Dear WJG Editorial Office,

Thank you for reviewing our manuscript and providing constructive feedback. Please find below the queries and comments that we have addressed.

Science editor:
Issues raised:

1. The abstract section is too long, and it should be no more than 250 words;

Thank you for your suggestion. We have included a 250-word abstract below. We have not included the 250-word abstract in the manuscript yet as the WJG guideline we have followed had different specifications (https://www.wjgnet.com/bpg/GerInfo/200).

Background: Image-guided radiotherapy (IGRT) has significantly improved the precision in which radiotherapy is delivered in cancer treatment. Typically, IGRT uses bony landmarks and key anatomical structures to locate the tumour. Recent studies have demonstrated the feasibility of peri-tumour fiducials in enabling even more accurate delineation of target and normal tissue. This article reports the long-term outcomes of using a standard gastroscopy to inject liquid fiducials for the treatment of oesophagogastric tumours with IGRT.

Methods: A retrospective cohort study of consecutive adults with oesophagogastric cancers referred for liquid fiducial (LF) placement before definitive/neo-adjuvant or palliative IGRT between 2013 and 2021 at a tertiary hospital was conducted. Up to four LFs were inserted per patient. Liquid fiducial-based IGRT (LF-IGRT) consisted of computer-assisted direct matching of the fiducial region on cone-beam computerised tomography at the time of radiotherapy. Radiotherapy was delivered to 54Gy in 30 fractions for curative patients and up to 45Gy in 15 fractions for palliative treatments.

Results: 52 patients were referred for LF placement within the study period. A total of 51 patients underwent LF implantation. Of these a total of 31 patients received radiotherapy. Twenty-seven out of the 31 patients were able to have LF-IGRT. The cohort overall survival post-radiotherapy was 19 months (range 0 to 87 months). Whilst the progression-free survival post-radiotherapy was 13 months (range 0 to 74 months).

Conclusion: LF-IGRT was feasible in 87.1% of patients undergoing liquid fiducial placement through standard gastroscopy injection technique. Further studies are warranted to determine the long-term outcomes of LF-IGRT.

2. The authors should provide The signed Conflict-of-Interest Disclosure Form and Copyright License Agreement The authors did not provide original pictures. Please provide the original figure files. Please prepare and arrange the figures

using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Thank you for pointing this out. We have completed a conflict-of-interest disclosure and copyright license agreement form. A PowerPoint with all our figures and tables have been included.

3. PMID and DOI numbers are missing in the reference list. Please provide them.

Thank you for your comment. We have updated the reference list to the format requirements of the World Journal of Gastroenterology.

Reviewer #1:
Comments:

1. The authors use the wording fiducials. It is quite uncommon to apply this for fluid-based injection. Therefore, to keep the uniqueness of the method especially the difference to classical fiducial I personally would avoid the misleading wording and rather focus on marker (or lipiodol-marker etc).

Thank you for your suggestion. We have updated our terminology to better reflect the uniqueness of liquid fiducial markers. Where it is appropriate, we have used the term lipiodol markers and have distinguished our markers as liquid fiducials.

2. The authors claim the method is less expensive, but do not provide the information/comparison.

Thank you for your suggestion. We have discussed the cost-saving of liquid fiducial when compared to EUS-guided in our discussion.

3. Study flow chart is not complete: how many were screened? How many were excluded? What was the selection process for the patients for lipiodol-marking?

Thank you kindly for your comment. We understand that this is a limitation of our study. We only have available to us the cohort of patients referred to our department for insertion of fiducials. All patients who were referred to our team after discussion in our institutes' upper gastrointestinal multidisciplinary team meeting are included in our manuscript.

4. Why no historical cohort or subjects that haven't received the lipiodol marker were included for comparison?

Thank you very much for your comment. This is a limitation of this study. We only have available to us patients referred to our department for insertion for liquid

fiducials. This study has focused on the long-term outcomes of this specific cohort. We have outlined in our discussion that further studies comparing outcomes for patients with and without lipiodol markers are required.

