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Perspectives and Commentaries

Value of CEA Determination in Biological Fluids and Tissues

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(A COMMENT ON: Faravelli B, Nosenzo M, Razzetti A, *et al.* Carcinoembryonic antigen in pleural malignant diseases. *Eur J Cancer Clin Oncol* 1985, **21**, 1083–1087.)

CARCINOEMBRYONIC antigen (CEA) can be considered to be a prototype marker of malignancy. It was initially considered to be specific for gastrointestinal cancers but introduction of sensitive radioimmunoassays has shown that serum CEA may be elevated in various neoplastic diseases and benign conditions (Table 1). After a clinical experience of about 20 years, blood level determination of this oncofetal antigen can contribute to the diagnosis of malignancy, to the monitoring of antitumoral treatment and to prognosis at initial presentation of the disease and possibly to the screening for cancer [1].

It should be emphasized that measurements by different assay methods will give different ranges of normal values because CEA is a family of related glyco-proteins. In order to avoid misinterpretation of results, each laboratory should thus establish its own normal values. A circadian rhythm of blood concentration of CEA measured by radioimmunoassay (normal range of values between 0 and 10 ng/ml) has been recently described in patients without cancer [2]; the daily peak occurred at approx. 4 p.m. with the daily low point at approx. 4 a.m. The overall circadian mean was 11.6 ± 1.5 ng/ml with a nearly 70% predictable excursion around that mean. Sampling time can thus influence blood level interpretation.

Serum levels of CEA is often very elevated in colorectal cancer in comparison to other diseases. When this disease is clinically or radiologically suspected, high levels of CEA (≥ 20 ng/ml) are strongly suggestive of the presence of colorectal adenocarcinoma. There is a clear correlation between the Dukes stage of the disease and the percentage of increased CEA. Initial CEA level has an important prognostic value: more than 80% of the patients with a pre-operative blood level above 20 ng/ml will relapse before 14 months following surgery. Serial determination of CEA during the follow-up can help in the diagnosis of recurrence if a sustained and progressive rise is observed [3].

In breast cancer, about 40% of the patients will initially present with an abnormal CEA blood level. Persistance of an elevated level after mastectomy is associated with an increased risk of relapse. There is no correlation between axillary lymph node involvement and CEA level but patients with relatively high initial CEA (above 10 ng/ml) have distant metastases in more than 50% of the cases already [4]. Highest levels are suggestive of bone and/or liver metastatic involvement. Serial CEA determinations are particularly helpful during the follow-up: each confirmed elevation of a previously low CEA level should be considered as a warning sign requiring clinical investigations [5].

In lung cancer, CEA can also be a useful biomarker. It is elevated in about two-thirds of the patients with non-small cell lung cancer (NSCLC) and one-third of those with small cell lung cancer (SCLC). Serum CEA levels are significantly increased in patients with malignant lung diseases

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Table 1. *Diseases in which CEA blood levels may be elevated*

Malignant diseases	Non-malignant conditions	
Colorectal adenocarcinoma	Smoking	
Pancreatic cancer		
Biliary tract cancer	Hepatic diseases:	cirrhosis
Gastric cancer		hepatitis
Esophagus cancer		obstructive jaundice
Hepatoma		
Breast cancer	Gastrointestinal diseases:	gastric ulcer
Ovarian cancer		gastritis
Cervix cancer		Crohn disease
Endometrial adenocarcinoma		ulcerative colitis
Choriocarcinoma		diverticulitis
Lung cancer		
Bladder cancer	Urologic diseases:	renal failure
Prostatic cancer		benign prostatic hypertrophy
Testis cancer		
Renal carcinoma		
Thyroid cancer	Lung diseases:	bronchitis
Osteosarcoma		emphysema

compared to those with benign lung disease [6] but the assay cannot distinguish between operable and inoperable cancers, although, again, preoperative CEA elevation is association with poorer prognosis in NSCLC. In SCLC, CEA has been shown to be a useful prognostic factor that is independent of other main prognostic factors such as extent of disease and ECOG performance status [7]. As shown in the table, CEA can also be helpful in other neoplastic diseases.

Determination of CEA concentration can be used as a diagnostic tool of malignancy in effusions (mainly pleural). Whereas neoplastic cells are found only in about 60% of malignant effusions, the CEA level is increased at the first puncture in 40–70% of these neoplastic effusions. Combined with cytologic examination, CEA determination increases the diagnostic yield of malignancy by 10–30%. Moreover, when pleural biopsy is also done, CEA measurement will still increase the yield of neoplasia by 5–20% [8, 9]. The choice of the cut-off level between benign and malignant effusions varies in the literature from 5 to 30 ng/ml [8, 9]. A concentration of 10 ng/ml seems to be a reasonable choice, giving a specificity of 95–100% without loosing much sensitivity when compared to lower cut-off levels. False-positive pleural CEA levels are actually easily recognized since they occur in empyemas [8, 10]. As reported by Faravelli *et al.* [11] in a recent issue of the Journal, CEA determination in pleural fluid may be helpful in excluding the diagnosis of mesothelioma, since one rarely finds CEA values of more than 15 ng/ml. Different methods have been proposed to improve the diagnostic usefulness of CEA level in effusion fluids. To eliminate the influence of simple leakage from the serum, the ratio effusion fluid/serum CEA level can be determined, a value of less than 1 being in favor of a benign origin. This approach is probably useful for 'borderline' CEA concentrations between 5 and 10 ng/ml [10]. Another interesting application of this gradient is the differential diagnosis between ascites due to peritoneal neoplastic involvement (ratio above 1) and ascites due to liver metastases and portal hypertension (ratio below 1). On the other hand, if repeated punctures increase the yield of neoplastic cells, it is much less likely that they will increase the diagnostic sensitivity of CEA determination. Simultaneous measurement of other tumor markers probably offer greater interest.

