

Diagnostic Value of CYFRA 21-1, CEA, CA 19-9, CA 15-3, and CA 125 Assays in Pleural Effusions: Analysis of 116 Cases and Review of the Literature

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ABSTRACT

Levels of tumor markers in pleural effusions may help to establish the diagnosis of pleural malignancy, but the precise diagnostic value of each marker remains unclear. The aim of this study was to assess the diagnostic value of five common pleural fluid tumor markers, carcinoembryonic antigen (CEA), cytokeratin fragment (CYFRA) 21-1, cancer antigen (CA) 15-3, CA 19-9, and CA 125, and to review the literature from the past 15 years. Pleural fluid samples were collected prospectively from 116 patients and assayed for CEA, CYFRA 21-1, CA 15-3, CA 19-9, and CA 125 levels. A MEDLINE search of the English-language literature from the past 15 years was also done.

Effusions were classified as benign or malignant on the basis of their definitive pathologic or cytologic diagnoses. The levels of all pleural tumor markers were

statistically significantly higher in the malignant group than in the benign group. The marker with the highest accuracy was CEA (85.3%); CA 15-3, CYFRA 21-1, and CA 19-9 had similar accuracies (75.2%, 72.4%, and 71.5%, respectively), and CA 125 had the lowest accuracy (40.5%). On univariate analysis, tumor-marker combinations did not result in a greater accuracy than that of CEA alone. On multivariate logistic regression, CA 15-3 and CYFRA 21-1 were significant predictors of malignancy. Among the nine reports in the literature comparing 11 different tumor markers, CEA, CA 15-3, and CYFRA 21-1 yielded the best results. We conclude that pleural fluid analysis should include CEA for the diagnosis of malignancy. CA 15-3 and CYFRA 21-1 may serve as alternative options. *The Oncologist* 2005;10:501–507

INTRODUCTION

Pleural effusions are common complications of a wide variety of diseases. It is important to elucidate their precise etiologies to differentiate benign from malignant effusions [1]. The initial diagnostic approach includes thoracentesis and cytologic, histologic, and biochemi-

cal examinations [2]. However, the sensitivity of these noninvasive techniques is only 40%–70% [3, 4]. To improve upon these rates, a number of tumor markers in the pleural fluid have been intensively evaluated. The most common markers found to be of diagnostic significance were carcinoembryonic antigen (CEA), can-

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cer antigen (CA) 15-3, CA 19-9, cytokeratin fragment (CYFRA 21-1), and CA 125 [2, 5–7]. However, their precise sensitivities in identifying malignant pleural effusions remain controversial. Moreover, few data exist on tumor-marker levels for different etiologies.

The aim of this study was to determine the diagnostic capabilities of these five tumor markers in pleural fluid. To reach practical conclusions, we reviewed the literature from the past 15 years.

PATIENTS AND METHODS

A total of 116 pleural fluid samples was prospectively collected from 116 patients at the Pulmonary Institute of Rabin Medical Center between March 2003 and December 2003. The study group included 65 men (56%) and 51 women (44%). The effusions were classified as benign or malignant on the basis of their definitive pathologic diagnoses.

The effusions were considered malignant if malignant cells were found on cytologic examination or in a biopsy specimen. In cases where cytologic examinations were negative ($n = 18$), we did closed pleural biopsies. Five patients underwent video-assisted thoracoscopic surgery (VATS).

The effusions were considered parapneumonic if they were associated with acute febrile illness with purulent sputum, pulmonary infiltrate, and responsiveness to antibiotic treatment or if a micro-organism was identified in the pleural fluid in the absence of any other cause of the pleural effusion. Tuberculous pleurisy was diagnosed by positive cultures for *Mycobacterium tuberculosis* or when the pleural biopsy specimen showed typical epithelioid cell granuloma. A diagnosis of congestive heart failure (CHF) was made by findings of an enlarged heart, pulmonary venous congestion on the radiograph, and peripheral edema, with response to CHF treatment and absence of malignancy or pulmonary infiltrates associated with an inflammatory process. The diagnosis of postcardiotomy syndrome (Dressler's syndrome) was made when the pleural effusion developed after injury to the heart and CHF, pulmonary embolism, and pneumonia were ruled out, and a response to treatment with anti-inflammatory agents or corticosteroids was noted.

