Original Article

CtDNA based molecular residual disease outcompetes carcinoembryonic antigen in predicting postoperative recurrence of non-small cell lung cancer

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Background: Carcinoembryonic antigen (CEA) has been routinely used as a postoperative monitoring biomarker for non-small cell lung cancer (NSCLC). Emergingly, circulating tumor DNA (ctDNA)-molecular residual disease (MRD) detection is a well-established prognostic marker, with better positive predictive value (PPV) and negative predictive value (NPV). However, the actual clinical efficiency of CEA in MRD context remain unknown. Hence, we conducted this study for direct comparison of CEA and MRD.

Methods: Two cohorts were analyzed in this study. To investigate the prognostic and predictive value of CEA, we retrospective enrolled NSCLC patient stage IA2–IIIA (8th tumor-node-metastasis staging system) with longitudinal CEA between 2018 and 2019. We also performed a paired comparison of CEA and MRD in our previous published cohort. Survival data were analyzed using the Kaplan-Meier method, and comparisons were performed using the log-rank test. Sensitivity, specificity, PPV and NPV were calculated using the R package "*epiR*". McNemar's test was used to analyze the paired data. Statistical differences were set at a P value <0.05.

Results: In the retrospective cohort, the sensitivity of longitudinal CEA was only 0.49 [95% confidence interval (CI): 0.37–0.60]. Even for patients with progressively elevated CEA levels, 32% of them still remained disease-free, with PPV of 0.68 (0.49–0.83) and NPV of 0.81 (0.77–0.85). Furthermore, we then compared CEA and MRD values in a previously described MRD cohort. As expected, CEA levels could not stratify the risk of recurrence in detectable versus undetectable MRD populations.

Conclusions: MRD is superior to CEA in postoperative monitoring. there is insufficient evidence to support its use as postoperative monitoring tumor marker.

Keywords: Carcinoembryonic antigen (CEA); non-small cell lung cancer (NSCLC); molecular residual disease (MRD)

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Introduction

Background

Serum carcinoembryonic antigen (CEA) is a well-known tumor biomarker in patients with non-small cell lung cancer (NSCLC) (1-3). It is also a predictor of disease recurrence and progression (4,5). Thus, CEA is routinely used by clinicians in some regions for postoperative surveillance. Emergingly, circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) detection has been proposed to predict disease recurrence for NSCLC patients after surgery (6,7).

Rationale and knowledge gap

In our previous study (8), we highlighted the predictive value of longitudinal MRD in the postoperative setting, with a positive predictive value (PPV) of 89.1% and negative predictive value (NPV) of 96.8%. However, other studies have shown limited value in consecutive CEA monitoring during follow-up (9). For predicting recurrence in patients after radical resection, the accuracy of serum CEA level was uncertain, considering that the sensitivity was only 46% (10). The direct comparison of CEA and MRD has not been reported.

Objective

In this particular context, we evaluated the advantage of ctDNA-MRD could be an alternative to CEA. Thus, in this study, we compared CEA with ctDNA-MRD as a predictor for recurrent NSCLC disease. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-507/rc).

Highlight box

Key findings

- Carcinoembryonic antigen (CEA) could not predict postoperative recurrence in patients with non-small cell lung cancer (NSCLC) with undetectable molecular residual disease (MRD).

What is known and what is new

- CEA is used routinely as an NSCLC tumor biomarker postoperatively, but there is insufficient evidence for its use as a postoperative monitoring marker, especially in MRD context.
- Our study shows that CEA could not further stratify patients with detectable and undetectable longitudinal MRD.

What is the implication, and what should change now?

- Circulating tumor DNA-based MRD had obvious advantages in terms of sensitivity, specificity, positive predictive value, and negative predictive value. Further confirmatory studies are required.

Methods

Study design and patients

This study was performed with two independent cohorts (*Figure 1*). To investigate the prognostic and predictive value of CEA, we retrospectively collected the data of NSCLC patients who underwent radical resection at Guangdong Provincial People's Hospital from 2018 to 2019. Patients who met the following criteria were included: (I) pathological staging of IA2–IIIA [8th tumor-node-metastasis (TNM) staging system], (II) pathological diagnosis of NSCLC, and (III) at least two serum CEA follow-up tests within 2 years after surgery. Patients without available clinical and radiological record was excluded.

