Cytokeratin 19 Fragment/Carcinoembryonic Antigen Ratio in Pleural Effusion Is a Useful Marker for Detecting Malignant Pleural Mesothelioma

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Abstract. *Background: The clinical utility of tumour markers in pleural effusion is still controversial with regard to the efficient detection of malignant pleural mesothelioma (MPM). Patients and Methods: The levels of carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA 21-1) were retrospectively studied in pleural effusion of unknown origin in patients who had undergone medical thoracoscopy under local anaesthesia. Results: The study included 134 patients (103 men and 31 women); among them, 33 had MPM. The level of pleural effusion CYFRA 21-1 and the CYFRA 21-1/CEA ratio were significantly different between MPM and other diseases ($p<0.01$). The sensitivity and specificity of the pleural effusion CYFRA 21-1/CEA ratio were 84.8% and 80.2%, respectively, when the CYFRA 21-1/CEA ratio cut-off value determined by receiver operating characteristic curve analysis was 19.1. Conclusion: MPM should be suspected when the CYFRA 21-1/CEA ratio in pleural effusion is greater than 19.1.*

Malignant pleural mesothelioma (MPM) is a fatal malignancy related to asbestos exposure. The diagnosis of MPM is difficult. Pleural effusion is the most common symptom, whereas cytological tests show low positive rates for pleural effusion; for example, one report showed a pleural effusion rate of 32% (1). Furthermore, on computed tomography (CT) imaging, it seems to be difficult to distinguish between MPM and pleural metastasis (2), and, to date, an optimal tumour marker has not yet been found.

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Previous studies have investigated the values of carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA 21-1), and carbohydrate antigen 19-9 in malignant pleural effusion mainly caused by lung cancer (3-13). A high value of CYFRA (14) or hyaluronic acid (15) was reported in pleural effusion caused by MPM, but a cut-off value has not yet been established. Medical thoracoscopy (MTS) is required to confirm the diagnosis in many cases.

To diagnose MPM more efficiently, the present study investigated the tumour marker value in pleural effusion and the relationship between MPM and other diseases in patients who underwent MTS.

Patients and Methods

All patients had undergone MTS under local anesthesia for pleural effusion and were examined between November 2001 and December 2009 at the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, Japan. Any patient who had recurrent malignant disease or clearly identified lung cancer or who simply underwent lung drainage was not a candidate for MTS. MTS was performed under local anaesthesia by using semi-rigid scopes (LTF-260; Olympus, Tokyo, Japan). Biopsy specimens were obtained from parietal pleura or supra-diaphragmatic lesions by using forceps and an insulated-tip diathermic knife was used in the case of extremely hard lesions or very thick pleura (16). Surgical biopsy was performed if diagnosis was not achieved after this procedure.

All malignant diseases were histologically confirmed. Tuberculosis was diagnosed by the presence of tuberculosis bacteria (polymerase chain reaction test or culture was performed) or epithelioid granuloma with a reaction to anti-tuberculosis drugs. Once inflammation was detected in a specimen, a final diagnosis of inflammation was determined after a follow-up of several months.

The values of CEA and CYFRA 21-1 were measured using an electrochemiluminescence immunoassay (Roche Diagnostics Co. Ltd., Basel, Switzerland). The data are shown as mean±standard deviation (SD), and the Mann-Whitney *U*-test was performed on the data set. The cut-off value of the measurement was determined using the receiver operating characteristic (ROC) curve. $P<0.05$ was