Pleural fluid was collected from each patient prior to any therapy. The supernatant was obtained by centrifugation at 300 rpm for 15 minutes and stored at -20°C until assayed. The clinicians who identified the tumor markers were blinded to the definitive diagnosis of the pleural effusions.

CEA and CA 19-9 levels were determined by the solid-phase, two-site chemiluminescent enzyme immunoassay, and CA 15-3 levels were determined by the sequential, two-site chemiluminescent enzyme immunoassay (Immulite[®]; Diagnostic Products Corpora-

tion, Los Angeles, <http://www.dpcweb.com>). CYFRA 21-1 levels were measured with commercially available enzyme-linked immunosorbent assay kits (CYFRA 21-1 Enzymun-Test[®]; Roche Diagnostics Corporation, Indianapolis, <http://www.roche-applied-science.com>). This test is based on the sandwich enzyme immunoassay with streptavidin technology. CA 125 analysis was performed with the BYK-Sangtec System radioimmunoassay-mat 280 (double-antibody immunoradiometric assay, Diasorin Diagnostic Group, Dietzenbach, Germany, <http://www.diasorin.com>).

The cutoff levels of CEA, CYFRA 21-1, CA 15-3, CA 19-9 and CA 125 were 0–5 ng/ml, 0–3.3 ng/ml, 0–30 U/ml, 0–37 U/ml, and 0–35 U/ml, respectively.

A MEDLINE search of the English-language literature from the last 15 years was performed using the key words “tumor marker,” “pleural effusion,” “CEA,” “CA 125,” “CA 19-9,” “CA 15-3,” “CYFRA 21-1,” and “malignant,” alone and in combination. Only reports that compared at least two tumor markers were included.

Statistical Analysis

Results are shown as mean \pm standard deviation. Pearson's correlation coefficients (r) and their corresponding significance values (p) were calculated between the variables. To analyze differences between the distributions of categorical data, a χ^2 test or Fisher's exact test was used, as appropriate. Sensitivity, specificity, positive and negative predictive values, and accuracy were calculated between patients with and without malignancies. Accuracy was defined as $(\text{true-positive} + \text{true-negative}) / (\text{true-positive} + \text{false-positive} + \text{true-negative} + \text{false-negative})$ [8].

Differences in means of continuous variables between two groups of patients (malignancy and nonmalignancy) were analyzed by the t -test.

To predict malignancy, a stepwise logistic regression model was fitted to the data. Odds ratios and 95% confidence intervals (CIs) were calculated from the model. A p value of .05 or less was considered statistically significant.

RESULTS

Seventy-two effusions were defined as benign and 44 were defined as malignant. Of the 72 patients with benign effusions, 46 (64%) were men and 26 were women, with a mean age of 69.6 ± 13.6 years (range 34–91). Of the 44 patients with malignant effusions, 20 were men and 24 were women, with a mean age of 70.3 ± 11.9 years (range 42–88). The causes of the benign and malignant pleural effusions are given in Table 1.

Of the 44 patients with malignancies, 21 had lung cancer. Only two of these had small-cell lung cancer and all the

others had non-small cell lung cancer. None of the patients was stage I. Four patients were stage II, seven patients were stage III, and 10 patients were stage IV.

The traditional pleural markers, including the cell count, blood and pleural fluid levels of total protein and lactate dehydrogenase (LDH), and the cytologic yields, are presented in Table 2. It should be noted that some parameters were statistically significantly different between the lung malignancy subgroup and the other subgroups.

Table 1. Etiology of pleural effusions

Cause	No.	Total
Benign	Parapneumonic	33
	Congestive heart failure	21
	Postsurgery	1
	Lung transplantation	7
	Collagen disease	5
	Tuberculosis	3
	Traumatic	1
	Vasculitis	1
Malignant	Lung	21
	Breast	5
	Colorectal	4
	Ovary	4
	Renal	3
	Lymphoproliferative	3
	Mesothelioma	2
	Prostate	2
Total		116

The means and standard deviations of the pleural fluid levels of CEA, CA 125, CA 19-9, CA 15-3, and CYFRA 21-1 in patients with benign and malignant effusions are presented in Table 3. The levels of all pleural tumor markers were statistically significantly higher in the malignant group than in the benign group. Table 4 shows the sensitivity, specificity, negative and positive predictive values, and accuracy of each tumor marker. CEA had the highest accuracy (85.3%), although its sensitivity was relatively low (63.6%). CA 15-3, CYFRA 21-1, and CA 19-9 had similar accuracies (71.5%, 72.4%, and 71.5%, respectively). The lowest accuracy was noted for CA 125 (40.5%).

