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Prognostic significance of CEA reduction rate in patients with abnormally high preoperative CEA levels who underwent surgery for lung cancer

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Abstract

Background The aim of this research was to investigates the prognostic importance of change in carcinoembryonic antigen (CEA) levels (particularly abnormal high concentration) in patients with non-small cell lung cancer (NSCLC) between before and after surgery.

Methods The study involved 68 patients with NSCLC (preoperative CEA value ≥ 10 ng/ml) who received curative operation from 2012 to 2020. Preoperative and postoperative serum CEA levels, CEA reduction, and other clinicopathological factors were determined on medical records. Receiver operating characteristic curves were used to calculate cut-off levels for prognostic markers. Multivariate analyses with a Cox proportional hazards regression model were performed to identify Independent prognostic variables.

Results The optimal cut-off was value for the CEA reduction rate was 77.3%. The area under the curve for the CEA reduction rate was greater compared with those for preoperative and postoperative CEA levels. The Kaplan–Meier method revealed a significantly worse prognosis in the low CEA reduction rate group versus the high CEA reduction rate group regarding overall survival (OS) ($p=0.002$). In the multivariate analysis, the CEA reduction rate (hazard ratio: 3.36, 95% confidence interval: 1.32–8.51, $p=0.011$) was identified as an independent and exclusive prognostic marker for OS.

Conclusions In NSCLC, which is characterized by high preoperative CEA levels, the CEA reduction rate after surgery is a useful prognostic factor. Importantly, it is a more powerful indicator for OS compared with postoperative CEA levels. Further, large-sample-size cohort studies focusing on this issue are warranted.

Keywords Non-small cell lung cancer, Carcinoembryonic antigen, Prognosis, Preoperative, Postoperative, Reduction rate

Background

Lung cancer is linked to poor prognosis; hence, appropriate treatment, as well as accurate preoperative diagnosis and staging, are crucial [1–3]. Computed tomography (CT) and positron emission tomography are currently the standard methods for the clinical staging of non-small cell lung cancer (NSCLC). The median sensitivity and specificity value of positron emission tomography-CT for

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the detection of mediastinal nodal disease are 80% and 88%, respectively [4]. Thus, there is a need to discovery new biomarkers that would improve the sensitivity of clinical staging and permit the selection of appropriate treatment.

The glycoprotein carcinoembryonic antigen (CEA) is an established tumor markers utilized for the detection of NSCLC. CEA levels occur in numerous tumor tissues (e.g., gastrointestinal cancer, breast cancer, carcinoid, liver cancer and lung cancer); in NSCLC, CEA levels have been recognized as an independent prognosis factor [5]. However, it is difficult to achieve excellent sensitivity and specificity for the detection of lung cancer through the use of a single serum marker.

CEA and cytokeratin fraction 21-1 (CYFRA21-1) are two important markers for diagnosis and disease monitoring in patients with lung cancer [6]. Maeda et al. [7] reported that an increase in preoperative serum CEA levels correlated with factors of tumor invasiveness, namely lymphatic permeation and visceral pleural invasion. Recently, it was demonstrated that blood-based markers, of inflammation, cell-free DNA, circulating tumor cells, microRNAs can serve as tumor markers for colorectal cancer [8]. However, these markers are not yet utilized in clinical settings.

The significance of postoperative serum CEA levels in predicting the overall survival (OS) of patients with esophageal squamous cell carcinoma has been investigated [9]. Ren et al. [10]

highlighted the predictive value of alterations in tumor markers such as CEA, carbohydrate antigen 19-9 (CA19-9) and CA125 between before and after operation for colorectal cancer. Several studies [6, 11, 12] have evaluated the postoperative tumor markers in NSCLC. In two studies [11, 12] high postoperative CEA levels were recognized as an independent factor of unfavorable prognosis in patients who underwent complete resection of NSCLC. However, there are no studies comparing the preoperative and postoperative levels of CEA.

The purpose of this research was to examine the prognostic importance of change in CEA levels (particularly abnormally high concentrations) in NSCLC between before and after surgery.

