Original Article

Serum Carcinoembryonic Antigen Level as a Surrogate Marker for the Evaluation of Tumor Response to Chemotherapy in Nonsmall Cell Lung Cancer

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Purpose: Carcinoembryonic antigen (CEA) is a tumor marker widely used for nonsmall cell lung cancer (NSCLC). The aim of this study was to evaluate changes in serum CEA levels as a surrogate marker for tumor response to chemotherapy in NSCLC.

Methods: From 1995 through 2005, we retrospectively analyzed 24 NSCLC patients who had high serum CEA levels (>5 ng/ml) and who received chemotherapy followed by surgery. We compared serum CEA levels with tumor response, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria, as well as with histological response.

Results: Serum CEA levels after chemotherapy significantly decreased in patients who achieved partial response, defined by RECIST or WHO criteria ($p = 0.004$ and $p = 0.008$, respectively), when compared with the CEA levels before chemotherapy. In contrast, there was no significant difference in CEA levels in patients with either stable disease or no response to chemotherapy. They decreased significantly, however, in patients in whom less than one-third of tumor cells was viable by pathological examination, but not in patients in whom more than a third was viable ($p = 0.008$). Using the receiver-operating characteristic (ROC) curve analysis, we found that a 60% reduction of CEA levels was an appropriate cutoff value in predicting a good response to chemotherapy. When the value was set at that level, the sensitivity of CEA for RECIST was 82%, and the specificity was 69%.

Conclusion: Serum CEA concentration was a useful surrogate marker for the evaluation of tumor response to chemotherapy and seemed to be comparable with RECIST in NSCLC patients who had elevated CEA levels prior to treatment. (Ann Thorac Cardiovasc Surg 2010; 16: 242–247)

Key words: tumor marker, WHO, RECIST

Introduction

The first criterion for the evaluation of tumor response was established in the 1960s. In 1979, the World Health Organization (WHO) devised a series of criteria that codify the evaluation method of tumor response[1]; however, several modifications brought to the WHO criteria raised objectivity and universality concerns. As an effort to clarify and simplify the rules of the assessment of tumor shrinkage, the final version of the Response Evaluation Criteria in

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Solid Tumors (RECIST) was proposed in 2000.[2] RECIST is based on the unidimensional measurement of tumors, which is simpler than the bidimensional measurement stipulated by WHO criteria. RECIST is now regarded as a standard method for evaluating tumor response, which is required for clinical trials, and its validity and reproducibility have also been demonstrated for nonsmall cell lung cancer (NSCLC).[3–5]

The carcinoembryonic antigen (CEA) is a significant tumor marker for malignant tumors, including NSCLC.[6–8] Several studies have revealed the role of serum CEA concentration as a prognostic factor or as a marker for early detection of postoperative recurrence in NSCLC.[9–11] Although evaluation criteria based on imaging modalities, including computed tomography (CT), have become standard in the evaluation of tumor response, serum levels of tumor markers are sometimes used in clinical settings to estimate tumor response, especially in patients with pleural dissemination or effusion and multiple pulmonary metastases, in which measuring tumor size is difficult. To date, the concordance between changes in the levels of tumor markers and tumor reduction evaluated by imaging approaches has not been analyzed extensively. Salgia et al. reported that the response and change in CEA with surgical therapy or chemotherapy in NSCLC.[12] They found a significant decrease in the CEA levels after treatment and suggested that it would be useful to compare changes of tumor marker concentrations with the levels of response to chemotherapy, especially in late-stage NSCLC.

The aim of this study was to determine the role of serum CEA levels in the evaluation of tumor response to preoperative chemotherapy in NSCLC by comparing serum CEA levels with WHO criteria and RECIST. We also analyzed the relationship between these criteria and histological response, which should most precisely reflect the effects of chemotherapy.

Materials and Methods

1. Patients

Approval for this study was obtained from the institutional review board, which waived the need for individual patient consent. During the 11-year period from 1995 through 2005, a total of 65 patients with primary NSCLC received preoperative chemotherapy at the Aichi Cancer Center Hospital in Japan. Among them, 24 with high-serum CEA levels (cutoff, 5 ng/ml) at presentation were analyzed, including 20 males and 4 females ranging in age from 40 to 70 years (median, 55). There were 16 (66.7%) adenocarcinomas, 3 (12.5%) squamous cell carcinomas, and 5 (20.8%) large-cell carcinomas. The cohort included 1 patient with clinical stage IB disease, 5 with IIB disease, 15 with IIIA disease, and 3 with IIIB disease. Platinum doublet chemotherapy was performed in 23 patients, and docetaxel was administered to 1 (Table 1).