On univariate analysis, combining the findings for CEA, CA 15-3, and CYFRA 21-1 (Table 6) resulted in a greater sensitivity than that of CEA alone. However, it produced a lower specificity, and therefore accuracy, than with CEA alone.

Table 3. Pleural fluid levels of CEA, CA 125, CA 19-9, CA 15-3, and CYFRA 21-1 in patients with benign and malignant effusions (mean \pm standard deviation)

	Benign (n = 72)	Malignant (n = 44)	p value
CEA	1.26 \pm 0.98	116.9 \pm 450	.03
CA 125	759 \pm 759	1,308 \pm 1,141	.024
CA 19-9	3.2 \pm 6.6	362 \pm 1131	.0079
CA 15-3	11.8 \pm 7.6	71.2 \pm 148.1	.0018
CYFRA 21-1	65.0 \pm 83.3	198.1 \pm 200	<.001

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CYFRA, cytokeratin fragment.

Table 2. Cell count, cytologic yields, and total protein and LDH levels in the blood and pleural fluid in the different subgroups (mean \pm standard deviation)

	Postsurgery (n = 12)	Parapneumonic (n = 20)	Congestive heart failure (n = 23)	Lung malignancy (n = 21)	Nonlung malignancy (n = 23)
WBC (μ l)	2,573 \pm 1,580	8,188 \pm 7,049 ^a	457 \pm 559 ^a	3,711 \pm 2,317	2,067 \pm 979 ^a
Neutrophil (%)	14 \pm 7 ^a	31 \pm 20	15 \pm 6 ^a	29 \pm 26	17 \pm 10
Lymphocyte (%)	67 \pm 11	28 \pm 24 ^a	43 \pm 15	49 \pm 31	60 \pm 25
Total protein – blood (g/dl)	6.9 \pm 0.8	6.6 \pm 1.1	2.7 \pm 0.5 ^a	7.0 \pm 0.4	6.8 \pm 0.5
LDH – blood (U/l)	260 \pm 28 ^a	311 \pm 28 ^a	375 \pm 90	360 \pm 28	470 \pm 223 ^a
Positive cytology, n (%)	–	–	–	5/21(24)	8/23 (35)
Total protein – pleural (g/dl)	4.2 \pm 1.0	5.2 \pm 0.6	2.6 \pm 0.75 ^a	4.8 \pm 0.9	6.8 \pm 0.6 ^a
LDH – pleural (U/l)	235 \pm 55 ^a	568 \pm 406	198 \pm 210 ^a	493 \pm 210	405 \pm 157

^aStatistically significant difference ($p < .05$) between the subgroup and the lung malignancy group. Abbreviation: LDH, lactate dehydrogenase.

Table 4. The sensitivity, specificity, negative and positive predictive values, and accuracy of CA 125, CEA, CA 19-9, CA 15-3, and CYFRA 21-1 in patients with malignant effusions

	Sensitivity	Specificity	NPV	PPV	Accuracy
CA 125	97.7(%) (43/44)	5.5(%) (4/72)	80(%) (4/5)	38.7% (43/111)	40.5% (47/116)
CEA	63.6% (28.44)	98.6% (71/72)	81.6% (71/87)	96.5% (28/29)	85.3% (99/116)
CA 19-9	25% (11/44)	100% (72/72)	68.6% (72/105)	100% (11/11)	71.5% (83/116)
CA 15-3	41.5% (17/41)	96.9% (62/64)	72.1% (62/86)	89.5% (17/19)	75.2% (79/105)
CYFRA 21-1	59.1% (26/44)	80.5% (58/72)	76.3% (58/76)	65% (26/40)	72.4% (84/116)

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CYFRA, cytokeratin fragment; NPV, negative predictive value; PPV, positive predictive value.