The paired comparison of longitudinal CEA and MRD was investigated in the prospective cohort (8). In this cohort, we screened patients with at least two serum CEA follow-up tests after surgery. The data of 204 patients with matched CEA and MRD data were analyzed. Recurrence was confirmed based on radiology.

The primary endpoint of this study was the sensitivity, specificity, PPV and NPV.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics and scientific committees of Guangdong Provincial People's Hospital (No. KY-Q-2021-202-01). Informed consent for the publication of details relating to an individual person has been obtained.

CEA and ctDNA-MRD detection

Serum CEA levels were measured at the clinical laboratory of Guangdong Provincial People's Hospital using chemiluminescence immunoassays. The cutoff value of CEA was set at 5 mg/L. The methods used for ctDNA-MRD detection have been previously described (8). The landmark CEA level was defined as the CEA level within 3 months after surgery. Longitudinal CEA was defined as the dynamic follow-up CEA record since landmark

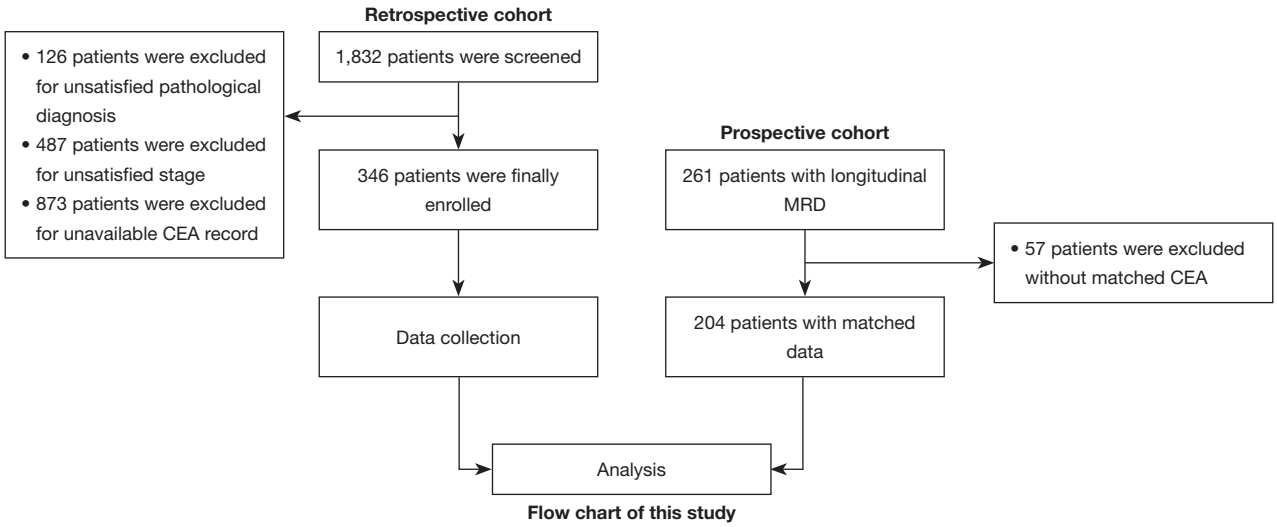

Figure 1 Flow chart of this study. CEA, carcinoembryonic antigen; MRD, molecular residual disease.

detection. Results of those examination were assessed independently. Analysis of the PPV and NPV was completed for patients with at least 180 days of follow-up since the correspondent CEA or MRD status.

Statistics

Statistical analyses were performed using R software (version 4.1.2) and GraphPad Prism 9. Survival data were analyzed using the Kaplan-Meier method, and comparisons were performed using the log-rank test. Sensitivity, specificity, PPV and NPV were calculated using the R package "*epiR*". McNemar's test was used to analyze the paired data. Statistical differences were set at a P value <0.05.