Table 1. Patient characteristics

		No. of patients
Gender	Male	20
	Female	4
Age (years)	Median (range)	55 (40–70)
Clinical stage	IB	1
	IIB	5
	IIIA	15
	IIIB	3
Histology	Adeno ca.	16
	Squamous ca.	3
	Large-cell ca.	5
Chemotherapy	CBDCA + PTX	5
	CBDCA + DOC	8
	CBDCA + VNR	1
	CBDCA + VP-16	1
	CDDP + VP-16	2
	MVP	6
	DOC	1

CBDCA, carboplatin; PTX, paclitaxel; DOC, docetaxel; VNR, vinorelbine; VP-16, etoposide; CDDP, cisplatin; MVP, mitomycin C + vindesine + cisplatin
Nine patients received preoperative radiation therapy.

The serum CEA concentration was measured by using a chemiluminescent immunoassay kit (Abbott, Japan). Time intervals between first measurement and the initiation of chemotherapy ranged from 49 to 65 days (median, 58.5 days), and intervals between postchemotherapeutic CEA measurement and the completion of chemotherapy ranged from 17 to 43 days (median, 29). The evaluation of tumor response on CT was performed by a thoracic surgeon (Futoshi Ishiguro). A confirmation of response for 4 weeks guided by RECIST was not mandated because the patients were scheduled for pulmonary resection just after chemotherapy.

2. Histological examination

The histological response to chemotherapy was evaluated by the following criteria from "General Rule for Clinical and Pathological Record of Lung Cancer" (6th edition, The Japan Lung Cancer Society): EF0, no histological response; EF1, more than one-third of the tumor cells

viable; EF2, less than one-third viable; EF3, no viable cells.

3. Statistical analysis

A comparison of the two groups was analyzed by a two-sided Wilcoxon signed rank test. A p value <0.05 was considered significant. Correlation between reduction rate and RECIST, WHO criteria, changes of serum CEA levels, and histological response were investigated by Spearman rank correlation.

Table 2. Evaluation of tumor response according to RECIST and WHO criteria

Criteria	No. of patients				Response rate (%)
RECIST	CR	PR	SD	PD	45.8
	0	11	13	0	
WHO	CR	PR	NC	PD	37.5
	0	9	14	1	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NC, no change.

Results

Using RECIST, we obtained a partial response (PR) in 11 patients, and stable disease (SD) was observed in 13. The response rate was 46%. Using WHO criteria, we obtained PR in 9 patients, no changes (NC) were observed in 14, and progressive disease (PD) was established in 1. The concordance between RECIST and WHO criteria was 83% (Table 2).

Comparison of serum CEA levels before and after chemotherapy and correlation with tumor response

A comparison of CEA levels before chemotherapy with those obtained after chemotherapy revealed a significant decrease of serum CEA concentration in patients with PR defined by RECIST (median, 17.3 ng/ml to 4.4 ng/ml, $p = 0.004$) or WHO criteria (median, 26.3 ng/ml to 4.3 ng/ml, $p = 0.008$). In contrast, no significant differences were observed in patients with SD (median, 16.8 ng/ml to 19.6 ng/ml, $p = 0.24$) or NC (median, 16.8 ng/ml to 9.9 ng/ml, $p = 0.24$) (Figs. 1A and 1B). Only one patient with PR defined by RECIST showed increased CEA levels after chemotherapy (9.3 ng/ml to 22.6 ng/ml). In that patient, brain metastases appeared 3 months after surgery, and the patient died 17 months later (20 months after surgery).

In regard to pathological findings, CEA levels decreased significantly in patients in whom less than one-third of the tumor cells were viable after surgery (median, 17.0 ng/ml to 4.4 ng/ml, $p = 0.008$), but not in patients in whom more than a third of tumor cells were viable (16.8 ng/ml to 7.9 ng/ml, $p = 0.06$) (Fig. 1C).