Table 5. Pleural fluid levels of CEA, CA 125, CA 19-9, CA 15-3, and CYFRA 21-1 in the different subgroups (mean \pm standard deviation)

	Postsurgery (n = 12)	Parapneumonic (n = 20)	Congestive heart failure (n = 23)	Lung malignancy (n = 21)	Nonlung malignancy (n = 23)
CEA	1.35 \pm 0.94 ^a	1.03 \pm 0.83 ^a	1.07 \pm 0.9 ^a	60.3 \pm 111.9	5.24 \pm 13.2
CA 125	702 \pm 638	1,041 \pm 967	460 \pm 562 ^a	1,118 \pm 888	1,527 \pm 1,587
CA 19-9	3.4 \pm 5.1	2.1 \pm 5.5	4.4 \pm 9.7	5.5 \pm 9.7	87.8 \pm 156.4 ^a
CA 15-3	11.2 \pm 5.4 ^a	16.5 \pm 9.1	8.5 \pm 4.0 ^a	28.5 \pm 26.9	46.4 \pm 63.3 ^a
CYFRA 21-1	43.8 \pm 37.3 ^a	59.7 \pm 114.3 ^a	12.9 \pm 15.8 ^a	176.7 \pm 210	153.9 \pm 173.2

^aStatistically significant difference ($p < .05$) between the subgroup and the lung malignancy group. Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CYFRA, cytokeratin fragment.

Table 5 presents the pleural fluid levels of CEA, CA 125, CA 19-9, CA 15-3, and CYFRA 21-1 in the different subgroups, including the postsurgery ($n = 12$), parapneumonic effusion ($n = 20$), CHF ($n = 23$), lung malignancy ($n = 21$), and nonlung malignancy ($n = 23$) subgroups. Only CEA and CYFRA 21-1 were statistically significantly different between the lung malignancy subgroup and all benign subgroups (postsurgery, parapneumonic, and CHF). The mean CA 15-3 level was statistically significantly different between the lung malignancy subgroup and the postsurgery, CHF, and nonlung malignancy subgroups. The mean CA 19-9 level in the lung malignancy subgroup was different only from that of the nonlung malignancy subgroup, whereas the mean CA 125 level in the lung malignancy subgroup was different only from that of the CHF subgroup.

When a multivariate logistic regression model was fitted to the data, the factors found to be statistically significantly predictive of pleural malignancy were CA 15-3 and CYFRA 21-1 ($p = .0037$ and $p = .0031$, respectively), with odds ratios of 1.058 (95% CI, 1.019–1.099) and 1.006 (95% CI, 1.002–1.010).

Review of the Literature

Our MEDLINE search yielded nine studies that compared 11 different tumor markers [7, 9–16]. Table 6 summarizes the reported sensitivity, specificity, and accuracy of the various tumor markers used in those studies and in the present study.

Six tumor markers, namely CA 72-4, CA 549, total sialic acid (TSA), squamous cell carcinoma (SCC) antigen, neuron-specific enolase (NSE), and mucinous carcinoma-associated antigen (MCA), were studied in only one or three studies [7, 9–11, 14–16]. Owing to the limited available data, we could not determine the diagnostic values of those markers. CA 125 was also assayed in only three reports, including ours [10, 11], which yielded conflicting results. CEA was assayed in eight of nine earlier studies. In three of those, it yielded the highest diagnostic value [12, 15, 16], as in the present study. In two studies, it was second to CA 15-3 [7, 14], and in one study, it was second to CYFRA 21-1 [13]. Only one report found both CYFRA 21-1 and CA 15-3 to be of higher diagnostic value than CEA [9].

CA 15-3 was assayed in five of nine studies in the literature [7, 9, 12, 14, 16]. In two of those studies, it yielded the highest diagnostic value [7, 14]. In one study, it was sec-

Table 6. Sensitivity, specificity, and accuracy of tumor markers in pleural fluids in the diagnosis of malignant pleural effusions: summary of the literature

