

Responses to issues raised in the peer-review report (Manuscript NO.: 86780, Case Report):

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (High priority)

**Specific Comments to Authors:** The manuscript is about a work trying to find an explanation for the occurrence of esophageal cancer and duodenal cancer. The authors explain very well the difference between cyclonic and metaclonic tumors. The manuscript is excellent and should be published, but the authors do not relate the association of esophageal cancer with duodenal cancer in the Chinese population. It should also be noted that the esophagus and duodenum originate in the foregut, and mutation of the lining cells during intrauterine life cannot be excluded.

Response:

At the prompting of the reviewers, we reviewed the literature and made the following additions:

Several studies have shown that both esophageal and duodenal cancers are associated with gastroesophageal reflux disease (GERD), which can lead to damage to the mucous membranes, thereby increasing the risk of cancer in China. Both tumors are associated with a number of genetic and environmental factors. For example, certain genetic mutations, smoking, alcohol consumption, poor nutrition, and other factors may, all increase the risk of esophageal and duodenal cancer. It should also be noted that the esophagus and duodenum originate in the foregut, and mutation of the lining cells during intrauterine life cannot be excluded in this case.

Reviewer #2:

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Rejection

**Specific Comments to Authors:** Huang et al described the case of a patient with metachronous esophageal squamous cell carcinoma and duodenal adenocarcinoma. Main comments: 1) I do not see any particular novelty in describing this case. Metachronous cancers are quite common. 2) I do not understand the significance of raised AFP. 3) Electro-gastroscopy??? 4) An abnormal duodenal picture was seen during first gastroscopy. I do not understand why a biopsy was not taken in that occasion. 5) The discussion is too long and not focused on the case.

Response:

- 1) Metachronous cancers are growing more prevalent, which are very rare in combination with duodenal adenocarcinoma. Currently, we have found only one article published in 2001 reporting duodenal adenocarcinoma complicated by quintuple carcinoma in the literature base. Furthermore, we have detailed analyses in TME and multi-omics of metachronous cancers, which are hardly published. Through the analysis of histology data, we sought to: 1) identify the reasons responsible for the poor prognosis and treatment resistance observed in this case; and 2) offer novel diagnostic and therapeutic approaches for MPMNs.
- 2) Some tumors have the AFP-secreting function. The presence of somewhat increased levels of AFP in this patient's peripheral blood is not clinically significant enough to diagnose an "AFP-secreting tumor". The diagnosis is often made when immunohistochemistry in pathological material detects AFP expression or when the serum alpha-fetoprotein level is more than 20 ng/ml. Therefore, we considered that mildly high AFP levels are not of clinical significance
- 3) The initial diagnostic endoscopy was performed at another regional center

hospital, so the patient only provided a discharge summary and we were unable to obtain high-resolution images and originals.

- 4) The initial diagnostic endoscopy was performed at another regional central hospital. We also mentioned the lack of further pathologic biopsy of duodenal bulb ulcers in our article. As noted, this is an empirical lesson for the clinician, who should thoroughly analyze each suspicious lesion to avoid missed diagnoses.
- 5) We have richly reviewed and discussed the diagnostic and therapeutic ideas of MPMN in light of this case and more excellent literature. We also synthesize the reasons for the poor prognosis and treatment resistance of this case through histological data. Therefore, the content of this part is large, but we will make appropriate deletions.

**Reviewer #3:**

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** STATUS: ACCETTABLE FOR PUBLICATION PENDING MINOR REVISIONS  
General considerations: This is a case report article. The paper is well-written. The work is very interesting and there are only a few articles in literature about this topic. Overall, the teaching that can be learned from reading the article makes it extremely useful for spreading the concept of MPMs, which remain few known to the public. I recommend its publication, pending minor revisions.  
Abstract: the abstract appropriately summarize the manuscript without discrepancies between the abstract and the remainder of the manuscript.  
Keywords: adequate.  
Paper On some aspects, the authors should address: 1)I would like you make a historical reference to the definition of Warren and Gate. -Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and statistical study. Am J Cancer 1932; 16: 1358-414. 2)In the text, I think it would be useful a deep-in

