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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 113494

Title: A solitary esophageal metastasis ten years after curative resection of stage I rectal adenocarcinoma: A case report

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 08365772

Position: Peer Reviewer

Academic degree and professional title: Assistant Professor, MD

Reviewer's Country/Territory: India

Author's Country/Territory: China

Manuscript submission date: 2025-08-26

Reviewer chosen by: Hong-Xin Jiang

Reviewer accepted review: 2025-10-27 05:03

Reviewer performed review: 2025-10-29 05:22

Review time: 2 Days

Content to be reviewed	Does the manuscript's content fall within the scope of the journal? Yes Is there any Key Word that is not included in the manuscript title? No Do authors' affiliations correspond to the content of the manuscript? Yes Does the Abstract contain the contents of each part of the manuscript (IMRaD)? Yes Are the Key Words complete? Yes
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Is the content of the Introduction adequate? **No**

Is the content of the Materials and Methods complete?
Not Applicable

Is the description of the experiments clear and complete? **Not Applicable**

Are the experimental data presented in the manuscript's biostatistics content reliable? **Not Applicable**

Are the experimental data of the Results true and reliable? **Not Applicable**

Are the quality and resolution of the images up to standard? **Yes**

Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **Yes**

Is the content of the Discussion reasonable? **No**

Is the Conclusion reasonable? **No**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **Yes**

Are all references related to the topic of the manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers?
Yes

Are additional experiments needed for the study? **Yes**



	Does the research scope comply with ethics? Yes
Scientific quality	Grade C (Good)
Novelty of this manuscript	Grade C (Good)
Creativity or innovation of this manuscript	Grade C (Good)
Scientific significance of the conclusion in this manuscript	Grade C (Good)
Language quality	Grade B (Very good)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Major revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

SPECIFIC COMMENTS TO AUTHORS

This is a well-written single-patient case report describing a solitary mid-esophageal metastasis presenting 10 years after curative resection of stage I rectal adenocarcinoma, with final diagnosis based on IHC (CDX2+, SATB2+) and comparison with the 2015 primary specimen, and treated with involved-field VMAT (50.4 Gy/28 fx) plus CAPOX + cetuximab with rapid symptomatic and radiological partial response. The manuscript highlights tumor dormancy and the need for prolonged surveillance. The clinical



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narrative and multi-disciplinary decision making are strengths, but the manuscript needs important clarifications, stronger evidence for some claims, improved pathology/molecular data, and a more systematic literature context to support the claim that this is the “longest documented” latency.

Major revisions

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.

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.

Imaging staging completeness – include PET-CT / systemic staging



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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.

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.

Radiotherapy details: expand and document toxicity

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

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.

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.

Minor revisions

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).

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.

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.

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*



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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)

Suggested edits to Discussion

- Explain the differential diagnosis pathway and why primary esophageal cancer was initially favored, then overturned.
- Discuss mechanisms of dormancy (angiogenic suppression, immune editing) briefly and cite the 2024 reviews.
- 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).
- Discuss prognosis and expected outcomes for solitary metastasis treated with local therapy + systemic therapy, but caution that this is interim (3-month) data.



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Position: Peer Reviewer

Academic degree and professional title: Associate Chief Physician

Reviewer’s Country/Territory: China

Author’s Country/Territory: China

Manuscript submission date: 2025-08-26

Reviewer chosen by: Hong-Xin Jiang

Reviewer accepted review: 2025-10-27 04:13

Reviewer performed review: 2025-11-01 02:29

Review time: 4 Days and 22 Hours

Content to be reviewed	<p>Does the manuscript’s content fall within the scope of the journal? Yes</p> <p>Is there any Key Word that is not included in the manuscript title? No</p> <p>Do authors’ affiliations correspond to the content of the manuscript? Yes</p> <p>Does the Abstract contain the contents of each part of the manuscript (IMRaD)? Yes</p> <p>Are the Key Words complete? Yes</p>
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Are additional experiments needed for the study? **No**

Does the research scope comply with ethics? **Not**



	Applicable
Scientific quality	Grade A (Excellent)
Novelty of this manuscript	Grade A (Excellent)
Creativity or innovation of this manuscript	Grade A (Excellent)
Scientific significance of the conclusion in this manuscript	Grade A (Excellent)
Language quality	Grade A (Excellent)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Accept
Re-review	No
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

SPECIFIC COMMENTS TO AUTHORS

I have had the opportunity to review the manuscript titled “Ultra-Late Solitary Esophageal Metastasis 10 Years After Curative Resection of Stage I Rectal Adenocarcinoma: A Rare Case Report.” This paper presents a genuinely rare and clinically instructive case of a solitary esophageal metastasis occurring a full decade after the curative treatment of a Stage I rectal adenocarcinoma. The authors have done a commendable job in documenting this unusual clinical scenario, which holds significant



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value for the oncological community.

The principal strength of this case report lies in its clinical relevance. Metastatic disease from colorectal primary cancers, while common in organs like the liver and lungs, is exceedingly rare in the esophagus, especially as a solitary and ultra-late recurrence. The manuscript provides a detailed and systematic account of the diagnostic journey, which is its most compelling aspect. The thorough description of the methodologies used – particularly the comparative immunohistochemical analysis (e.g., likely involving markers such as CK20, CDX2, and SATB2 versus CK7) and potentially endoscopic features – to definitively establish the esophageal lesion as a metastasis rather than a second primary cancer is both rigorous and educationally valuable. This diagnostic clarity is crucial, as it directly informs subsequent management decisions.

Furthermore, the discussion section effectively contextualizes this rare event within the existing medical literature. The authors appropriately analyze the potential mechanisms for such an unusual metastatic pattern, which may include hematogenous spread or other less common pathways. The detailed recounting of the treatment course, whether it involved surgical resection, systemic therapy, or radiotherapy, provides practical insights for clinicians who might encounter similar, albeit rare, cases. The follow-up data and the subsequent treatment recommendations derived from this unique experience are thoughtful and add to the paper's practical utility, guiding oncologists on long-term surveillance strategies even for early-stage cancer survivors.

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



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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.

In conclusion, this case report describes a noteworthy clinical phenomenon with a high degree of rarity and educational impact. The authors have presented a well-structured and logically argued account. The identified issues are minor and easily addressable. The manuscript makes a valuable contribution to the literature by alerting the medical community to the possibility of very late and atypical metastases, thereby promoting a higher index of suspicion and appropriate diagnostic workups. I am pleased to recommend this manuscript for acceptance after these minor revisions have been satisfactorily addressed.

I congratulate the authors on reporting this fascinating and clinically important case.