Study	No. of patients	Tumor markers	Sensitivity	Specificity	Accuracy
Villena et al. [7]	207	CA 15-3	55	97	84
		CA 72-4	51	98	83
		CEA	53	100	82
		CA 19-9	20	100	75
Villena et al. [14]	252	CA 549	49	99	79
		CA 15-3	44	99	77
		CEA	35	100	74
		CA 72-4	35	98	73
Alatas et al. [9]	74	CYFRA 21-1	91	90	91
		CA 15-3	80	93	85
		TSA	80	67	74
		CEA	52	77	62
		CA 19-9	36	83	55
Paganuzzi et al. [13]	106	CYFRA 21-1	78	80	78
		CEA	30.6	91	49
Romero et al. [12]	115	CEA	57	99	83
		CA 15-3	48	97	79
		CYFRA 21-1	38	82	66
Ferrer et al. [10]	146	CEA	40	100	ND
		CA 125	37.2	100	ND
		CYFRA 21-1	23.8	100	ND
		SCC antigen	4.6	100	ND
		NSE	0	100	ND
Kuralay et al. [11]	61	NSE	100	95	ND
		CA 19-9	90	97	ND
		CA 125	95	95	ND
		MCA	52	95	ND
Salama et al. [15]	196	CEA	55.6	95	ND
		CYFRA 21-1	50.5	95	ND
Ustun et al. [16]	102	CEA	58.5	90	ND
		CA 15-3	51.2	75	ND
		CA 19-9	39	72.5	ND
		CA 72-4	46.3	95	ND
Present report	116	CEA	63.6	98.6	85.3
		CA 15-3	41.5	96.9	75.2
		CYFRA 21-1	59.1	80.5	72.4
		CA 19-9	25	100	71.5
		CA 125	97.7	5.5	40.5
		CEA + CYFRA 21-1	82	82	81.9
		CEA + CA 15-3	73	82	78.5
CEA + CA 15-3 + CYFRA 21-1	91	78	82.8		

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CYFRA, cytokeratin fragment; MCA, mucinous carcinoma-associated antigen; ND, no data; NSE, neuron-specific enolase; SCC, squamous cell carcinoma; TSA, total sialic acid.

ond to CEA, in agreement with the present study, and in one study it was second to CYFRA 21-1 [9].

CYFRA 21-1 was assayed in five reports in the literature [9, 10, 12, 13, 15]. Two found it to be the best tumor marker of malignant pleural effusion [9, 13] and, in three studies, it was second to other markers. Our findings agree with the latter reports.

CA 19-9 was assayed in four studies [7, 9, 11, 16]. None of them found it to be one of the best tumor markers. This was true of the present study as well. In three reports, CA 19-9 had the worst results [7, 9, 16].

DISCUSSION

The determination of tumor markers in pleural effusions has been proposed as an alternative, noninvasive way of establishing a diagnosis of pleural malignancy. However, the use of these measurements in clinical practice remains controversial.

The results of the present study demonstrate that the determination of CEA alone in pleural effusions yields the best results. Our review of the literature led to a similar conclusion.

The CYFRA 21-1 assay, which detects a soluble fragment of cytokeratin 19 that is expressed by all histologic

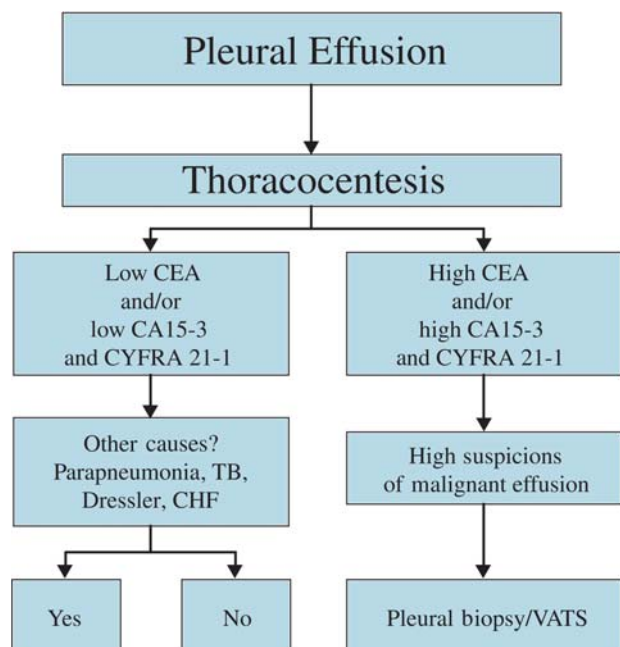


Figure 1. Management of pleural effusion: a clinical practice algorithm based on tumor-marker profile. Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CHF, congestive heart failure; CYFRA, cytokeratin fragment; TB, tuberculosis; VATS, video-assisted thoracoscopy surgery.

types of lung cancer [17], has been proven capable of detecting epithelial carcinomas, especially SCC [18]. Its sensitivity most likely depends on the prevalence of squamous cell malignancies in the studied population. Studies on the diagnostic significance of the CYFRA 21-1 level in pleural effusions in differentiating malignant from benign lung disease [19, 20] found it to be a reliable marker. The present study supports those findings.