Definition of the CEA cutoff value by receiver operating characteristic (ROC) curve

To assess the applicability of CEA concentration as a marker for the evaluation of tumor response to chemotherapy, we next tried to determine the cutoff value of relevant CEA reduction ratio. It was defined as follows: CEA concentration before treatment minus the concentration after treatment divided by the concentration before treatment.

We set the cutoff values of the CEA reduction ratio to 15, 20, 30, 50, 60, 70, and 80%. A patient was considered a good responder when the ratio was superior to each cutoff value, and a poor responder when this parameter was inferior to each value. An ROC curve analysis was carried out based on the sensitivity and specificity of the reduction of the CEA ratio for RECIST or WHO criteria, respectively (Figs. 2A and 2B). The analysis revealed that a 60% reduction in CEA levels was an appropriate cutoff value for the prediction of a good response to chemotherapy, using both RECIST and WHO criteria. At a 60% reduction, the sensitivity of CEA for RECIST was 82.8%, the specificity was 69.2%, the positive predictive value was 69.2%, and the negative predictive value was 75.0%.

A correlation between histological response and CEA reduction ratio was evaluated by RECIST, WHO criteria, or changes in serum CEA levels.

We examined the correlation between histological response and CEA reduction ratio evaluated by RECIST, WHO criteria, and changes in serum CEA levels. The contribution ratio evaluated by RECIST was $r^2 = 0.396$ ($p = 0.003$), by WHO criteria it was $r^2 = 0.426$ ($p = 0.001$), and by CEA reduction ratio it was $r^2 = 0.212$ ($p = 0.04$). The correlation between histological response and CEA reduction ratio evaluated by RECIST, WHO criteria, and changes in CEA values was not significant (Figs. 3A, B and C).

Discussion

The purpose of cancer chemotherapy is to improve the overall survival of patients. In clinical settings, tumor response evaluated by RECIST is an important surrogate marker for survival; however, it cannot be applied in patients with no measurable lesions, including those with