Materials and methods

Study design

All analyses were carried out in accordance with the standards established by the Ethics Committee of Kochi Medical School (Nankoku, Japan), as well as the tenets stipulated in the 1964 Declaration of Helsinki and subsequent amendments. Owing to the retrospective nature of this monocentric study, the requirement for informed patient consent was waived.

Patients

Between January 2012 and December 2020, 767 patients with primary lung cancer surgery at our institution. Seventy-five patients with a preoperative CEA value ≥ 10 ng/ml were registered. The exclusion criteria were as follows: non-radical resection; presence of multiple lung lesions or tumors in other organs at the time of surgery for lung cancer; undetermined postoperative CEA values; and insufficient clinicopathological information (Fig. 1).

Data collection and follow-up

Data on age, sex, body mass index, smoking history, preoperative and postoperative serum CEA levels, consolidation / tumor (C/T) ratio, standardized uptake value, operative procedure, tumor histology type, clinical and pathological stage, and the status of epidermal growth factor receptor (EGFR) and, programmed cell death-ligand 1 (PD-L1), as well as the administration of induction, adjuvant and post recurrent treatment were obtained from the medical records of the patients. Preoperative and postoperative evaluation of CEA levels was performed up to 1-month before, and up to 3 months after surgery, respectively. During postoperative, follow-up, the patients underwent physical examination, blood testing, and chest X-ray analysis every 3 months for the first 3 years and every 6 months thereafter. In addition, chest and abdomen CT was performed at least once annually. Clinicopathological characteristics, OS, disease specific survival (DSS), and recurrence free survival (RFS) were retrospectively evaluated.

Reduction rate of CEA

The CEA reduction rate was defined as follows: (Preoperative CEA levels—Postoperative CEA levels) / Preoperative CEA levels.

Statistical analysis

Data are presented as medians and interquartile ranges or numbers and percentages. OS, DSS, and refer to the time period from resection to death or the most recent follow-up, death due to a specific disease, and disease recurrence, respectively. Receiver operating characteristics (ROC) curves were used to calculate cut-off values for prognostic markers. The Kaplan–Meier method and log-rank test were utilized to conduct survival analyses based on clinicopathological and prognostic factors. Multivariate analyses with a stepwise Cox proportional hazards regression model were performed to identify independent prognostic variables. The 95% confidence interval (CI) was employed to determine correlations between independent factors and survival. JMP Pro (Version. 12)

