Response Letter

Dear etidor and reviewers:

We extend our deepest gratitude to the reviewers for their rigorous evaluation and expert guidance. Each comment has been meticulously considered, leading to critical enhancements in case interpretation and scholarly rigor. The following responses detail all changes implemented, with corresponding revisions tracked in the manuscript using yellow font (new content).

Peer-Review Report(s):

Reviewer #1:

Comment 1: In terms of revisions, I have only minor suggestions to enhance the manuscript's polish and readability: Technical Presentation: It would greatly facilitate the review process, both now and for future readers, if the manuscript included standardized page and line numbers. This is a standard practice that allows for precise referencing of comments and corrections. Language and Typographical Errors: The scientific content is clear, but the manuscript would benefit from a final, careful proofread. I identified two specific instances of typographical errors: In the second paragraph of the Discussion section, the second line contains a duplicated word, "originating." In the third paragraph of the Discussion, the third line contains a duplicated word, "or." A thorough check to eliminate such minor errors will improve the overall flow and professionalism of the text.

Response: Thank you for your sincere suggestion. For Technical Presentation, we have made page and layout adjustments in accordance with the requirements of this magazine. For Language and Typographical Errors, we have carefully checked and verified the article multiple times, and after making the revisions, we sent the article to an English professional editing agency again for language polishing.

Reviewer #2:

Major revisions

Comment 1: Soften / verify the “longest documented latency” claim

The manuscript repeatedly states this is the “longest documented interval” to esophageal metastasis from CRC. Unless the authors performed a systematic review of the literature (methods + search dates) this definitive claim is not supportable. Either: (A) run and report a short systematic search (years/databases/search terms) or (B) rephrase to “one of the longest reported intervals” / “an ultra-late solitary esophageal metastasis”.

Add a Methods paragraph describing your literature search (databases, dates, key terms) or revise language in Abstract/Discussion.

doi: 10.1002/ijc.34871. PMID: 38323453.

Response: I sincerely appreciate your insightful comments. Thanks to your kind reminder, we have realized that our wording was indeed inappropriate. Currently, there is no report of

cases of a solitary mid-esophageal metastasis presenting 10 years after curative resection of stage I rectal adenocarcinoma. For the sake of scientificity and accuracy, we have rephrased all the relevant expressions to "one of the longest reported intervals" / "an extremely late solitary esophageal metastasis".

I have carefully read the article you mentioned "Nors J, Gotschalck KA, Erichsen R, Andersen CL. Incidence of late recurrence and second primary cancers 5-10 years after non-metastatic colorectal cancer. Int J Cancer. 2024;154(11):1890-1899. doi:10.1002/ijc.34871". This article does not advocate conducting follow-up for colorectal cancer patients beyond a five-year follow-up period based on big data. Our case study does not dispute their conclusion. What we would like to emphasize instead is that even for early-stage tumors, if the standard follow-up period has been exceeded, the possibility of atypical site metastasis still exists. This should draw the attention of clinicians. We have also made this expression more precise and rigorous. The latest statement is "Even beyond standard follow-up windows, early-stage tumors still have the possibility of metastasizing to atypical sites, which should draw the attention of clinicians".

Comment 2:Pathology and molecular clonality: strengthen evidence of origin

The IHC panel (CDX2+, SATB2+, CK7−, CK20+) supports colorectal origin, but for a unique/ultra-late metastasis, stronger comparative molecular proof is desirable. You report KRAS wild-type and p53 mutant pattern in both samples — but you do not present NGS / identical mutation calls or allelic profiles.

Ideally need to perform targeted NGS (if available) on both 2015 primary and 2025 esophageal lesion and show shared somatic mutations (oncogenic driver(s)). If NGS not available, explicitly state this limitation and provide the full IHC/molecular report (dates, labs, assay versions). Add a sentence discussing the limitations of using only IHC for clonal assignment.