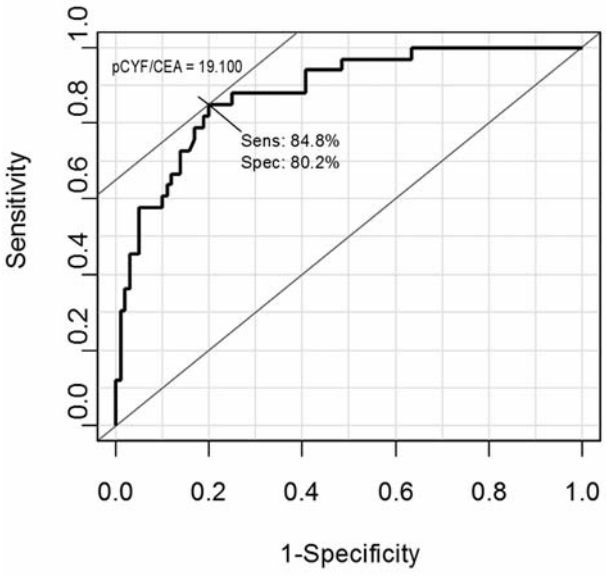

Figure 1. *Receiver operating characteristic curve of the ratio cytokeratin 19 fragment (CYFRA 21-1)/carcinoembryonic antigen (CEA) in pleural effusion distinguishes mesothelioma from other malignant diseases. CYF, CYFRA 21-1; Sens, sensitivity; Spec, specificity.*

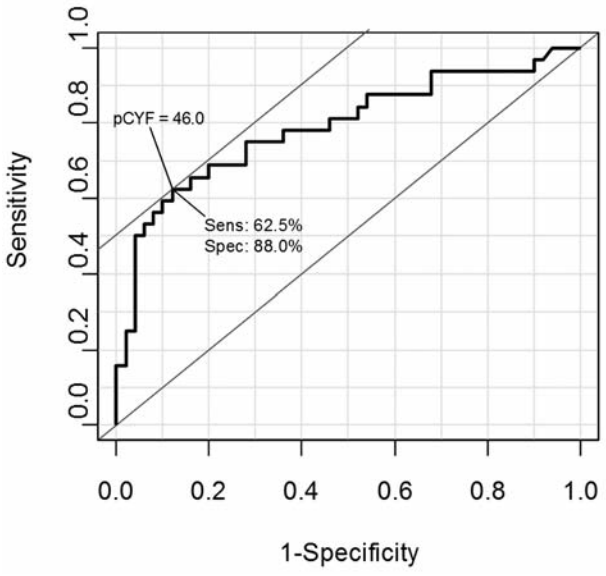

Figure 2. *Receiver operating characteristic curve of cytokeratin 19 fragment (CYFRA 21-1) in pleural effusion distinguishes mesothelioma from other malignant diseases in patients with carcinoembryonic antigen (CEA) <5 ng/ml.*

considered statistically significant. All data were analysed using software R, ver2.8.1 (available at: http://www.R-project.org.; R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 161 patients underwent MTS. Twenty-seven patients were excluded from the study because of missing data, and 134 patients (103 men and 31 women; median age, 69.5 years) were included in the study. Baseline disease characteristics included 50 cases of lung cancer, 6 of other types of cancer, 4 of malignant lymphomas, 33 of MPM, and 41 of benign diseases (including 12 cases of tuberculosis) (Table I). In MPM, the level of pleural effusion CEA was significantly lower than that in other diseases (2.7±9.0 *vs*. 374.7±1106.0 ng/ml; $p<0.01$) (Table II). The level of pleural effusion CYFRA 21-1 was significantly different between MPM and other diseases (546.5±1303.0 ng/ml *vs*. 113.6±258.9 ng/ml; $p<0.01$) (Table II). The sensitivity and specificity of pleural effusion CYFRA 21-1 were 57.6% and 61.0%, respectively, when the CYFRA 21-1 cut-off value was 69.7 ng/ml. Furthermore, the CYFRA 21-1/CEA ratio in pleural effusion showed a significant difference between MPM and other diseases (702.9±1541.0 *vs*. 33.2±179.0; $p<0.01$) (Table II). The sensitivity and specificity of the pleural effusion CYFRA 21-1/CEA ratio were 84.8% and 80.2%, respectively, when the CYFRA 21-1/CEA ratio cut-off value was 19.1 (Figure 1). Additionally, in the CEA<5 group (82 patients), the sensitivity and specificity of pleural effusion CYFRA21-1 were 62.5% and 88.0%, respectively, when the CYFRA 21-1 cut-off value was 46.0 ng/ml (Figure 2).