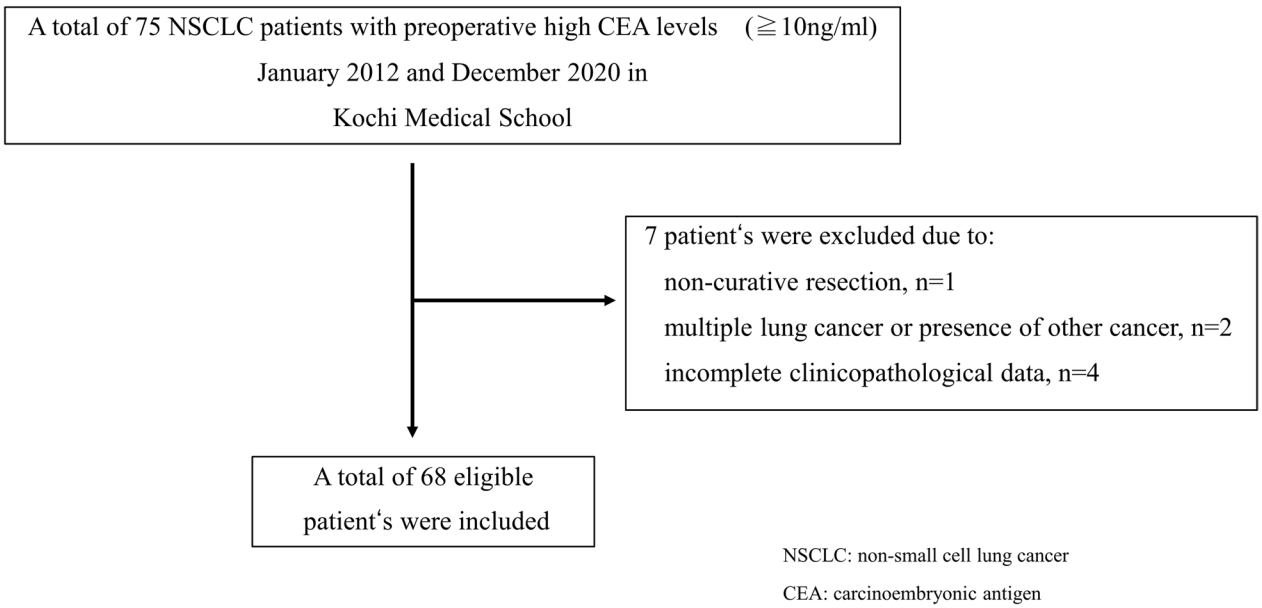

Fig. 1 Flow chart of patient selection. CEA, carcinoembryonic antigen.; NSCLC, non-small sell lung cancer

Table 1 Demographic and clinical characteristics

Variables		Number of patients
Age	Median (IQR): years	75 (44–88)
Gender	Male / female	43 / 25
BMI	Median (IQR): kg/m^2	22.6 (17.0–31.3)
Smoking histoly	Never / Ever	21 / 47
Preoperative CEA level	Median (IQR): ng/ml	15.7 (10.3–271.6)
Postoperative CEA level	Median (IQR): ng/ml	5.0 (1.4–74.5)
C/T ratio	Mean Median (IQR)	0.92 1 (0–100)
SUVmax value	Mean Median (IQR)	7.0 6.1 (1.6–19.9)
Operative procedure	PR / Seg / Lob	4 / 8 / 56
Histology	Ad / Sq / Others	51 / 7 / 10
clinical Stage	IA / IB / II / III	26 / 18 / 14 / 9
pathological Stage	IA / IB / II / III	19 / 12 / 19 / 18
Up staging	non-up / up	40 / 28
EGFR mutation	N/A /negative/Positive	20 / 34 / 14
PD-L1	N/A /negative/Positive	47 / 10 / 11
Induction	Absent / Present	64 / 4
Adjuvant	Absent / Present	29 / 39
Post recurrent treatment	Absent / Present	9 / 17

(SAS Institute, Inc, Cary, NC, USA) software was utilized for data analysis; p-values <0.05 indicate statistically significant differences.

Results

Patient characteristics

Eventually, 68 patients were analyzed in this study. Median follow-up period was 56 months (interquartile range: 7–118 months). Table 1 includes the clinicopathological data. Median age of patients was 75 years (range: 44–88 years); 43 patients (63.2%) were male; and 47 patients (69.1%) had smoking history. Furthermore, 12 patients (17.6%) underwent sublobar resections. Most patients (75.0%) had adenocarcinoma, while 28 cases were upstaged. Four and 39 patients received induction and adjuvant therapy, respectively. 26 patients experienced disease recurrence after surgery; 17 of those had received some type of treatment.

ROC curves of CEA levels for the prediction of OS

Figure 2 shows the ROC curves for CEA reduction rate, and preoperative and postoperative CEA levels. The optimal cut-off values for CEA reduction rate, preoperative CEA levels, and postoperative CEA levels were 77.3%, 14.5 ng/ml and 6.7 ng/ml, respectively. The area under the curve for the CEA reduction rate was greater (0.612; 95% CI: 0.562–0.642) compared with those for preoperative and postoperative CEA levels. Demographic and clinical characteristics between the low and high CEA reduction groups are shown in Table 2. The maximum standardized uptakes value was higher in the high CEA reduction rate group compared with the low CEA reduction rate group ($p=0.01$). Lobectomy was performed more frequently in the high CEA reduction rate group than the low CEA reduction rate group ($p=0.03$).