Although investigated much less, the determination of CEA levels in cerebrospinal fluid seems also useful in diagnosing meningeal carcinomatosis and in assessing the effects of therapy [12]. This approach should be helpful in evaluating antitumoral responses for therapeutic trials.

CEA can also be detected by immunocytochemistry in neoplastic tissue. However, its specificity for detecting cancer is very low because CEA is present in high amounts in the normal tissue such as the large bowel, in various non-neoplastic diseases and in benign tumors [13]. CEA staining can nevertheless be useful in determining the tumor type. For example, in breast and lung cancers, the locus of CEA expression has been related to the grade of cell maturation. Another application is the differential diagnosis between tumors

when histology is in question, for instance pleural involvement by mesothelioma or another malignant disease [11].

CEA cell staining by immunocytochemistry could also increase the diagnostic sensitivity of CEA measurement in the effusion fluid [11]. There exists a good correlation for the presence of CEA in the malignant cells of the primitive tumor and in the different metastatic sites [14]. This observation suggests that the immunocytochemical method could have a diagnostic potential for detecting micrometastases of CEA-positive cancers.

Among the immunoenzymatic techniques, the PAP method and the biotinstreptaviolin–peroxidase assay are the most sensitive for CEA detection, irrespective of the tissue fixation and histological preparation [15]. The presence of cross-reacting glycoproteins with CEA antisera requires absorption procedures [14] to improve the specificity of the commercially available anti-CEA antisera, especially if one wants to compare immunocytochemical results between different laboratories. Monoclonal anti-CEA antibodies may improve specificity to tumor-associated antigens in the future.

In conclusion, CEA is a useful biomarker for cancer. It can be used both to determine levels in body fluids or as an immunohistochemical marker. It can help the oncologist in the diagnosis, the prognosis and the management of various malignant diseases. Further investigations are necessary to determine more precisely its indications in these various applications.

REFERENCES

1. Fletcher RH. Carcinoembryonic antigen. *Ann Intern Med* 1986, **104**, 66–73.
2. Focan C, Focan-Henrard D, Frere MH, *et al.* Circadian CEA variability: when to sample. *J Clin Oncol* 1986, **4**, 607–608.
3. Arnaud JP, Koehl C, Adloff M. Carcinoembryonic antigen (CEA) in diagnosis and prognosis of colorectal carcinoma. *Dis Colon Rectum* 1980, **23**, 141–144.
4. Beard DB, Haskell CM. Carcinoembryonic antigen in breast cancer. Clinical review. *Am J Med* 1986, **80**, 241–245.
5. Chata IF. Use of serial CEA assay in detecting relapses in breast cancer involving high risk of metastasis. *Eur J Cancer* 1980, **17**, 233–238.
6. Muller T, Marshall RJ, Cooper EH, Watson DA, Walker DA, Mearns AJ. The role of serum tumour markers to aid the selection of lung cancer patients for surgery and the assessment of prognosis. *Eur J Cancer Clin Oncol* 1985, **21**, 1461–1466.
7. Sculier JP, Feld R, Evans WK, *et al.* Carcinoembryonic antigen: a useful prognostic marker in small-cell lung cancer. *J Clin Oncol* 1985, **3**, 1349–1354.
8. Rittgers RA, Loewenstein MS, Feinerman AE, *et al.* Carcinoembryonic antigen levels in benign and malignant pleural effusions. *Ann Intern Med* 1978, **88**, 631–634.
9. Loewenstein MS, Rittgers RA, Feinerman AE, *et al.* Carcinoembryonic antigen assay of ascites and detection of malignancy. *Ann Intern Med* 1978, **88**, 635–638.
10. Nystrom S, Dyce B, Wada J, Bateman JR, Haverback B. Carcinoembryonic antigen titers on effusion fluid. A diagnostic tool? *Arch Intern Med* 1977, **137**, 875–879.
11. Faravelli B, Nosenzo M, Razzetti A, *et al.* The role of concurrent determinations of pleural fluid and tissue carcinoembryonic antigen in the distinction of malignant mesothelioma from metastatic pleural malignancies. *Eur J Cancer Clin Oncol* 1985, **21**, 1083–1087.
12. Yap BS, Yap HY, Fritsche HA, Blumenschein G, Bodey GP. CSF carcinoembryonic antigen in meningeal carcinomatosis from breast cancer. *JAMA* 1980, **244**, 1601–1603.
13. Stenger RJ, Chabon AB, Primus FJ, Wolff WI. Immunoperoxidase localization of carcinoembryonic antigen in benign and malignant colorectal tumors and related mucosa. *Mount Sinai J Med N.Y.* 1979, **46**, 185–189.
14. Nap M, Ten Hoor KA, Fleuren GJ. Cross-reactivity with normal antigens in commercial anti-CEA sera, used for immunohistology. The need for tissue controls and absorptions. *Am J Clin Pathol* 1983, **79**, 25–31.
15. Primus FJ, Clark CA, Goldenberg DM. Immunohistochemical detection of carcinoembryonic antigen. In: De Lellis, ed. *Diagnostic Immunochemistry*. New York, Mason, 1980, 263–276.