Identifying Patients at Risk of Early Postoperative Recurrence of Lung Cancer: A New Use of the Old CEA Test

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Background. **In the current study, we report the carcinoembryonic antigen (CEA) capability to predict early tumor relapses after a pulmonary resection for nonsmall cell lung cancer (NSCLC).**

Methods. **We studied 118 consecutive NSCLC patients who were clinically judged operable and were eventually operated upon. Anthropometric, clinical, and CEA data along with the results of both preoperative and postoperative stage classifications were recorded. All patients were followed up for at least 1 year after surgery and the time to the first clinical recurrence recorded. Receiver-operating characteristic (ROC) curves and diagnostic formulas were used for data analysis.**

Results. **In this series the CEA test was among the most accurate methods to predict an early postoperative recurrence (ROC area: 0.72, 95% confidence interval [CI]: 0.60 to 0.85, $p = 0.001$; accuracy rate for CEA at the threshold of 10 ng/mL: 83%, CI: 76% to 90%). Also predictive was the postoperative pathologic stage of disease (ROC area: 0.68, CI: 0.56 to 0.80, $p = 0.007$). In tumors pathologically classified in stage Ia to IIb, a preoperative CEA level higher than 10 ng/mL was associated with a 67% probability of tumor relapse. In the same stages of disease, a CEA level less than 10 ng/mL increased the baseline probability of no recurrence from 80% to 88%.**

Conclusions. **In operable patients with NSCLC the frequency of abnormal serum concentrations of CEA is low (17% in our series). However, it is important to identify such a small group of high-risk patients as many of them (in our study, 55% and 70% of those with a CEA value in excess of, respectively, 5 and 10 ng/mL) will develop an early postoperative recurrence. Such patients should be investigated preoperatively by mediastinoscopy or positron emission tomography in even in the absence of suspicious symptoms and signs. Then after an apparently successful operation, they should be carefully followed up. These patients could represent a suitable target for neoadjuvant clinical trials of selected high-risk groups.**

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In nonsmall cell lung cancer (NSCLC), carcinoembryonic antigen (CEA) remains one of the most used tumor markers [1, 2]. A role of CEA in this malignancy was first postulated in the 1970s [3], not many years after its description [4]. Then in the early 1980s it was agreed to perform a preoperative serum CEA test in all patients with bronchial carcinoma because of its correlation with the stage of disease and prognosis [5]. Opinions have changed, however, during the last 2 decades and dubious [6] and even negative positions [7] have began to emerge.

We have a long-standing experience with CEA, which we have found helpful in a variety of clinical situations and complementary to the use of cytokeratins, other valuable serum markers [8–12]. There are, however, other uses of CEA that have not been investigated so far. A potentially useful one is the prediction of surgical failure in patients apparently cured by tumor removal. We hypothesized that this might be a fruitful application, stimulated by the discovery of a surprisingly high correlation observed in our database between CEA and the variable postoperative treatment failure.

This report describes the results of a prospective study of CEA measurements obtained preoperatively from subjects who were operated for NSCLC and then followed up for 1 year after operation. It focuses on the CEA capability to provide an estimate of the risk of early postoperative recurrence.

Patients and Methods

Patient Database and Study Design

Since 1982 all lung cancer patients referred to the department of Pulmonary Medicine of the "S. Croce e Carle" Hospital in the city of Cuneo, Piedmont, Italy, are managed uniformly. Initially data regarding 44 clinical variables was collected for each new patient with a cytologically or pathologically documented diagnosis [13] and recorded on computer. Such a database included anthropometric and clinical characteristics, routine laboratory tests, serum CEA, TNM descriptors, and a computer-derived stage of disease. Since TNM definitions changed throughout the recording period, patients' charts were

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reviewed and TNM variables upgraded. This work was done as soon as the revision of the International Staging System for Lung Cancer was formalized [14]. Every 4 to 5 years the structure of the database was modified while the number of variables increased progressively. However, the core variables of the early database remained unchanged, allowing for careful analyses and time-related comparisons. Of the 1,498 new lung cancer patients seen during the years 1982 to 2000, 1,336 underwent a pretreatment CEA test. Part of this population has been the object of prior publications [8, 9].