discussion about the rare possibility of metastatic involvement in duodenum. In this setting, you must read, discuss and cite the following article, which describe superlatively a metastatic involvement the duodenum: -Campanile F, Maurea S, Mainenti P, et al. Duodenal involvement by breast cancer. *Breast J*. 2012 Nov-Dec;18(6):615-6. doi: 10.1111/tbj.12034. Epub 2012 Oct 30. 3)About the digestive system MPMs, try to take a cue from the following article in which the authors describe the occurrence of four primary adenocarcinomas of the colon and ileum, in which you can find also an imaging and pathology characterization of liver metastases: -Synchronous mucinous colonic adenocarcinoma and multiple small intestinal adenocarcinomas: report of a case and review of literature. *Clin Imaging*. 2015 May-Jun;39(3):538-42. doi: 10.1016/j.clinimag.2014.12.019. Epub 2015 Jan 7. PMID: 25744428. 4)You need to discuss about the role of imaging in the diagnosis and staging of MPMs. The following article demonstrates the multivalence of contrast-enhanced Computed Tomography (CT). Additionally, you can use case the data of this article to compare it to yours. Discuss the article and cite it. -Synchronous tumours detected during cancer patient staging: prevalence and patterns of occurrence in multidetector computed tomography. *Pol J Radiol*. 2020 May 26;85:e261-e270. doi: 10.5114/pjr.2020.95781. PMID: 32612725; PMCID: PMC7315052. Reference: please, add the ones that I suggested you.

Response:

- 1) Following the reviewer's suggestion, we will make a historical reference to the definition of Warren and Gate in the part of the INTRODUCTION.
- 2) We will add a deep discussion about the rare possibility of metastatic involvement in the duodenum according to related articles.
- 3) Referring to the article recommended by the reviewer, we searched for more literature on MPMNs of the digestive system and analyzed the pathological and imaging features of multiple tumors of the digestive system in the article.
- 4) We will add to the article a discussion of the role of imaging in the diagnosis and staging of MPMNs.

**We think that these three reviewers gave sincere and valuable comments,  
which were of great help to us in revising the article.**



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## JOURNAL EDITORIAL BOARD'S REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Surgery

**Manuscript NO:** 86780

**Title:** Metachronous primary esophageal squamous cell carcinoma and duodenal adenocarcinoma: A case report and review of literature

**Journal Editor-in-Chief/Associate Editor/Editorial Board Member:** Osman Nuri Dilek

**Country/Territory:** Turkey

**Editorial Director:** Jin-Lei Wang

**Date accepted review:** 2023-10-16 05:14

**Date reviewed:** 2023-10-17 08:57

**Review time:** 1 Day and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	language polishing	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Major revision

## JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

Well documented paper and interesting patient presentation. Rare entity. May be helpful and innovative approach for readers.

### **Response to reviewer comments. (Manuscript NO.: 86780, Case Report) :**

Thanks for the comment, and we believe it will be helpful and innovative approach for readers.

## JOURNAL EDITORIAL BOARD'S REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Surgery

**Manuscript NO:** 86780

**Title:** Metachronous primary esophageal squamous cell carcinoma and duodenal adenocarcinoma: A case report and review of literature

**Journal Editor-in-Chief/Associate Editor/Editorial Board Member:** Raja Kalayarasan

**Country/Territory:** India

**Editorial Director:** Jin-Lei Wang

**Date accepted review:** 2023-10-16 09:59

**Date reviewed:** 2023-10-17 11:14

**Review time:** 1 Day and 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	language polishing	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Major revision

## JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

The authors have satisfactorily responded to the queries raised by the reviewers and modified the discussion accordingly.

### Response to reviewer comments. (Manuscript NO.: 86780, Case Report) :

Thanks for the comment, and we hope to present a more satisfying article through revisions.

## JOURNAL EDITORIAL BOARD'S REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Surgery

**Manuscript NO:** 86780

**Title:** Metachronous primary esophageal squamous cell carcinoma and duodenal adenocarcinoma: A case report and review of literature

**Journal Editor-in-Chief/Associate Editor/Editorial Board Member:** Vishal Gupta

**Country/Territory:** India

**Editorial Director:** Jin-Lei Wang

**Date accepted review:** 2023-10-16 14:54

**Date reviewed:** 2023-10-17 11:32

**Review time:** 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair		<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Major revision

## JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

1. Manuscript needs a major revision in terms of its language.
2. It is recommended to use standard universal terminology. Terms like electro-gastroscopy, drainage of spinal metastases, mid-lower esophagus occupancy, occupancy in the descending duodenum, puncture biopsy, puncture pathology etc are confusing for the international readers.
3. What was the purpose of getting barium study after endoscopy. Is it routine protocol at the authors institute. What is the significance of tumor markers CEA, CA19.9, and AFP in squamous cell carcinoma of the esophagus.
4. What the actual surgical procedure performed for the ca esophagus.
5. Discussion part is too long and needs to be shortened.
6. Discussion: Dont agree with statement that "Distinguishing metastasis from tumor recurrence is essential for an accurate diagnosis of MPMNs" Rather tumor recurrence (including metastases) should be distinguished from second primary for an accurate diagnosis of MPMNs.
7. Could author identify common genetic



aberration(s) involved in this case which could explain synchronous double primary malignancies. It would be surprising to find any as both the primaries were different histologically.

