words/phrases to revise: "prognostic behaviours" "orthodox dysphagia" "immunopositive" positive on IHC? expressed // on IHC "bigger tumors" larger tumors? "reported in literature" reported in the medical literature? "a risk of haemorrhaging does exist" risk of hemoragia? "CT" CT-scan "pathological examination" possibly ambiguous, histological analysis? microscopy-analysis? "just few cases" please nothe the approximative number, ex less than N cases? "may occur together" may associate? "discovered accidentally" incidentally? "pathological exam" examination? "almost always" in almost all reported cases? "by endoscopic means" by endoscopy? "under 2.5 cm" less than 2.5 cm "is needed" is required? "wart-like presentation" wart-like lesion? "it's" it is "synaptofisin".

We revised and modified all the words/phrases as requested.

Reviewer 2

Thank you for your kind revision.



Reviewer 3

1 As this manuscript is submitted to a GI journal, and a vast majority of these neoplasms are submucosal, the reviewer suggests 1–2 EUS images. This is particularly important as our approach to both diagnose and potentially remove such lesions is contingent upon which layer, mucosa (to include lamina propria and muscularis mucosa), submucosa, and muscularis propria is involved. Lesions that involve the muscularis propria are more commonly approached with submucosal tunneling (third space endoscopy), as opposed to ESD. Likewise, 1 or 2 CT or MR images would enhance this manuscript.

Thank you for your comments. We added EUS images as requested.

2 The reviewer suggests referencing Figure 1 images in the text, e.g., Oesophageal lipoma (OL). Figure 1F, Oesophageal neuroendocrine tumors (ONETs) and Carcinomas (ONECs), Figure 1A.

We added the images references in the main text.

3 Minor grammar suggests a. Kaposi Sarcoma: There are four forms of Kaposi Sarcoma... b. Conclusions: ...patients' prognosis is more subject... c. Conclusions: ...histology should always be taken in to account...

We corrected the grammar in those sentences as requested.

Reviewer 4

This is a well-written review about histopathologic features of rare benign and malignant esophageal neoplasms. The following remarks should be taken into account: 1. The text looks more like a book chapter and is very long for the purpose of a gastroenterology journal. 2. It would be probably more suitable for a pathology journal, however it offers precious information for a specialist in gastroenterology who wants to have a thorough study of esophageal lesions met in very rare occasions. 3. Consider splitting the text in two or three parts (eg rare benign lesions, rare malignant epithelial lesions, rare malignant non epithelial lesions) to make it more suitable for a medical journal and not a chapter in a book.

Thank you for your comments. We tried our best to describe the complexity of rare oesophageal neoplasms' landscape. The main text has been subdivided according to your suggestion in i) Introduction, ii) primitive benign/borderline tumours, iii) primitive malignant tumours of epithelial origin, iv) malignant tumours of non-epithelial origin, v) secondary tumours and vi) conclusion. The subdivision of the text aims to reflect the refinement of the taxonomy of oesophageal tumours, which are entities often with marked differences in their biology, epidemiology and clinical/surgical management. This subdivision is not merely academic, but necessary for the pathologist in order to consider all the differential diagnosis during his/her work and, ultimately, to make the correct diagnosis.



Reviewer 5

Thank you for your revision.

We hope you will find our manuscript suitable for publication and look forward to hearing from you.

Sincerely,

Matteo Fassan
Professor of Pathology
University of Padua, Italy



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DIPARTIMENTO DI MEDICINA (DIMED)
Sezione di Anatomia Patologica Generale

To Lian-Sheng Ma, Company Editor-in-Chief,

June, 19th 2020

Dear Editor,

Thank you for giving us the opportunity to re-submit our R1 manuscript entitled "The histopathological landscape of rare oesophageal neoplasms" for your consideration for publication as an original research article in the *World Journal of Gastroenterology*.

In your letter, you mentioned a file named "54931_List of issues that need to be addressed by authors in conditionally accepted manuscript" that was not available in my dashboard. However, the Scientific Editor uploaded the file "54931_RevisionReviewReport" and we modified the manuscript according to the reviewer's questions.

Below is a point-by-point response.

Reviewer 02803865

Thank you for your comments that significantly improved our submission.

Our manuscript has been revised by the Author Service of the Springer Nature that edited the grammar of the text. The correctness of the English language used in our manuscript is certified and guaranteed by this recognized editing service. Whilst taking into consideration all your suggestions, in some cases we preferred to maintain the phrasal constructions that have been provided by the service itself. Nevertheless, when your suggestions in grammar/vocabulary clearly improved the quality of our manuscript, we changed the text accordingly.

1. The authors could add a sentence on presenting which of the tumor types are rare and very rare

The incidence or the number of cases of each tumour are reported. This is more objective and the most updated references are cited.

2. Long and complex sentences should be simplified, ex 1 idea/1 sentence page 4 "Primary benign tumours //"



We modified the sentence in “Primary benign tumours of the oesophagus are overall rare, accounting for 1% or less of all oesophageal tumours at autopsy. In this category, the most common tumour type is leiomyoma ^[3]”.

3. page 7 "These neoplasms are usually //";

We modified the sentence in: “These neoplasms are usually found in subcutaneous tissues of distal extremities, but they can also occur in different anatomic sites. In particular, oesophageal glomus tumours (OGTs) are extremely rare, with fewer than ten cases described in the literature” ^[14].