Response: We sincerely appreciate the reviewer's careful and thoughtful evaluation.Based on the laboratory testing conditions, we did not conduct a comparison using NGS testing. However, we have conducted immunohistochemical(IHC) and fluorescence PCR analyses on the primary rectal lesion and the esophageal metastatic lesion. And according to your request, detailed information about IHC and molecular testing has been presented in the article. IHC evidence has confirmed the homology of the two. Genetic status testing can not only support this judgment but also provide important basis for the treatment of patients. However, we must admit that using NGS for whole-genome sequencing to identify cancer-causing genes is the most rigorous approach. Therefore, in the discussion section, we have outlined the relevant limitations as follows, "However, it must be noted that while IHC profiles are highly indicative, they do not constitute definitive proof of clonal origin. The most conclusive

evidence would be the demonstration of identical somatic mutation patterns via next-generation sequencing in both lesions[16], which could not be performed in this case. Nonetheless, in clinical practice, a conclusive IHC profile remains a robust and widely accepted diagnostic tool[15]".

Comment 3: Imaging staging completeness — include PET-CT / systemic staging

The manuscript says "comprehensive imaging (including pelvic imaging) revealed no other disease" but does not state whether a whole-body PET-CT was performed. PET-CT is often used to exclude occult systemic disease and would strengthen the diagnosis of solitary esophageal metastasis.

State explicitly which modalities were performed, dates, and results (CT chest/abdomen/pelvis vs PET-CT). If PET-CT was not done, justify. Add representative PET images if available.

Response: We sincerely thank the reviewers for their valuable suggestions and the recommended references. In fact, when the patient visited the thoracic surgery department with dysphagia in March, the thoracic surgeon had recommended the patient undergo a PET-CT examination to determine the tumor stage. The examination indicated that the lesion was confined to the esophagus fused with enlarged lymph nodes, and no recurrence in the rectum or other distant metastasis signs were observed. This was also one of the reasons why the thoracic surgeon misdiagnosed the patient as having primary adenocarcinoma of the esophagus. After knowing that the esophageal lesion originated from the rectum, considering the inaccuracy of the original treatment plan, the MDT team immediately arranged the patient to undergo CT scans of the neck, chest and abdomen, magnetic resonance imaging(MRI) of the head and pelvis, radionuclide bone imaging, and colonoscopy to confirm that there was no distant metastasis in the patient within the past two months. The relevant results indicated that there was no recurrence in the local rectum and no abnormalities were found in other parts of the body (May 10, 2025, Department of Imaging, Affiliated Hospital of NSMC, Endoscopy Center of Affiliated Hospital of NSMC). The colonoscopy was normal.

We admit that in the article, this description was not very clear. In the manuscript, we immediately provide a detailed explanation. We stated that the patient had undergone PET-CT examination when visiting the thoracic surgery department, and attached the whole-body uptake map with SUVmax = 27. We described it in the original text as follows, "The Positron Emission Tomography-Computed Tomography (PET-CT) examination indicated a tumorous esophageal lesion integrating with an enlarged mediastinal lymph node , with no sign of local recurrence of the rectum or systemic metastasis observed on

February 17th, 2025 (Nuclear Medicine Department of the Affiliated Hospital of North Sichuan Medical College (NSMC)) (Figure 5).“

At the same time, we also explained that after the diagnosis of esophageal metastasis, the patient underwent neck, thoracic, full abdominal CT, head and pelvic magnetic resonance, and colonoscopy. The examination results supported the diagnosis of solitary esophageal metastasis.We described it in the original text as follows, “Given the inaccuracy of the previous treatment plan, the patient immediately underwent CT scans of the neck, chest and abdomen, MRI of the head and pelvis, radionuclide bone imaging, and colonoscopy, in order to determine whether new lesions had appeared among the past two months (March 22th, 2025, Imaging Center and Endoscopy Center of the Affiliated Hospital of NSMC). All results supported a solitary esophageal metastasis without local recurrence of the rectum or distant metastasis.”