Survival analysis according CEA levels

The high CEA reduction rate (≥77.3%) group included 25 patients (36.8%), while the low CEA reduction rate

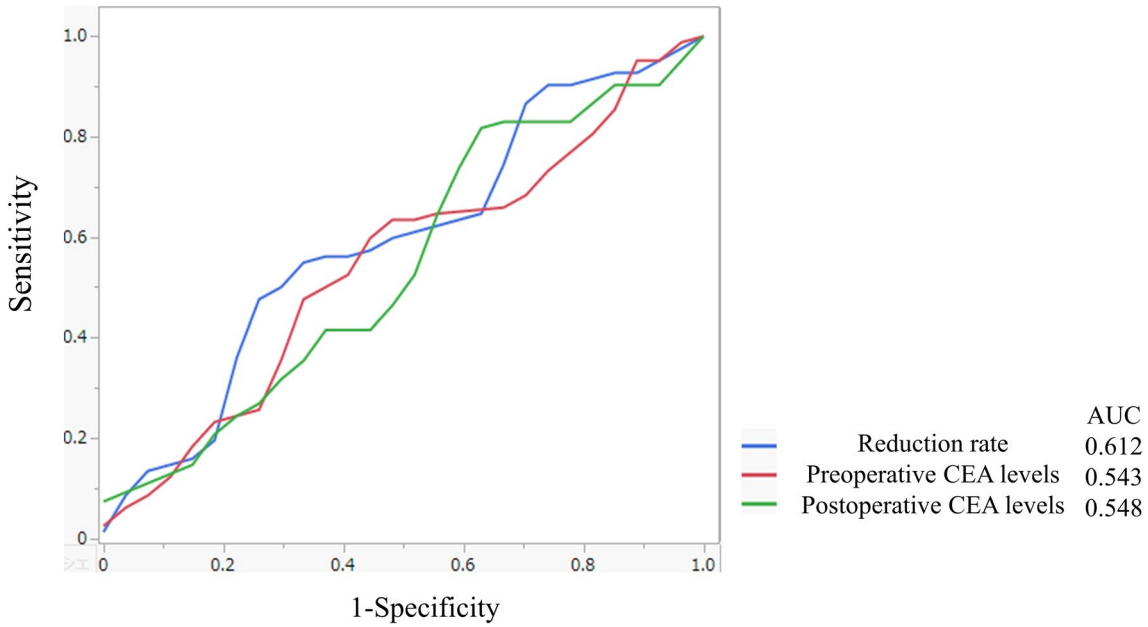

Fig. 2 Comparison of AUC between CEA reduction rate, and preoperative and postoperative CEA levels. AUC, area under curve; CEA, carcinoembryonic antigen

Table 2 Demographic and clinical characteristics by CEA reduction rate

Variables		A group: Reduction rate < 77.3% n = 38	A group: Reduction rate ≧77.3% n = 30	*p* value
Age	Median (IQR): years	77 (56–88)	72 (44–82)	0.03
Gender	Male / female	26 / 12	17 / 13	0.32
BMI	Median (IQR): kg/m^2	22.7 (17.0—31.3)	22.5 (17.7—28.5)	0.68
Smoking histoly	Never / Ever	11 / 27	10 / 20	0.80
C/T ratio	Mean Median (IQR)	0.89 1 (0–100)	0.95 1 (0–100)	0.28
SUVmax value	Mean Median (IQR)	5.9 5.2 (1.6—12.4)	8.6 7.9 (1.9—19.9)	0.01
Operative procedure	PR / Seg / Lob	3 / 7 / 28	1 / 1 / 28	0.03
Histology	Ad / Sq / Others	25 / 6 / 7	26 / 1 / 3	0.16
clinical Stage	IA / IB / II / III	18 / 11 / 5 / 4	8 / 7 / 9 / 5	0.18
pathological Stage	IA / IB / II / III	13 / 6 / 11 / 8	6 / 6 / 8 / 10	0.36
Up staging	non-up / up	22 / 16	18 / 12	0.86
EGFR mutation	N/A /negative/Positive	14 / 15 / 9	6 / 19 / 5	0.13
PD-L1	N/A /negative/Positive	28 / 2 / 8	19 / 8 / 3	0.03
Induction	Absent / Present	37 / 1	27 / 3	0.19
Adjuvant	Absent / Present	20 / 18	9 / 21	0.06
Post recurrent treatment	Absent / Present	7 / 9	2 / 8	0.34