Results

Unsatisfactory monitoring value of CEA

The clinical characteristics of the cohorts are listed in *Table 1*. In the retrospective cohort, 346 patients were enrolled. The median follow-up time was 40.6 months, and 80 patients had disease relapse by June 11, 2022. Among 268 patients with landmark CEA records, a significant superior disease-free survival (DFS) was observed for patients with normal CEA levels as opposed to that for patients with abnormal CEA levels [not reached *vs.* 37.6 months, P<0.001, hazard ratio (HR) =0.16, 95% confidence interval (CI): 0.14–0.44, *Figure 2A*]. However, in terms of recurrence predictive efficiency, the sensitivity was only 0.27 (95% CI: 0.16–0.39), and the PPV was 0.55 (95% CI: 0.36–0.73, *Table 2*). Moreover, in the context of longitudinal CEA, 24 additional patients had abnormal CEA levels in the subsequent follow-up. As expected, the longitudinal CEA also had a significant prognostic value (not reached *vs.* 37.6 months, P<0.001, HR =0.20, 95% CI: 0.11–0.37, *Figure 2B*). However, the sensitivity was only close to one-half (0.49, 95% CI: 0.37–0.60, *Table 2*), and the PPV of longitudinal CEA was not significantly high (0.57, 95% CI: 0.44–0.68, *Table 2*). We Further investigated CEA in adenocarcinoma and the other pathological type. CEA elevation mainly occurred in adenocarcinoma and was a significant prognostic factor (HR =0.075, 95% CI: 0.039–0.146, P<0.001, *Figure 2C*) while not a prognostic factor for other pathological type (P=0.345).

Furthermore, we focused on patients with progressively elevated CEA levels. Of the 69 patients with abnormal postoperative CEA levels, 31 showed progressively elevated levels. However, 32.3% (10/31) of the patients remained disease-free, with a PPV of 0.68 (95% CI: 0.49–0.83) (*Figure 2D*, *Table 2*). Overall, these data suggested that postoperative CEA did not provide satisfactory value for monitoring disease progression in NSCLC patients.

MRD outperforms CEA in predicting postoperative recurrence

In the prospective cohort, there were 204 patients with matched longitudinal CEA data. The sensitivity, specificity,

Table 1 Baseline clinical characteristics of the retrospective and prospective cohorts

Clinical characteristics	Retrospective cohort (n=346)	Prospective cohort (n=204)
Sex		
Male	183 (52.9)	127 (62.3)
Female	163 (47.1)	77 (37.7)
Age at diagnosis (years)	60 [54–66]	61 [55–66]
Smoking history		
Yes	123 (35.5)	76 (37.3)
No	223 (64.5)	128 (62.7)
Pathology		
Adenocarcinoma	269 (77.7)	160 (78.4)
Squamous cell carcinoma	53 (15.3)	25 (12.3)
Others	22 (6.4)	19 (9.3)
Stage		
IA	150 (43.4)	80 (39.2)
IB	73 (21.1)	43 (21.1)
II	56 (16.2)	41 (20.1)
III	67 (19.4)	40 (19.6)
Perioperative treatment		
Yes	85 (24.6)	55 (27.0)
No	261 (75.4)	149 (73.0)

Data are presented as n (%) or median [interquartile range].

PPV, and NPV of longitudinal MRD and CEA in this cohort are shown in *Table 2*. The sensitivity and specificity of MRD were significantly better than those of CEA (P<0.001) (*Figure 2E*). As shown in *Figure 2F*, no significant difference was observed between abnormal and normal CEA levels in the MRD detectable or undetectable groups (P=0.17 in detectable MRD group, P=0.82 in undetectable MRD group).

Next, we focused on one representative case in this cohort. This patient was a 56-year-old female diagnosed with lung adenocarcinoma (pT2aN0M0, stage IB), harboring an *EGFR* L858R mutation. After complete resection, this patient underwent adequate imaging and follow-up with evaluation of CEA and MRD. Interestingly, this patient exhibited progressive elevation of CEA levels after resection, but multiple imaging scans, including positron emission tomography/computed tomography and MRD, did not detect any signs of recurrence. The endoscopic and ultrasound examination also excluded second primary tumors from the digestive and reproductive systems.