Comment 4:Rationale for systemic regimen and sequencing

The choice of neoadjuvant immunochemotherapy (nedaplatin + nab-paclitaxel + tislelizumab) initially (when lesion was thought to be primary esophageal adenocarcinoma) is non-standard for esophageal adenocarcinoma. After reclassification, treatment changed to CAPOX + cetuximab (KRAS WT) concurrent with RT. Provide the rationale and evidence basis for:

Add a short paragraph in Methods/Case explaining MDT rationale and cite relevant literature on cetuximab in KRAS WT metastatic CRC and on chemoradiation regimens for esophageal lesions.

Response: We sincerely appreciate your thoughtful and constructive feedback. Initially, when the esophageal lesion was presumed to be a primary esophageal adenocarcinoma based on endoscopic appearance and biopsy pathology, the neoadjuvant regimen of nedaplatin, nab-paclitaxel, and tislelizumab were selected by thoracic surgeon. According to the guidelines of CSCO and ASCO, for primary adenocarcinoma of the esophagus, fluorouracil should be the main treatment drug, and the chemotherapy regimen of paclitaxel combined with platinum is not currently recommended. During the MDT discussion, the MDT team also raised doubts. The thoracic surgeon responded that based on their experience, the combination of fluorouracil and platinum-based drugs has a higher chance of causing adverse reactions in patients and their combination, while not the global standard, is explored in clinical trials for locally advanced esophageal carcinoma in some regions, aiming to leverage potential synergistic effects of immunotherapy with chemotherapy(Neoadjuvant Therapy of PD-1 Blockade Combined With Chemotherapy for Esophageal Carcinoma ClinicalTrials.gov ID NCT05777707). However,we admit that this option is not a standard

treatment plan lack of high-quality clinical evidence and have also pointed out in the manuscript that this pattern is not standard.

Upon definitive pathological reclassification confirming metastatic colorectal adenocarcinoma (CDX2+, SATB2+, CK7-, CK20+) with KRAS wild-type status, the therapeutic plan was promptly adjusted to align with guidelines for metastatic CRC. The MDT recommended concurrent chemoradiation with CAPOX (capecitabine and oxaliplatin) and cetuximab. The rationale was twofold:

For systemic control: The addition of cetuximab, an anti-EGFR monoclonal antibody, to a doublet chemotherapy backbone is a standard-of-care and guideline-recommended option for patients with RAS wild-type metastatic CRC, based on improved outcomes demonstrated in pivotal trials.

For local control: Concurrent radiotherapy was delivered to the solitary metastasis to achieve maximal local tumor debulking and symptom relief. The CAPOX regimen was chosen as the radiosensitizing systemic component due to its efficacy in CRC and the known activity of fluoropyrimidines (capecitabine) with radiotherapy.

We have added a short paragraph in Case explaining MDT rationale and cite relevant literature on cetuximab in RAS WT metastatic CRC and on chemoradiation regimens for esophageal lesions in discussion:"The MDT immediately adjusted the treatment plan for metastatic CRC. Adding cetuximab to chemotherapy including capecitabine and oxaliplatin (CAPOX) in *RAS* wild-type metastatic CRC has shown to significantly increase response rates and prolong survival. In order to quickly alleviate the patient's dysphagia, simultaneous radiotherapy was performed on the solitary metastatic lesion, which enabled the local tumor to shrink to the greatest extent and relieved the symptom. Concurrent oral administration of capecitabine has also been proven to be an effective radiosensitizing component. On March 24th, 2025,".

Comment 5:Radiotherapy details: expand and document toxicity

Add a short RT Planning subsection with these dosimetric parameters and acute toxicity reporting (CTCAE v5.0).