4. page 12 ""A critical prerogative //"

We modified the sentence in: “A critical prerogative of GCTs is their potential malignant degeneration (1-2% of cases). In light of this, the diagnostic approach for these diseases should primarily be aimed at excluding the malignant behaviour of these lesions ^[38]”.

5. "The typical endoscopic appearance //"

We modified the sentence in: “The typical endoscopic appearance of benign OGCTs is a yellowish, smooth surfaced, firm lesion covered by intact mucosa. Conversely, mucosal ulceration is suspicious for malignancy ^[36]”.

6. The authors could avoid repetitive words in a same paragraph

We modified the text as suggested.

7. The authors could discuss the presence of cartilage in esophageal hamartomas briefly



We discussed the presence of mature cartilaginous tissue.

8. They could also add informations on multiple granular cell tumors: only esophageal, esophageal and extra-esophageal

Although extremely interesting, this topic does not fulfil the purpose of our manuscript(which is already too long for 2 out of the 5 reviewers).

9 the authors could add "to the knowledge of the authors" as medical literature/literature is vast, difficult to evaluate. They could note "as evaluated by PubMed/other databases search results", similar.

We underlined that the last literature review was performed in April 2020 and add this sentence "Biological features, clinicopathologic characteristics, major diagnostic issues and potentially useful diagnostic means will be discussed for each entity as evaluated by PubMed search results (April 2020)."

10 "have never been reported in inherited syndromes"

We added to the knowledge of authors, as suggested.

11 "SMA" note as entire words at 1st occurrence in the manuscript text

"Smooth muscle actin (SMA)" is reported at page 9, talking about the oesophageal leiomyomas.

12 The authors could also add available informations on the sizes (minimal, maximal) for each type of tumor presented. A classification into infra-centimetric, larger, milimetric could be of interest.



Although interesting, this part could not be satisfyingly developed due to the lack of statistically significant information about the size of many tumours.

13 "Small lesions // approximately 2-5 cm //" The authors could add a comment on what is understood by small tumors, the size of 2 cm is considered relatively large

We have cancelled the word "small" for sake of simplicity. As is described in the text, "small" are considered those lesions whose major axis is comprised between 2 and 5 cm and could be treated by endoscopic resection.

14 "these diseases" these tumors

We have changed the word as suggested.

15 "principal treatment modality" main treatment modality?

We have changed the word as suggested

16 "more common in Asians than in people from other continents" more frequent in the Asian race? Asian people than in non-Asian people?

Less than 100 cases of oesophageal adenoid cystic adenocarcinoma are described in literature, and half of them have been described in Asians living in Asiatic. Since the risks factor of that neoplasm are not understood we cannot assume that only ethnic/genetic factors are involved, excluding the environmental ones "a priori". The sentence was modified as "OACCs are more common in Asians and generally affect men in their seventh decade of life [48,49]. OACCs typically occur in the middle third of the oesophagus [50]."

17 "according to the primary component alone" according to the predominant component



We have changed the word as suggested

18 "Patients are generally male" are of male gender "

Sorry but the correction is not suitable in that context. We are talking about biological sex, not about gender (i.e. the fact of being male or female, especially when considered with references to social and cultural differences, not differences in biology)

19 The origin of OMEC is unclear" is not precised

In English language precise is not a synonym for clear.

20 "the most accredited" the most accepted "

We have changed the word as suggested

21 "it is important to recognize those entities" too general

We changed the sentence in "it is important to recognize those entities in order to decide the most suitable treatment for the patient"

22 "against angiogenic mechanisms" interfering with angiogenic mechanisms?

The sentences have been changed in "Finally, in recent years, a few clinical trials ^[79] have suggested the possible therapeutic value of molecular-targeted drugs inhibiting angiogenic mechanisms (e.g., bevacizumab)"

23 are needed" are required



We changed the word as suggested

24 "is more extensive" is more extensive microscopically?

We have changed the sentence as suggested in "Moreover, it is useful to assess resection margins since in most cases, the tumour is more extensive microscopically than is seen on gross examination of the resected specimen".

25 "just 40 cases" less than 50 cases, approximatively 40 cases

We have changed the sentence as suggested

26 All these features lead to major issues in the differential diagnosis" please precise "/"

We modified our sentence in "All these features help in the differential diagnosis from other oesophageal sarcomas, such as leiomyosarcomas and high-grade GISTs and occasionally metastatic desmoplastic melanoma [109,110,112,114]."

27 are beyond extremely rare, with just one case reported //" please simplify

We simplified the sentence as suggested.

28 "vague fascicles" vaguely delimited/formed fascicles?

We modified the sentence as suggested.

29 "irregular vasculature" irregularly disposed vessels? vessels of irregular form/aspects?



We modified the sentence in "...forming vessels of irregular morphology or slits...".

30 "Kaposi sarcoma is positive for //" expressed //?

We modified the sentence in "On immunohistochemistry, Kaposi sarcoma expresses ERG, CD31, CD34, and HHV-8, with HHV-8 being 100% specific for Kaposi sarcoma [144,146]."

31 "skin, subcutis"

We deleted "subcutis"

32 "little cytoplasm" scant cytoplasm

We changed the word as suggested

33 "FISH is important to support the diagnosis" which FISH?

We modified the sentence in "FISH analysis for the t(11;22) translocation is important to support the diagnosis".

34 "might seriously decrease" significantly decrease?

We changed the word as suggested.

35 "whole surgically removed lesion" entire?

We changed the word as suggested.



We hope you will find our manuscript suitable for publication and look forward to hearing from you.

Sincerely,

Matteo Fassan
Professor of Pathology
University of Padua, Italy