CEA, carcinoembryonic antigen

(<77.3%) group included 43 patients (63.2%). The Kaplan–Meier method was utilized to conduct survival analyses according to the CEA reduction rate. The results indicated a significantly poorer prognosis in the low CEA reduction rate group versus the high CEA reduction rate group regarding OS (5-year OS: 57.3% vs. 90.2%, respectively, $p=0.002$), DSS ($p=0.07$), and RFS ($p=0.04$) (Fig. 3). Figure 4 shows the OS of patients in the high and low CEA level groups. There was no statistically significant difference observed between the preoperative and postoperative CEA groups ($p=0.11$ and $p=0.061$, respectively).

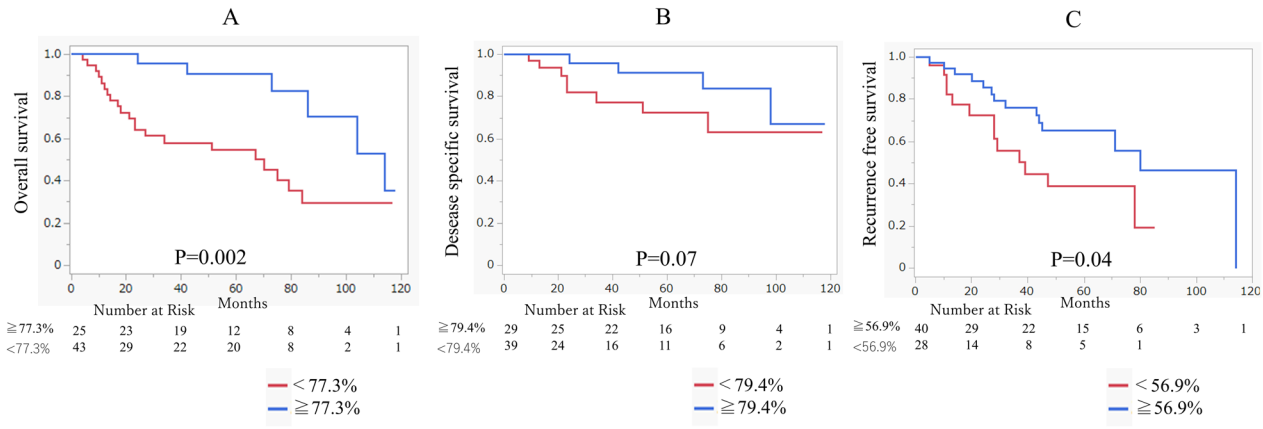

Fig. 3 Kaplan–Meier curves for **A** overall survival, **B** disease-specific survival, and **C** recurrence-free survival based on the CEA reduction rate. CEA, carcinoembryonic antigen