Elevated levels of pleural CEA have also been demonstrated in malignant lung disease [21, 22]. In our series, CEA had the best diagnostic accuracy (85.3%) of all the markers tested, in agreement with earlier studies (Table 6). CEA synthesis is known to be increased by malignant cells. It has been suggested that decreased lymphatic drainage due to the obstruction of the lymphatics by malignant cells and pleural invasion may increase pleural fluid CEA levels [10].

Five patients with negative cytologies of their pleural effusions had positive CEA levels. All of them were eventually shown to have a malignancy. In addition, 21 patients had cytologies that were equivocal or suspicious for malignancy. Thirteen of them had CEA elevation and all of them proved to have malignancies. Based on the available data, we recommend the use of CEA as a marker in cases of suspected malignant pleural effusion (Fig. 1).

CA 15-3, which apparently has a high specificity for breast cancer, has not been as extensively evaluated in the differen-

tial diagnosis of malignant pleural effusions as CEA. The few relevant studies, however, in addition to ours, indicate that it may be one of the more specific tumor markers [10, 12].

Earlier studies reported that the pleural fluid CA 19-9 level had a low sensitivity but a high specificity in the diagnosis of malignant effusions [23]. We also found CA 19-9 to have a low sensitivity and a high specificity, and a similar accuracy to CYFRA 21-1 and CA 15-3.

According to immunohistochemical studies, CA 125 is released from the pleura and peritoneum [24, 25]. Only two reports compared CA 125 with other markers, and both found it to have a high sensitivity for discriminating malignant from benign pleural effusions, but a low specificity [23, 26]. The authors of those studies concluded that CA 125 alone was insufficient for diagnosis and was of value only with concurrent measurements of other tumor markers. Similarly, in our study, CA 125 had a high sensitivity and a low specificity. Therefore, we do not recommend its use in the tumor-marker profile of patients with suspected malignant pleural effusions.

Data on CA 72-4, CA 549, NSE, TSA, and SCC antigen remain sparse [7, 9, 11, 14], and further studies are needed to establish their diagnostic value in malignant pleural effusion.

On analysis of the diagnostic role of various tumor-marker combinations (Table 6), we found that both CA 15-3 and CYFRA 21-1, when combined with CEA, resulted in a greater sensitivity than that of CEA alone, but a lower specificity and accuracy than CEA alone.

Based on our findings and the review of the literature, we suggest using the algorithm outlined in Figure 1. This algorithm is based on the high specificity and positive predictive value of CEA as well as CA 15-3 and CYFRA 21-1 (Table 4).

In conclusion, our data suggest that measurement of CEA levels in pleural effusions yields the highest diagnostic accuracy. Other tumor markers, especially CA 15-3 and CYFRA 21-1, could serve as alternatives when CEA assay is not available. CA 125 and CA 19-9 are not contributory. CEA assay should be included in the evaluation of every patient with suspected malignant pleural effusion.

Based on our data, we think that every patient with unexplained pleural effusion should undergo thoracentesis with tumor-marker evaluations. Patients with negative cytologic examinations and positive tumor-marker levels should undergo further invasive procedures, and the final step should rest upon demonstration of positive cytology or biopsy of the pleura, which would result in management decisions.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