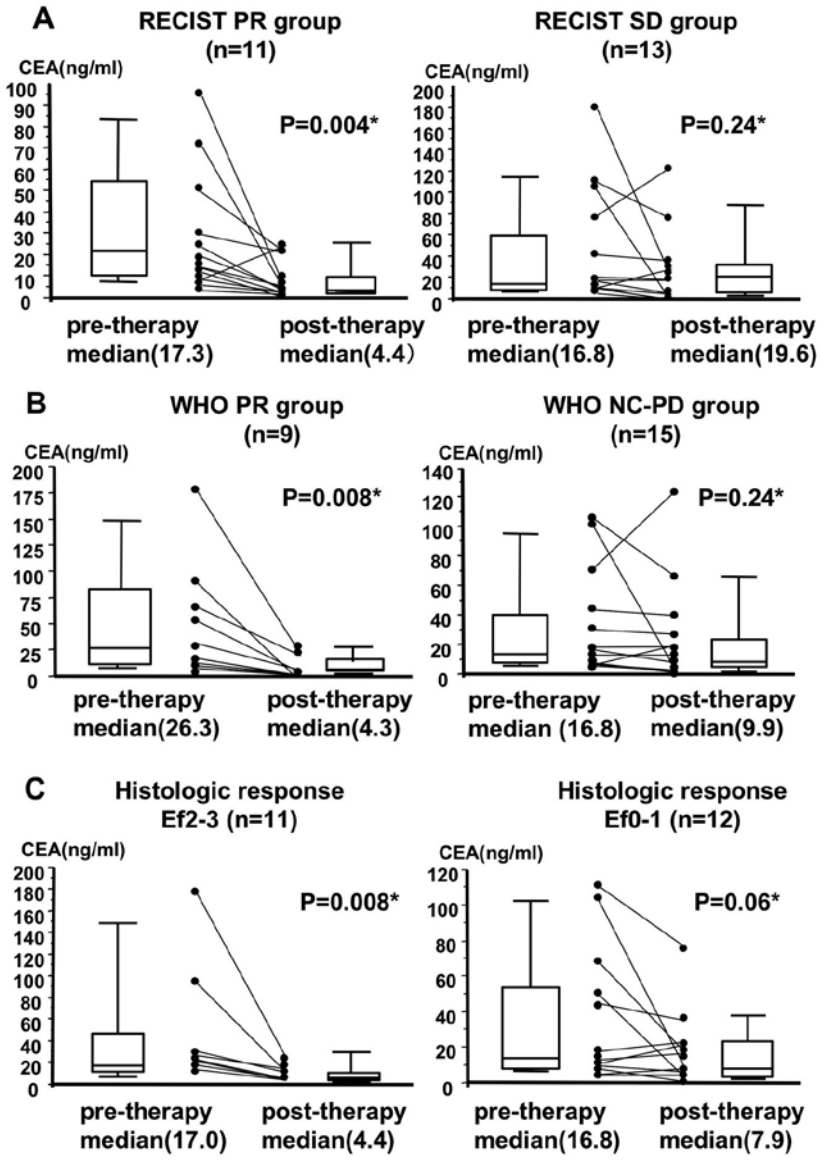

Fig 1. Correlation between serum CEA levels before and after chemotherapy, and responsiveness to treatment as defined by RECIST (**A**), WHO criteria (**B**), and histological response (**C**). The box shows lower quartile, median, and upper quartile. Each bar shows the largest and smallest nonoutlier observation. *The *P* value was calculated using the Wilcoxon signed rank test.

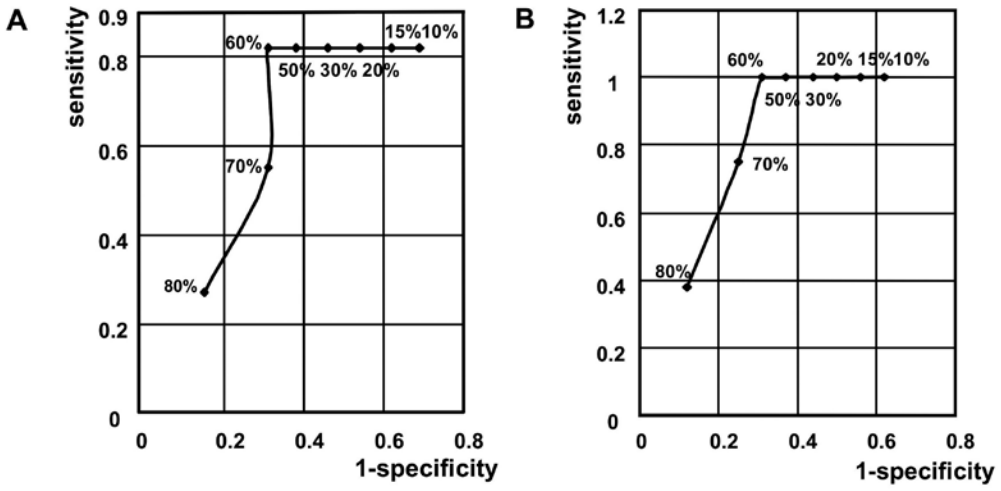

Fig. 2. Receiver operating characteristic (ROC) curve analysis to determine the cutoff value of CEA concentration. Each curve was evaluated using RECIST (**A**) and WHO criteria (**B**).

pleuritis carcinomatosa, pleural effusion, or small lesions. Because it is also difficult to evaluate antitumor effects by RECIST when the patient has minute multiple pulmonary metastases or irregularly shaped tumors, we evaluated changes in serum CEA levels as a surrogate marker for tumor response to chemotherapy. A previous report compared the evaluation of responsiveness by chest CT with that performed by histological examination.[13] Only one report analyzed changes in CEA value in relation to tumor response.[14] In this study, we showed that changes in CEA levels in the serum reflected tumor response evaluated by RECIST, WHO criteria, or histological examination.

We also used an ROC curve to show that a 60% reduction in CEA levels was appropriate for predicting a good response to chemotherapy. In RECIST and WHO criteria, a similar volume reduction ratio is thought to be adopted. Partial response evaluated by RECIST (i.e., a 30% decrease of the "longest diameter" of target lesions) is equivalent to a 50% reduction of the tumor area (i.e., $1 - 0.7^2$), which is a definition of PR by WHO criteria. This degree of tumor shrinkage is considered to be equal to a 65% reduction in tumor volume (i.e., $1 - 0.7^3 = 0.657$). If the CEA reduction ratio is assumed to reflect shrinkage of the tridimensional volume of the tumor, the cutoff value of 60% obtained here appears reasonable.