Response: Thank you for your suggestion. Based on the patient's radiotherapy plan, we have documented the radiotherapy techniques, segmentation methods, prescribed doses, and doses to major organs at risk. Additionally, we have added the occurrence of Grade 1 bone marrow suppression in the patient. We revised it in the original text as follows,"the patient received involved-field radiotherapy using Volumetric Modulated Arc Therapy (VMAT). The planning target volume (PTV), encompassing the esophageal metastasis and involved mediastinal lymph nodes, was prescribed a total dose of 50.4 Gy in 28 fractions (1.8 Gy per fraction), delivered five days per week (Figure 8). The doses to surrounding organs at risk were

rigorously constrained within accepted tolerance limits to minimize toxicity, as detailed below: Lungs: the mean dose(Dmean) was kept below 8.05 Gy, with the volume of lungs receiving 20 Gy below 9.01% and 5 Gy below 48.14%; Spinal cord: the maximum dose was strictly limited to below 41.46 Gy; Heart: the Dmean was kept below 21.96 Gy, with the volume of heart receiving 30 Gy below 18.63% and 40 Gy below 7.11%. ".

Comment 6: Follow-up duration and outcomes

Current oncologic outcome is only 3 months follow-up (PR by RECIST). For claims about durable control / surveillance implications, readers need longer follow-up or caution in interpretation. State clearly the date of last follow-up and that outcome is interim. Avoid overinterpretation.

Response: We thank the reviewer for highlighting this important point. We agree that the follow-up duration is short and that claims regarding durable control would be premature. Accordingly, we have made the following changes to the manuscript to ensure cautious interpretation.

We have explicitly stated that the date of the last follow-up in the results section is "On August 1st,2025".

We have clearly labeled the current outcome as a "short-term" partial response. We have revised the discussion to avoid any overinterpretation regarding long-term control. Instead, we now emphasize the rationale for the chosen treatment approach, and the initial positive response to this tailored therapy, while explicitly stating that ongoing surveillance is essential to determine long-term outcomes. We revised it in the original text as follows, "This early outcome highlights radiotherapy as a highly effective modality for rapid symptom palliation in such scenarios. However, it is critical to emphasize that our data represent only an interim analysis of three months. The long-term efficacy and durability of this combined-modality approach remain to be established through ongoing follow-up.".

Comment 7: Systematic mini-review / table of prior cases

To contextualize rarity, include a concise table summarizing previously reported esophageal metastases from CRC: author/year, interval from primary, primary stage, site in esophagus, diagnostic method, treatment, and outcome. This directly addresses the "longest latency" claim and is an excellent addition for readers.

Response: We appreciate the reviewer's valuable suggestion. Following this recommendation, we performed a focused literature search in PubMed, Embase, and Web of Science (search date: November 12, 2025) using the terms "(colorectal OR colon OR rectal) AND (esophagus OR esophageal OR oesophageal) AND (metastasis OR metastases OR secondary OR

metastatic)". Reports describing metastasis to the esophagus from a colorectal primary were included, and relevant data—such as the interval from primary diagnosis, tumor stage, lesion site, diagnostic method, treatment, and outcome—were extracted. A summary table (Table 1) has been added to the revised manuscript. It includes seven published cases of colorectal-to-esophageal metastasis (rectal or colonic origin) and the present case. Among these, our patient—developing a solitary esophageal metastasis 10 years after resection of stage I rectal adenocarcinoma—represents an ultra-late, exceptionally rare occurrence, now described as "one of the longest reported intervals". We discussed it in the first paragraph of the discussion as follows, "PubMed, Embase, and Web of Science databases were systematically queried on November 14th, 2025, using the following search terms: ("colorectal" OR "colon" OR "rectal") AND ("esophagus" OR "esophageal" OR "oesophageal") AND ("metastasis" OR "metastases" OR "secondary" OR "metastatic"). No language or date restrictions were applied. Titles and abstracts were screened. Reports describing metastasis to the esophagus originating from a colorectal or rectal primary were included. Data extracted from each report included: interval between the primary tumor and esophageal metastasis, primary tumor site and stage, location and characteristics of the esophageal lesion, diagnostic method, treatment, and outcome(Table 1). ".

Minor Revisions

Comment 8: Abstract

Make language precise: replace "represents the longest documented interval" with "one of the longest reported intervals" unless you add a literature search. Add follow-up time (e.g., "at 3 months follow-up").

Add a single line on diagnostic method used to confirm metastatic origin (IHC + comparison).