REFERENCES

- 1 Light RW. Malignant pleural effusion. In: Light RW, ed. *Pleural Diseases, Third Edition*. Baltimore: Williams and Wilkins, 1995:94–116.
- 2 Light RW. Clinical manifestations and useful tests. In: Light RW, ed. *Pleural Diseases, Third Edition*. Baltimore: Williams and Wilkins, 1995:36–74.
- 3 Marel M, Stastny B, Melinova L et al. Diagnosis of pleural effusions. Experience with clinical studies, 1986 to 1990. *Chest* 1995;107:1598–1603.
- 4 Prakash UB, Reiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. *Mayo Clin Proc* 1985;60:158–164.
- 5 Pavese F, Lotzniker M, Cremaschi P et al. Detection of malignant pleural effusions by tumor marker evaluation. *Eur J Cancer Clin Oncol* 1988;24:1005–1011.
- 6 Shimokata K, Totani Y, Nakanishi K et al. Diagnostic value of cancer antigen 15-3 (CA 15-3) detected by monoclonal antibodies (1158D8 and DF3) in exudative pleural effusions. *Eur Respir J* 1988;1:341–344.
- 7 Villena V, Lopez-Encuentra A, Echave-Sustaeta J et al. Diagnostic value of CA 72-4, carcinoembryonic antigen, CA 15-3, and CA 19-9 assay in pleural effusion. A study of 207 patients. *Cancer* 1996;78:736–740.
- 8 Griner PF, Mayewski RJ, Mushlin AI et al. Selection and interpretation of diagnostic tests and procedures. Principles and applications. *Ann Intern Med* 1981;94:557–592.
- 9 Alatas F, Alatas O, Metintas M et al. Diagnostic value of CEA, CA 15-3, CA 19-9, CYFRA 21-1, NSE and TSA assay in pleural effusions. *Lung Cancer* 2001;31:9–16.
- 10 Ferrer J, Villarino MA, Encabo G et al. Diagnostic utility of CYFRA 21-1, carcinoembryonic antigen, CA 125, neuron specific enolase, and squamous cell antigen level determinations in the serum and pleural fluid of patients with pleural effusions. *Cancer* 1999;86:1488–1495.
- 11 Kuralay F, Tokgoz Z, Comlekci A. Diagnostic usefulness of tumor marker levels in pleural effusions of malignant and benign origin. *Clin Chim Acta* 2000;300:43–55.
- 12 Romero S, Fernandez C, Arriero JM et al. CEA, CA 15-3 and CYFRA 21-1 in serum and pleural fluid of patients with pleural effusions. *Eur Respir J* 1996;9:17–23.
- 13 Paganuzzi M, Onetto M, Marroni P et al. Diagnostic value of CYFRA 21-1 tumor marker and CEA in pleural effusion due to mesothelioma. *Chest* 2001;119:1138–1142.
- 14 Villena V, Lopez-Encuentra A, Echave-Sustaeta J et al. Diagnostic value of CA 549 in pleural fluid. Comparison with CEA, CA 15.3 and CA 72.4. *Lung Cancer* 2003;40:289–294.
- 15 Salama G, Miedouge M, Rouzaud P et al. Evaluation of pleural CYFRA 21-1 and carcinoembryonic antigen in the diagnosis of malignant pleural effusions. *Br J Cancer* 1998;77:472–476.
- 16 Ustun H, Borazan A, Bilgicli N et al. Diagnostic value of tumoural markers in pleural effusions. *Int J Clin Pract* 2004;58:22–25.
- 17 Lai RS, Hsu HK, Lu JY et al. CYFRA 21-1 enzyme-linked immunosorbent assay: evaluation as a tumor marker in non-small cell lung cancer. *Chest* 1996;109:995–1000.
- 18 Stieber P, Hasholzner U, Bodenmuller H et al. CYFRA 21-1. A new marker in lung cancer. *Cancer* 1993;72:707–713.
- 19 Satoh H, Sumi M, Yagyu H et al. Clinical evaluation of CYFRA 21-1 in malignant pleural fluids. *Oncology* 1995;52:211–214.
- 20 Toumbis M, Rasidakis A, Passalidou E et al. Evaluation of CYFRA 21-1 in malignant and benign pleural effusions. *Anticancer Res* 1996;16:2101–2104.
- 21 Gandhi AK, Nayar M, Bihari N et al. Diagnostic value of carcinoembryonic antigen assay of pleural & peritoneal effusions in malignancy. *Indian J Med Res* 1989;90:22–26.
- 22 Toumbis M, Chondros K, Ferderigos AS et al. Clinical evaluation of four tumor markers in malignant and benign pleural effusions. *Anticancer Res* 1992;12:1267–1270.
- 23 Mezger J, Permanetter W, Gerbes AL et al. Tumour associated antigens in diagnosis of serous effusions. *J Clin Pathol* 1988;41:633–643.
- 24 Vergote IB, Onsrud M, Borner OP. CA125 in peritoneal fluid of ovarian cancer patients. *Gynecol Oncol* 1992;44:161–165.
- 25 Gullu I, Yalcin S, Tekuzman G. Tumor markers in effusions: a comparative study of tumor marker levels in sera and effusions. In: Travis CC, ed. *Use of Biomarkers in Assessing Health and Environmental Impacts of Chemical Pollutants*. New York: Plenum Press, 1993:265–272.
- 26 Kandylis K, Vassilomanolakis M, Baziotis N et al. Diagnostic significance of the tumour markers CEA, CA 15-3 and CA 125 in malignant effusions in breast cancer. *Ann Oncol* 1990;1:435–438.

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