5. How long is the persistence of the marker in the tissue?

For all patients that proceeded with liquid fiducial-based IGRT, the whole treatment could be done using the liquid fiducials with a median time to treatment of 19 days and a median treatment duration of 30 days. In no patients did the liquid fiducials became invisible during the period of treatment. After this period, we did not routinely perform cross-sectional imaging to assess the persistence of the marker in the tissue.

6. I have no concerns regarding the retrospective data analysis, but the use of a new tool may probably need the written agreement from the patients on the use of the medical product (at least off label use) while having approved alternatives?

An initial ethics approval was obtained for the implantation of the liquid fiducial markers. This is outlined in reference 20. After this study, our ethics committee has approved the use of liquid fiducial as standard practice in our institute. Individual consents are obtained before every endoscopic procedure.

7. More images from CT showing the correct placement would be very welcome.

Thank you for your suggestion. We have included further two images to figure 5 to help illustrate the benefit of LF-IGRT.

8. What is the explanation of non-visibility of lipiodol-based markers? Why was IGRT not possible in 2 patients?

Thank you kindly for your comment. Even though we do not have a definite explanation as to why they were not seen. We have described our hypothesis in the discussion.

9. What is the histological view of the marker after surgery which was performed in some of the patients?

Thank you for your question. Unfortunately, this was not the focus of our study. This was covered in a previous paper (reference 20).

10. What is the time to treatment (table 2)?

Thank you for pointing this out. We have updated table 2 to include this.

11. The use of S-IGRT with 4 patients makes little sense to me, rather, historical or additional cohorts would be welcome. Why did the authors not used larger cohort including also the patient that were excluded for other issues.

The study aimed to describe the long-term outcomes for all patients referred for liquid fiducial placement with the gastroenterology department. Hence, the four patients were part of our defined cohort. Unfortunately, we do not have access to the data of the patients that were not referred to our department. Nevertheless, we have included in our discussion that further studies comparing outcomes between those with LF-IGRT and S-IGRT are warranted.

12. Kaplan Meier Curves would benefit from inclusion of patient numbers at risk/follow up.

Thank you very for your suggestion. We have added this detail to our Kaplan Meier Curves.

13. Figure 5 needs to be expanded by more images and probably also including the patients with S-IGRT.

Thank you for your suggestion. We have added more images to Figure 5.

14. What is the explanation for the low range of F-IGRT?

Our technical success rate is different to other studies as we have a different definition for technical success. We have further elaborated on impact of using a different technical success definitions in our discussion.

15. Table 1 would benefit from inclusion of additional columns related to the F-IGRT and S-IGRT since it is part of the key analysis.

Thank you for your suggestion. We have added more rows to table 2 to provide further details on the sub-groups F-IGRT and S-IGRT. We felt that the information was better presented in table 2.

16. The conclusion on survival, PFS is speculative as have not been studied in this work (no comparison group)

Thank you for your comment. We have updated our conclusion to better reflect our findings.

Revison-Review:

The authors have addressed my comments and where appropriate updated limitations section.

Thanks for your comments.

Reviewer #2:
Feedback from reviewer #2 was positive and did not require updates to the manuscript.

Reviewer #3:

Comments:

1. Discussion "the lack of a direct comparison with S-IGRT" >> Suggest to comment on CBCT fusion based on soft tissue [not bone] matching [for example, see ACR-ASTRO Practice Parameter for Image-guided Radiation Therapy (IGRT), Am J Clin Oncol . 2020 Jul;43(7):459-468] vs on fiducial markers in the current manuscript.

Thank you for your suggestion. The discussion on CBCT fusion based on soft tissue matching has been included in our discussion.

2. References. "there are conflicting data regarding the efficacy of increased radiation dose in treating oesophageal cancer.29" >> suggest to update ref-29 as its full paper "J Clin Oncol. 2021 Jun 8:JCO2003697. doi: 10.1200/JCO.20.03697. Online ahead of print.PMID: 34101496", may also cite another randomized controlled trial [Zhonghua Yi Xue Za Zhi. 2020 Jun 16;100(23):1783-1788., https://pubmed.ncbi.nlm.nih.gov/32536123/]

Thank you very much for your suggestion. We have updated reference 29 to the full paper and have added the suggested randomised control trial to our references.

Once again, thank you very much for your time and consideration of our manuscript.

Kind regards,

Dr Kim Hay Be