Discussion

Key findings

In this study, we analyzed the monitoring value of CEA in the postoperative context. CEA did not effectively predict disease recurrence for NSCLC patients after surgery, even for those with progressively elevated CEA levels. Moreover, MRD outperformed CEA in the paired analysis.

Strengths and limitations

Our study reported the comparison of longitudinal CEA and MRD data in a prospective cohort, which provided high quality evidence for MRD monitoring after radical

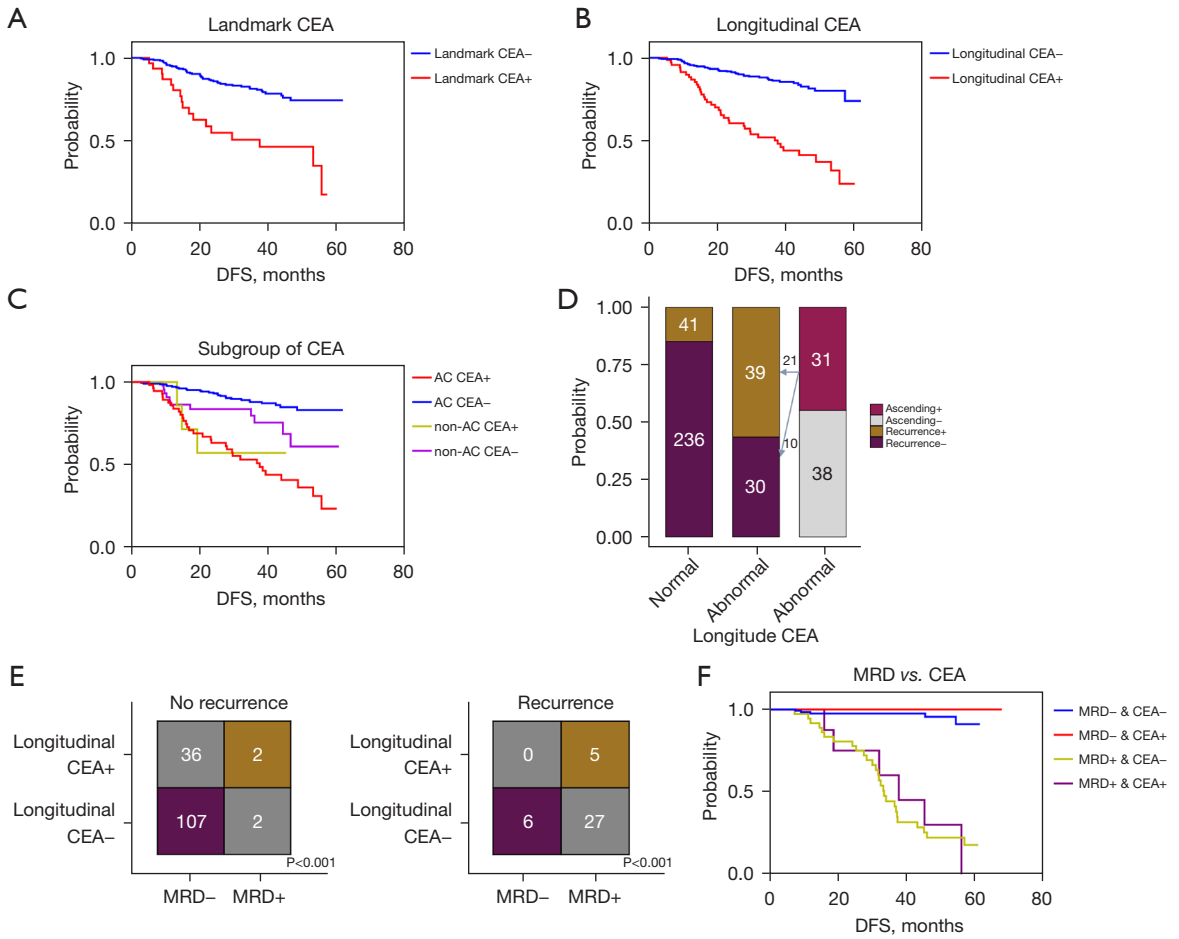

Figure 2 Postoperative CEA and MRD monitoring for NSCLC patients after radical resection. (A) Kaplan-Meier curve of DFS stratified by landmark normal and abnormal CEA levels in the retrospective cohort. (B) Kaplan-Meier curve of DFS stratified by longitudinal normal and abnormal CEA levels in the retrospective cohort. (C) The proportion of recurrence in the longitudinal normal and abnormal CEA groups, and the outcome for patients with progressively elevated CEA levels in the retrospective cohort. (D) The matched 2×2 tables for longitudinal CEA and longitudinal MRD in patients with and without disease relapse. (E) The Kaplan-Meier curve of DFS stratified by longitudinal CEA and longitudinal MRD. (F) Representative case from the prospective cohort. CEA, carcinoembryonic antigen; DFS, disease-free survival; CEA+, abnormal CEA level; CEA–, normal CEA level; MRD–, undetectable longitudinal MRD; MRD, molecular residual disease; MRD+, detectable longitudinal MRD; NSCLC, non-small cell lung cancer.

Table 2 The sensitivity, specificity, PPV, and NPV of CEA and MRD

Cohort	Biomarker	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Retrospective cohort	Landmark CEA	0.27 (0.16–0.39)	0.93 (0.89–0.96)	0.55 (0.36–0.73)	0.80 (0.75–0.85)
	Longitudinal CEA	0.49 (0.37–0.60)	0.89 (0.84–0.92)	0.57 (0.44–0.68)	0.85 (0.80–0.89)
	Progressively elevated CEA	0.26 (0.17–0.37)	0.96 (0.93–0.98)	0.68 (0.49–0.83)	0.81 (0.77–0.85)
Prospective cohort	Longitude MRD	0.88 (0.76–0.95)	0.95 (0.91–0.97)	0.80 (0.67–0.90)	0.97 (0.94–0.99)
	Longitudinal CEA	0.16 (0.06–0.31)	0.76 (0.69–0.82)	0.13 (0.05–0.26)	0.80 (0.73–0.86)

PPV, positive predictive value; NPV, negative predictive value; CEA, carcinoembryonic antigen; MRD, molecular residual disease; CI, confidence interval.