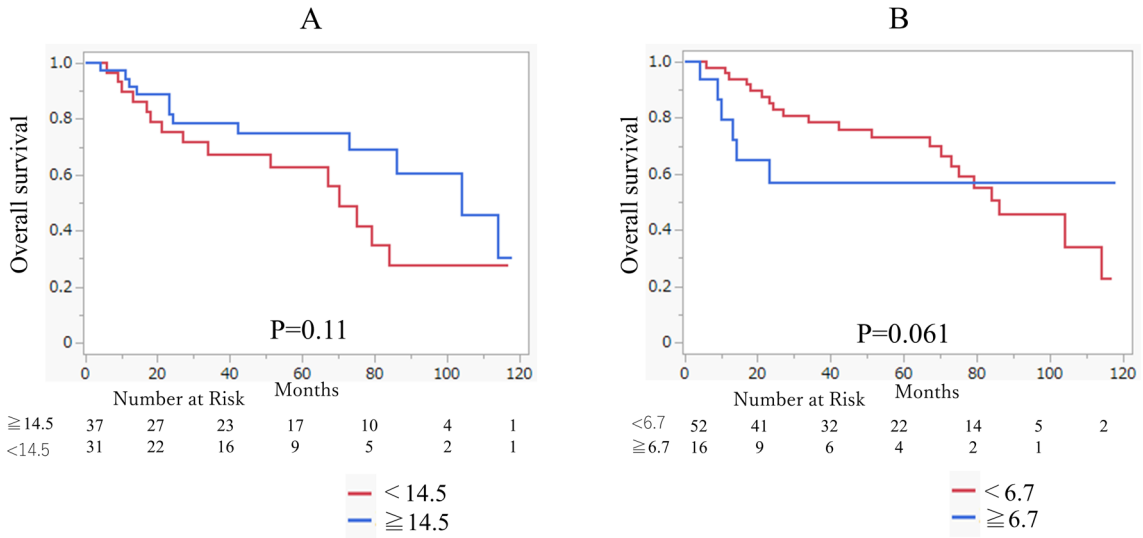

Fig. 4 Kaplan–Meier curves for preoperative and postoperative CEA levels. CEA, carcinoembryonic antigen

Prognostic value of CEA reduction rate and other clinicopathological factor

As shown in Table 3, in the univariate analysis, sex ($p=0.04$), body mass index ($P=0.04$), CEA reduction rate ($p=0.003$), and lymphatic invasion ($p=0.02$) were identified as significant predictors of OS. In the multivariate analysis, CEA reduction rate (hazard ratio: 3.36, 95% CI: 1.32–8.51, $p=0.011$) was recognized as an independent and exclusive prognostic marker of OS.

Discussion

Tumor markers commonly utilized in clinical practice for the diagnosis and treatment of various types of cancer [13], particularly NSCLC [14, 15]. However, few studies thus far have suggested the clinical significance of tumor markers for the early detection of cancer. In contract, several studies have indicated the usefulness of a combination of tumor markers. In the present study, we examined cases of NSCLC with high preoperative CEA levels. The findings, indicated that the postoperative reduction rate was useful for predicting prognosis, particularly OS.

The CEA exhibits high levels in colon cancer, gastric cancer, breast cancer, ovarian cancer and NSCLC. The mechanism underlying the prognostic role of serum CEA currently is unknown. Kozu et al. [12] not detect significant correlations among CEA levels and histologic types; nonetheless, they concluded that this relationship remains controversial. CEA values are affected by renal function and smoking status [16]. This study excluded cases with impaired renal function and other cancers.

Table 3 Univariate and multivariate Cox proportional hazards regression analysis for overall survival

	Univariate Analysis				Multivariate Analysis			
	HR	95% C.I		*P* value	HR	95% C.I		*P* value
Age	0.99	0.93	1.05	0.72				
Gender	3.02	1.05	9.66	0.04	2.15	0.85	5.45	0.11
Smoking history	2.86	0.93	9.76	0.07				
BMI	4.58	1.09	31.40	0.04	2.97	0.67	13.2	0.15
Histology	2.06	0.68	6.42	0.20				
SUVmax value	2.20	0.72	5.73	0.18				
Operative procedure	7.30	1.01	14.70	0.06				
cStage IA	1.01	0.37	2.71	0.98				
pStage IA	1.30	0.43	3.90	0.63				
Preoperative CEA	1.87	0.87	4.02	0.11				
Postoperative CEA	2.14	0.89	5.16	0.09				
Reduction rate	4.94	1.72	15.9	0.003	3.36	1.32	8.51	0.011
Ly	3.41	1.24	9.79	0.02	1.83	0.81	4.12	0.15
V	1.07	0.40	2.81	0.89				
pl	1.49	0.56	4.06	0.43				

Cases of cancer with high preoperative CEA values are at a higher risk of advanced disease and have poor prognosis.