Response: To enhance the scientific nature and accuracy, we have made all the descriptions in the entire text change to "one of the longest reported intervals"/ "an ultra-late solitary esophageal metastasis".

We have clarified that the follow-up period is three months after the completion of radiotherapy. We described it in the abstract as follows,Three-month follow-up imaging after radiotherapy demonstrated a partial response. The patient was on cetuximab maintenance..

We made a modification based on your suggestion, and added a single line in the summary regarding the diagnostic method used to confirm the metastatic origin (IHC + comparison). We described it in the abstract as follows,"However, a multidisciplinary team re-evaluation, utilizing comparative IHC for the esophageal lesions and rectal specimens, confirmed the diagnosis as a solitary esophageal metastasis from rectal adenocarcinoma (*RAS* wild-type). "

Comment 9: Clarify questionnaires / scoring

You use EORTC QLQ-C30 dysphagia numbers (40 → 90 etc.). Confirm whether you mean the specific dysphagia item (usually in QLQ-OES18) or overall QLQ-C30 scores. Cite the instrument and scoring method.

Response: Thank you for your suggestion. We used the dysphagia scale of OES18 from the EORTC QLQ questionnaire according to "EORTC Quality of Life Group. EORTC QLQ-OES18 Questionnaire and Scoring Guidelines". We cite this instrument in the manuscript.

Comment 10: Ethics / consent

You state written consent and ethics approval — good. Move the ethics approval number to the Methods or Ethics statement in a standard journal position and ensure the consent statement explicitly confirms consent to publish images.

Response: Thank you for your kind reminder. Our research has been reviewed by the ethics committee of our institution. The patient in this case was also informed and gave consent for us to publish all the relevant textual materials and images. According to the requirements of the magazine, I have submitted the ethical approval document(approval number: 2025ER291-1), the patient treatment consent form, and the informed consent form for disclosing patient-related information.

Comment 11: References

Several references are older case reports — add/update with more recent ctDNA and dormancy literature (I list suggestions below). Ensure Vancouver formatting is consistent.

Suggested recent references to cite (add to your list and discuss in text)

(These are recent, high-relevance items you should cite in Discussion for dormancy, ctDNA-MRD, and RT dosing)

1. Collignon E. Unveiling the role of cellular dormancy in cancer (review). Curr Opin Oncol. 2024. (Use for dormancy clinical implications). (PubMed)
2. Nors J, et al. Incidence of late recurrence and second primary cancers 5–10 years after non-metastatic colorectal cancer. Int J Cancer. 2024;154:1890–1899. (Useful support for late recurrence incidence and screening). (PubMed)
3. Additional: include some representative case reports/reviews of esophageal metastasis

from CRC (Thomasset SC 2008; Simchuk/Low 2001; Chen 2022) — you already cite many; add the recent case reports you find in your mini review. (PubMed Central)

Response: We sincerely thank the reviewer for this excellent suggestion. We have now comprehensively updated and revised our reference list to include the most recent and relevant literature as recommended.

We have added the two highly relevant, recent publications suggested by the reviewer (Collignon et al., Curr Opin Oncol. 2024 and Nors et al., Int J Cancer. 2024) to the reference list.

We have integrated citations to these new references within the Discussion section to strengthen our arguments: The Collignon et al. (2024) review is now cited when discussing the clinical implications and mechanisms of tumor dormancy. The Nors et al. (2024) population-based study is now cited to provide robust, contemporary epidemiological support for the incidence of late recurrence beyond 5 years, which directly contextualizes our case .

We have also added the recent case report by Thomasset SC 2008; Simchuk/Low 2001; Chen 2022 to ensure our list includes up-to-date case reports.

We have meticulously checked the entire reference list to ensure strict consistency with the Vancouver formatting style, including standardizing journal abbreviations, author listings, and punctuation.

The updated reference list and their integration into the discussion provide a much stronger and more current foundation for our case report. The changes can be found in the Discussion section (Page five) and the updated Reference list.

