Peer Review File

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Reviewer A

Comment 1: Since CEA is mainly a tumor marker of adenocarcinoma, it should be analyzed only with adenocarcinoma.
Reply 1: Thank you for kind comment. We agree that CEA elevation is more common in adenocarcinoma. The subgroup analysis of prognostic result of CEA in adenocarcinoma in Figure1C also showed the prognostic value of CEA in adenocarcinoma. However, ctDNA is appliable for all pathological subtype of NSCLC. Hence, we compared ctDNA and CEA in all pathological subtype. As the huge gap between ctDNA and CEA, we believed this will not change the conclusion.

Comment 2: Since there are background confounders in CEA and ctDNA, multivariate analysis and propensity score matched analysis should be performed.
Reply 2: Thank you for your kind comment. We compare CEA and MRD in one sample.

Comment 3: PPV and NPV are analyzed with the end point as a recurrence, but it is not appropriate because there is a time lead bias.
Reply 3: Thank you for your thoughtful question. The PPV and NPV were calculated after 180 days follow-up in this study. We have updated the method, please see the revision on Page 4, line 104-105.

Comment 4: Please specify the main and secondary endpoints.
Reply 4: Thank you for your comment. The primary and secondary endpoint have been added in the method, please see the revision on Page4, line 95.

Comment 5: Use Flow-chart to indicate patient selection.
Reply 5: Thanks for your comment. The Flow-chart was added. Please see the revision on Figure 1.

Comment 6: Line 36; In ABSTRACT, Background should write a general background, so it is better to refrain from writing specific numbers.
Reply 6: Thanks for your comment. The abstract has been refrained.

Comment 7: Methods; Please indicate the Exclusion criterion

Reply 7: Thanks for your comment. Exclusion criterion has been added.

Comment 8: Line 77; Duplication as indicated by inclusion criterion. Please erase.
Reply 8: Thanks for your careful comment. The inclusion criterion in line 77 was essential to state the analysis method in the prospective cohort.

Comment9: Line 83; Please state the method briefly.
Reply 9: Thank you for your comment. The method has been refined. Please check the revision.

Reviewer B

Comment 1: How many cases had normal CEA and MRD before surgery?
Reply 1: Thanks for you kindly asking. Preoperative MRD was not tested.

Comment 2: Is there a correlation between preoperative CEA and MRD and prognosis?
Reply 2: Since no paired preoperative CEA and MRD was record. The correlation between preoperative CEA and MRD was not clear.

Comment 3:
In patients with normal preoperative CEA and MRD, did the postoperative CEA trend reflect prognosis?
There are two "4.3" in the discussion.
Reply 3: Thanks for your thoughtful asking. Even in patients with normal preoperative CEA, the postoperative CEA evaluation means worse prognosis.

Comment 4: There are two "4.3" in the discussion.
Reply 4: Thank you for your careful review. The serial number of discussions was corrected.

Reviewer C

Comment 1: Introduction (line 57) states CEA is routinely used-do you have evidence for this? In what places is it routine? Perhaps more common in the Asian context?
Reply 1: Thanks for your kindly comments. CEA is widely used as a biomarker in non-small cell lung cancer. Routinely CEA testing is not only common clinically, but also widely used in some clinical trials or studies. For example, a study presented in 2022 WCLC routinely tested CEA and MRD for as recurrence monitor.

Comment 2: Methods-the lack of a well-defined protocol of the timing of CEA testing and re-testing is a major limitation. Any surveillance test must be understood in the context that it is used, and different timings will have different performance characteristics.
Reply 2: Thanks for your thoughtful comments. The method was further supplemented. Please check the revision.

Comment 3: Another major criticism is a lack of information about how positive CEA was investigated, including timing and type of imaging modality. It seems possible that microscopic disease may have been missed if a single imaging test was performed without longitudinal follow up, especially since the study found that CEA was predictive of DFS.
Reply 3: Thanks for your kindly criticism. The timing and type of imaging follow-up were followed the NCCN guideline (2022), which was longitudinal and the PPV and NPV were calculated after 180 days follow-up in this study.

Comment 4: Inclusion of a single case from a cohort of over 200 patients is highly inappropriate and adds nothing to the scientific understanding of this issue
Reply 4: Thanks for your comments. A representative case may help to understand the superiority of MRD.

Comment 5: The logic of this paper is confusing to me as well. Given that CEA is presumably cheaper and much more widely available than ctDNA testing, and the literature has already demonstrated superior predictive ability of ctDNA, I don't understand why the authors would want to use CEA to stratify ctDNA positive patients. It might make sense to take patients with positive CEA, used as a cheap and easy screening surveillance test, and stratify those patients with ctDNA. But the way the data is presented here doesn't add much to what is already in the literature.
Reply 5: Thanks for your comments. In prospective cohort which MRD was routinely tested, it would be more reasonable to stratify the MRD with CEA rather than the opposite.

Reviewer D

Comment 1: What was the post-operative follow up strategy. Were patients seen every 6 months, every year, etc. How often were CEA levels drawn and what type of radiographic follow up was performed (xray or CT scan). At the study institution are CEA levels drawn routinely for all post-resection patients. Who was following up with the patients (surgeons or oncologists).

Reply 1: Patients were seen every 6 months in 5 years after surgery and every year after that. CT and PET-CT was applied for follow up. Surgeons was following up with the patients.

Comment 2: In table 1 is the stage clinical stage or pathologic?
Reply 2: The stage is pathologic stage.

Comment 3: It would be helpful if the authors provided additional information on surgical resection. What types of resection were performed (wedge, segmentectomy, lobectomy) and how were they performed open, VATS, or RATS. How was nodal staging performed?
Reply 3: Thanks for your comments. The patients enrolled in our study underwent radical resection. Wedge resection and segmentectomy resection was acceptable to those with pathology stage IA1-IA2. For those with higher stage, lobectomy was performed for radical resection. The aim of this study is to compare the prognostic and predictive value of MRD and CEA. Hence, the specific procedure of surgery may be less necessary.

Comment 4: Most importantly, as the authors have written and cited, CEA is known to be associated with recurrence of NSCLC, but is not particularly sensitive or specific. MR disease and ctDNA are attractive methods for surveilling patients with potentially better sensitivity and specificity as the authors have previously reported. I am concerned that in its present form this article rehashes old information and offers little new information.
Reply 3: Thanks for your comments. CEA is known as a recurrence biomarker in NSCLC. The emerging MRD and ctDNA showed potentially better sensitivity and specificity. But the application of CEA in MRD context was unclear.