resection. The present study has several limitations. The sample size was relatively small and the follow-up duration was not long enough.

Comparison with similar researches

Several studies have indicated that patients with abnormal CEA levels had a poorer prognosis (10,11). Buccheri *et al.* (9) showed that the specificity and sensitivity of CEA were 90% and 46%, respectively, in 118 patients who underwent resection, which is consistent with our results observed in the retrospective cohort. Although the specificity of CEA was 0.89, only 50% of the patients with recurrence had abnormal CEA levels. Even progressively increasing CEA levels did not improve the PPV to a satisfactory level. Generally, CEA level is a prognostic factor for NSCLC after radical surgery, but it is not an effective indicator of recurrence.

Explanation of findings

Considering the advantage of MRD, CEA levels were not a satisfactory predictor of recurrence in patients with NSCLC after radical resection. Since CEA could not further stratify the risk of recurrence in the longitudinal detectable MRD and undetectable populations, there was little benefit from CEA monitoring in MRD context.

Implications and actions needed

MRD monitoring in an emerging and strong predictor for NSCLC recurrence with high NPV and PPV, which might further stratify patients and even provide instruction for adjuvant therapy. Larger study for further confirmation is required.

Conclusions

In conclusion, although CEA is a well-established tumor biomarker in NSCLC, there is insufficient evidence to prove the monitoring value of CEA in the postoperative context. On the other hand, MRD had obvious advantages in terms of sensitivity, specificity, PPV, and NPV.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-507/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-507/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-507/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics and scientific committees of Guangdong Provincial People's Hospital (No. KY-Q-2021-202-01). Informed consent for the publication of details relating to an individual person has been obtained.

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