Comment 12: Suggested edits to Discussion

Explain the differential diagnosis pathway and why primary esophageal cancer was initially favored, then overturned.

Response: Thank you for your suggestions. As for the patient, no abnormalities were detected in the thoracoabdominal computed tomography (CT) and endoscopy conducted in 2024. Therefore, when the patient visited the doctor in February 2025, based on the biopsy results and PET-CT examination results, the doctor wrongly diagnosed it as primary esophageal adenocarcinoma. After the patient completed two cycles of chemotherapy, his difficulty in

swallowing worsened. During the MDT discussion, the MDT team pointed out the possibility of rectal metastasis to the esophagus, although it is a rare occurrence. And comparative IHC was also performed. The results are identical(CDX-2+, SATB2+). We revised it in the manuscript as follows, The radiation oncologist initiated a MDT discussion. The MDT pointed out that the patient's neoadjuvant treatment plan was not standard, but considering that the history of rectal adenocarcinoma, a thorough re-evaluation of the esophageal pathology specimens was undertaken. " and "Given the inaccuracy of the previous treatment plan, the patient immediately underwent CT scans of the neck, chest and abdomen, MRI of the head and pelvis, radionuclide bone imaging, and colonoscopy, in order to determine whether new lesions had appeared among the past two months (March 22th, 2025, Imaging Center and Endoscopy Center of the Affiliated Hospital of NSMC). All results supported a solitary esophageal metastasis without local recurrence of the rectum or distant metastasis. ".

Comment 13: Suggested edits to Discussion

Discuss mechanisms of dormancy (angiogenic suppression, immune editing) briefly and cite the 2024 reviews.

Response: Thank you for your suggestion. We have briefly discussed the main positive aspects of the hibernation mechanism: angiogenic suppression and immune editing. The 2024 review was also recited. We revised it in the manuscript as follows,"Mechanistically, tumor dormancy can be sustained by angiogenic suppression, where DTCs remain avascular and unable to expand until neovascularization is triggered, and by immune editing, in which cytotoxic immune surveillance maintains equilibrium by eliminating proliferative clones[17,20].Studies have shown that non-metastatic CRC can still occur late recurrence and secondary primary cancers within five to ten years after curative treatment[21]".

Comment 14: Suggested edits to Discussion

Add a paragraph on the emerging role of ctDNA for extended MRD surveillance and the implications for detecting ultra-late relapse; cite Nakamura et al. (2024).

Response: Thank you for your suggestion. We have already discussed the mechanism, briefly explaining the significance of monitoring ctDNA and MRD, as well as the potential

value of them as long-term monitoring indicators. This enhances the depth of the article and provides a meaningful direction for potential future research directions. We revised it in the manuscript as follows,"ctDNA-based minimal residual disease(MRD) assays permit sensitive detection of molecular relapse prior to radiographic or clinical progression[22]. Studies find that ctDNA positivity strongly predicts recurrence and survival in resectable CRC, and serial monitoring increases detection yield[22]".

Comment 15: Suggested edits to Discussion

Discuss prognosis and expected outcomes for solitary metastasis treated with local therapy + systemic therapy, but caution that this is interim (3-month) data.

Response: Thank you for your suggestion. We have evaluated the short-term effectiveness of our treatment plan, but at the same time we have also cautioned readers that the long-term efficacy and durability of this method remain to be determined. We revised it in the manuscript as follows," This early outcome highlights radiotherapy as a highly effective modality for rapid symptom palliation in such scenarios. However, it is critical to emphasize that our data represent only an interim analysis of three months. The long-term efficacy and durability of this combined-modality approach remain to be established through ongoing follow-up.

The reviewers' expertise has been instrumental in elevating this work to meet the journal's high standards. We have tried our best to incorporate the suggestions. Once again, we sincerely appreciate the constructive feedback from the reviewers and the editorial team. We believe that these revisions have significantly strengthened the clarity, rigor, and impact of our work. We kindly request that you consider our revised manuscript for publication. We remain available for any follow-up requests.

Sincerely

Yu Zhang