**Response to reviewer comments. (Manuscript NO.: 86780, Case Report) :**

1. Manuscript needs a major revision in terms of its language.

We have revised and certified the language and will polish it even more.



2. It is recommended to use standard universal terminology. Terms like electro-gastroscopy, drainage of spinal metastases, mid-lower esophagus occupancy, occupancy in the descending duodenum, puncture biopsy, puncture pathology, etc are confusing for international readers.

We have modified the above terms using standardized generic terminology. In the part of "Figure Legends" and "Imaging examinations" sections, we changed "electro-gastroscopy" to "gastroscopy", "drainage of spinal metastases" to "identification of spinal metastases", "mid-lower esophagus occupancy" to "localization in the lower-middle esophagus", "the descending duodenum" to "descending portion of the duodenum", "puncture biopsy" to "needle biopsy", "puncture pathology" to "needle biopsy", etc.

3. What was the purpose of getting barium study after endoscopy. Is it routine protocol at the authors institute. What is the significance of tumor markers CEA, CA19.9, and AFP in squamous cell carcinoma of the esophagus.

1) Firstly, as mentioned in the article, endoscopy and surgery were performed in different hospitals, and the indications for surgery need to be assessed preoperatively, including "site, size", etc., which are not described in detail in the endoscopy report (The presence of ulcerative lesions

in the left wall of the esophagus. These lesions were brittle and prone to bleeding when touched.).

2) Secondly, barium meal can better show mucosal lesions, and tumor length, dynamically observe the movement status of the esophageal wall, and show the relationship between the esophagus and surrounding tissues. This is a level II recommendation for diagnosing esophageal cancer, according to the Chinese Society of Clinical Oncology (CSCO, 2023).

3) Thirdly, blood tumor markers are widely used in gastric, colorectal, and pancreatic cancers, etc., whether for staging examination or postoperative follow-up and treatment evaluation. Unfortunately, in esophageal squamous carcinoma, the specificity and sensitivity of blood tumor markers are very poor, and it is difficult to apply tumor markers to judge the prognosis and therapeutic efficacy in clinical observation. Previous studies have found that many patients have very small changes in the values of tumor markers, which cannot be applied to judge the condition and evaluate the therapeutic effect. Therefore, blood tumor markers such as CEA, CA199, and AFP, have very little significance in staging and judging the prognosis of squamous esophageal carcinoma. Additionally, some tumors have an AFP-secreting function. The presence of somewhat increased levels of AFP in this patient's peripheral blood is not clinically significant enough to diagnose an "AFP-secreting tumor". The diagnosis is often made when immunohistochemistry in pathological material detects AFP expression or when the serum alpha-fetoprotein level is more than 20 ng/ml.

4. What the actual surgical procedure performed for the ca esophagus.

We mentioned in lines 11-13 of the "**History of past illness**" section that the patient underwent a "thoroscopic laparoscopy combined with radical resection of esophageal tumors".

5. Discussion part is too long and needs to be shortened.

Considering the comprehensive examination and evaluation of this patient, we have richly reviewed and discussed the diagnostic and therapeutic ideas of MPMN in light of this case and more excellent literature. We also synthesize the reasons for the poor prognosis and treatment resistance of this case through histological data. Therefore, the content of this part is large, but we have made appropriate deletions.

6. Discussion: Dont agree with statement that "Distinguishing metastasis from tumor recurrence is essential for an accurate diagnosis of MPMNs" Rather tumor recurrence (including metastases) should be distinguished from second primary for an accurate diagnosis of MPMNs.

We agree with the editorial board. Because of the inappropriate use of prepositions in this sentence, a different viewpoint is expressed. We have corrected it as "Tumor recurrence (including metastases) should be distinguished from the second primary for an accurate diagnosis of MPMNs".

7. Could author identify common genetic aberration(s) involved in this case which could explain synchronous double primary malignancies. It would be surprising to find any as both the primaries were different histologically.

Based on the available literature and data, we could not identify common genetic aberration (s) involved in this case that could explain the synchronous double primary malignancy. As mentioned in the article, ESCC often has mutations in CDKN2A, TP53, EP300, and CCND1, while APC and SMAD4 are commonly altered genes in small bowel cancer, which is consistent with the results of this case. Combined with a PubMed index, this phenomenon is in accordance with the "multiple origins theory".