In patients with pathological stage IA NSCLC, the preoperative serum levels of CEA were not identified as an independent predictor of poor prognosis. However, in such patients preoperative CEA levels are an important indicator of tumor invasiveness and lymph node metastasis. Hence, preoperative assessment of serum CEA is essential in patients with early-stage NSCLC [7]. In NSCLC, the combination of preoperative serum CEA levels and other factors, such as C-reactive protein [17] and, Krebs von den Lungen 6 (KL-6) [18], may serve as a more accurate and useful prognostic factor versus individual variables.

The serum levels of tumor markers will change following tumor resection [19, 20]. Comparison of changes between the preoperative and postoperative CEA levels can be used to predict the prognosis of colorectal cancer [10], rectal cancer [21], and NSCLC [6, 11, 12], this offers guidance for the development and implementation of personalized treatment strategies. Duan et al. [6] reported that patients with high serum CEA or CYFRA 21–1 levels prior to and after following surgery had shorter OS and RFS than those with low levels. Tomita et al. [11] reported that, in patients with NSCLC, postoperative serum CEA is a more useful prognostic factor than the post/preoperative serum CEA ratio.

In our study, the CEA reduction rate was a more reliable prognostic factor compared with the postoperative CEA levels. In our study, the target CEA value was 10 ng/ml; in the study conducted by Tomita et al. [11], this value was ≥ 5 ng/ml. It can be considered that the postoperative change is more reflected. We recorded statistically significant differences in OS and RFS, as well as a non-significant difference in DSS. Adjuvant therapy was administered to 69.2% and 55.2% of patients with low and high CEA reduction rate, respectively. The lack of a significant difference in DSS may be partly attributed to the difference in the administration of adjuvant therapy.

The CEA levels were decreased after surgery in most cases, whereas they were increased in three cases. Case 1 had pathological stage IB disease, and pleural dissemination was observed 47 months after surgery. The patient expired 80 months after surgery. Case 2 presented with pleural dissemination and expired due to acute exacerbation of interstitial pneumonia 4 months after surgery. Case.3 had pathological stage IA2 disease and developed bone metastasis 28 months after surgery; the patients expired duo to the cancer 34 months after surgery. Although the number of cases included in this investigation is small, all patients experienced disease recurrence resulted in death.

This study was characterized by several limitations, namely its retrospective nature, single-center investigation, and the limited number of cases included in the analysis. Most tests for preoperative CEA were performed within 1 month before surgery; however, there was no clear timeline for postoperative CEA measurements. Numerous other reports have examined the combination of CEA with multiple markers; nevertheless, the present study focused exclusively on CEA. In this study, we only included cases with

CEA values ≥ 10 ng/ml. In the future, we plan to conduct a study including cases with CEA values ranging 5—10 ng/ml.

Conclusions

In NSCLC, which is characterized by high preoperative CEA levels, the CEA reduction rate after surgery is a useful prognostic factor. Importantly it is more powerful indicator for OS compared with postoperative CEA levels. This factor has the potential to help develop strategies for the postoperative treatment of NSCLC patients in the future. Further, large-sample-size cohort studies focusing on this issue are warranted.

Abbreviations

CEA	Carcinoembryonic antigen
NSCLC	Non-small cell lung cancer
OS	Overall survival
CT	Computed tomography
CYFRA21-1	Cytokeratin fraction 21-1
CA19-9	Carbohydrate antigen 19-9
C/T ratio	Consolidation / tumor ratio
EGFR	Epidermal growth factor receptor
PD-L1	Programmed cell death-ligand 1
DEE	Disease specific survival
RFS	Recurrence free survival
ROC	Receiver operating characteristics
CI	Confidence interval
KL-6	Krebs von den Lungen 6

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Author contributions

MT and NF participated in data analysis and acquisition, and MT drafted the manuscript. MT also participated in study design. TS, MY, RM, and HO contributed to data and statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent participate

This study was approved by the Ethics Committee of Kochi Medical School.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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