Discussion

An important finding of this study was that MPM should be strongly suspected when the CYFRA 21-1/CEA ratio is greater than 19.1 in pleural effusion. Salama *et al*. were the first to report that a high CYFRA 21-1 value in pleural effusion is indicative of MPM (6). They examined pleural effusion in 196 patients, and MPM was diagnosed on the basis of low CEA values and high CYFRA 21-1 values. Using a cut-off value of 46 ng/ml, Paganuzzi *et al*. reported that the sensitivity and specificity of CYFRA 21-1 for MPM were 87.5% and 80%, respectively (14). They diagnosed 93.2% cases of MPM on the basis of this CYFRA 21-1 value, low CEA value, and cytological tests for pleural effusion. It should be noted, however, that within the patient group of previous studies, the proportion of patients with MPM was far lower than that of patients with lung cancer. Therefore, an objective cut-off value of CYFRA 21-1 in pleural effusion is still undetermined.

The present study had a high clinical efficacy because the cut-off value of the CYFRA 21-1/CEA ratio was clearly identified using many MPM cases. Moreover, there are clear advantages in using the CYFRA 21-1/CEA ratio, as opposed to CYFRA 21-1. First, the sensitivity falls only by CYFRA

Table I. *Patient clinical characteristics*.

	Number of patients
Malignacy	93
Mesothelioma	33
Epitheliod type	24
Sarcomatous type	5
Biphasic type	3
Desmoplatic type	1
Lung cancer	50
Adenocarcinoma	38
Small cell carcinoma	5
Squamous cell carcinoma	4
Large cell carcinoma	1
Other type	2
Ovarian cancer	3
Thyroid cancer	1
Colon cancer	1
Breast cancer	1
Malignant lymphoma	4
Benign	41
Non-specific inflammation	14
Tuberculosis	12
Benign asbestosis-related pleural effusion	5
Bacterial inflammation	4
Collagen disease	2
Other benign diseases	4

21-1 even if we studied in the low CEA group. Second, low CYFRA21-1 value patients comprised about 10% of the mesothelioma group in present study. Third, the CYFRA 21-1/CEA ratio can be easily used in practice because CYFRA 21-1 and CEA is widely commercially available.

Recently, new markers such as mesothelin-related protein and osteopontin are being tested for the diagnosis of MPM. Scherpereel *et al*. reported that serum mesothelin-related protein appears in MPM, and they used a cut-off value of 10.4 nM/l with a sensitivity and specificity of 76.7% and 76.2%, respectively, for MPM (17). Pass *et al*. showed that serum osteopontin had a cut-off value of 48.3 ng/ml with a sensitivity and specificity of 77.6% and 85.5 %, respectively (18). These new markers do not confirm the diagnosis of MPM. A combination of these markers and other tests, such as a positron-emission tomography (PET) scan or clinical symptoms, are required to diagnose MPM.

The present study had several limitations. Pleural effusion of unknown origin, which is difficult to diagnose, was used in this study. The cut-off value may change when cases that are easier to diagnose are included in the study population. Furthermore, the serum CYFRA 21-1 level is elevated in lung cancer, especially in squamous cell carcinoma (7). CYFRA 21-1 in pleural effusion may parallel CYFRA 21-1 rise in serum in pleuritis carcinomatosa of squamous cell carcinoma.

Table II. *Carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA 21-1) and their ratio in pleural effusion*.

		Mean±SD (ng/ml)	*P*-value
CEA	Mesothelioma	2.69±9.00	5.27×10^{-7}
	Non-mesothelioma	374.66±1106.33	
CYF	Mesothelioma	546.45±1302.99	0.001
	Non-mesothelioma	113.57±258.83	
CYF/CEA	Mesothelioma	702.86±1540.99	4.73×10^{-16}
	Non-mesothelioma	33.15±179.00	

CYF, CYFRA21-1; SD, standard deviation.

In conclusion, when the CYFRA 21-1/CEA ratio is >19.1 in pleural effusions of unknown origin, MPM should be suspected, and further evaluations such as MTS should be performed. A combination of new markers such as osteopontin and mesothelin with CT imaging or PET scan may improve the probability of accurate diagnosis of MPM.

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