Histological response should reflect tumor response precisely and is expected to be the best surrogate marker for the survival of patients; however, the correlation obtained in this study between histological response and other criteria was not significant. One possible explanation for this discrepancy is the possibility that the interstitial tissue remained as scar or necrotic tissue after treatment, which would mask tumor shrinkage even if tumor cells had disappeared. Another explanation could be that the tumor was resected before the maximum reduction effect was achieved because the interval between the end of chemotherapy and surgery was relatively short. Because the tumors in the 11 patients in our cohort had invaded thoracic walls, they could not shrink uniformly, and the effect of tumor reduction was not reflected appropriately in chest CT imaging. Another report suggested that CEA levels increase transiently for the first 20–60 days after the onset of chemotherapy or radiotherapy.[15]

In this study, we reviewed only patients with high CEA levels (>5 ng/ml). Because the proportion of NSCLC patients with elevated CEA was suggested to be less than 50%, the possibility arises that patients with normal preoperative serum CEA levels should also be evaluated. Moreover, the targets of this study were surgically treated

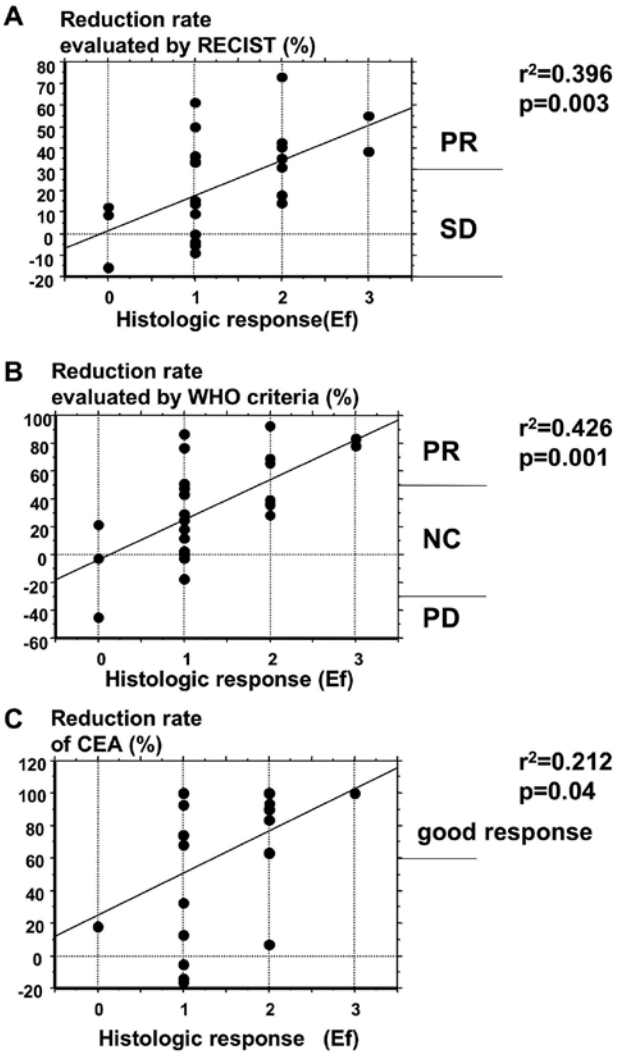

Fig. 3. (**A**) Correlation between histological response and tumor reduction rate evaluated by RECIST. (**B**) Correlation between histological response and tumor reduction rate evaluated by WHO criteria. (**C**) Correlation between histological response and reduction rate of serum CEA levels.

patients: it remains unclear whether these patients and highly advanced NSCLC patients were equally treated, though the chemotherapy regimen was similar in both scenarios. Larger-scale studies targeting postoperative recurrence cases and unresectable NSCLC cases are expected in the near future.

RECIST is a "ruler" standardized as the criteria of evaluation of tumor response. The reproducibility of RECIST is clear, and the evaluation of tumor response using RECIST can be easily carried out by surgeons, pulmonologists, or radiation oncologists, but not by radiologists.[16] On the other hand, we frequently measure

serum CEA levels during the treatment of NSCLC patients because this parameter can be assessed easily; therefore serum CEA concentration may also be a useful surrogate marker for patients with lesions that are not measurable.

Conclusion

Serum CEA levels appeared to be a useful surrogate marker for the evaluation of tumor response to chemotherapy, and it seemed to be comparable with RECIST in patients with NSCLC who had elevated CEA levels prior to treatment.

Note: The main results of this paper were previously published in Japanese in the *Japanese Journal of Lung Cancer*.[17)]

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