In the mid 1990s we updated the CEA statistics referring to a population of 964 patients (unpublished data). The interim analysis confirmed that CEA increased with the stage of disease [14] and correlated with survival. The correlation between preoperative CEA and the variable postoperative treatment failure (Spearman Rho = 0.321, $p = 0.000$) was intriguing. We decided to investigate further such a finding in a new study conducted on a recent and homogeneously treated population. In 1996 we started considering patients with a new pathologic diagnosis of NSCLC [13] for potential enrolment. To be eligible they should had undergone each of the following: (1) complete and accurate evaluation of disease extent indicating probable or possible tumor resectability; (2) pretreatment CEA test; (3) thoracotomy made with curative intent, which had resulted in mediastinal exploration and pathologic diagnosis of the T and N status; and (4) postoperative follow-up observation of 1 year at least (unless the tumor recurred before). In addition patients should have been ineligible for experimental protocols of neoadjuvant treatment. No patient consensus was required for this prospective study because all the investigational and therapeutic procedures including biomarker assays were considered part of our best practice, independently of a possible investigational subsequent use. One hundred and eighteen patients met the eligibility criteria and were assessable for analysis. Their clinical characteristics are shown in Table 1.

Table 1. Clinical Characteristics of the Study Population

Characteristic	Median (Range)/Frequency
Sex (male/female)	99/19
Age (years)	63 (38–77)
Weight loss (n/y)[a]	75/43
ECOG performance status (0/1/2)	34/69/15
CEA: serum levels (ng/ml), no. of abnormal	20
Tumor cell type (A/S/L/M)	58/47/11/2
Type of operation (ET-SE-LO-BI-PN)	15/7/67/6/23
Stage of disease (Ia/Ib/IIa/IIb/IIIa/IIIb/IV)[b]	27/40/5/12/16/15/3
T factor (1/2/3/4)	34/56/12/16
N factor (0/1/2)	78/22/18
M factor (0/1)	114/4
Tumor recurrence within 1 year from operation (n/y)	94/24
Maximum tumor diameter (cm)	4 (0.4–12)
Postsurgical follow-up time (months)	20 (9–64)
Status (alive/dead)	62/56

[a] Loss of body weight equal or greater that 10% of the weight recorded 6 months before operation. [b] Post-operatively confirmed pathological stage.

A = adenocarcinoma; BI = bilobectomy; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; ET = exploratory thoracotomy; L = large cell carcinoma; LO = lobectomy; M = mixed or undefined histology; PN = pneumonectomy; S = squamous cell carcinoma; SE = segmentectomy.

CEA Assays

Sera for CEA were stored at −20°C and assayed three times per week in the central laboratory of "S. Croce e Carle" Hospital. The laboratory is located in the "S. Croce" Hospital; it receives blood samples from many medical and surgical wards, including the lung department at the "A. Carle" Hospital. Since we provide no clinical information, biologists have no means of knowing even the disease for which a particular test is required.

Assays were performed using commercial kits (CEA test; CIS Bio International, France), and following the manufacturer's instructions. Normal reference values for CEA were up to 5 ng/mL.

Preoperative and Intraoperative Staging Procedures

Diagnostic and staging techniques did not vary considerably during the 5 years of study; furthermore the coexistence of experimental protocols aimed to optimize diagnostic and staging procedures ensured an overall accurate clinical assessment. All patients received a bone scan along with a computed tomography (CT) of brain, thorax, and upper abdomen. Their base line evaluation included also physical examination, routine laboratory tests, bronchoscopy, and functional respiratory tests. In half of the sample the baseline workup was supplemented by nonroutine imaging studies such as the anti-CEA monoclonal antibody scintigraphy [15]. Other imaging tests were optional and performed as clinically indicated. Any information obtained in this way was considered part of the preoperative clinical evaluation. This was particularly reliable in 12 patients (10% of the cohort) who had a preoperative pathologic stage assessment by mediastinoscopy (11 subjects) or CT-guided biopsy of suspected (and unconfirmed) bone metastasis. No clinical decision was made solely on the basis of the results of either anti-CEA immunoscintigraphy or biomarker assays. All these staging tests were obtained within a 3- to 4-week period and no thoracotomy was performed later than 30 days after the first physical examination.

At surgery all nodal stations that were positive on CT were carefully inspected and sampled even when lymph nodes appeared macroscopically normal. All enlarged, palpable, or visible nodes were totally removed. In apparently normal mediastina with negative preoperative studies a minimum sampling of three node stations was

required to reject the hypothesis of N2 disease. Removed lymph nodes were fixed separately and in 10% neutral buffered formalin and labeled according to the American Thoracic Society (ATS) criteria [16].

The clinical and pathologic extent of disease was defined using the new revised staging classification [14]

Follow-Up and Assessment of Tumor Recurrence

We scheduled to perform clinical reevaluations 1 month after surgery and then every 3 months for the first 2 years, every 6 months for the next 3 years, and every year thereafter. Each follow-up visit was supplemented by chest radiographs, serum biochemistry, tumor marker assay, and any other test required to confirm or reject a suspicion of tumor recurrence. A complete restaging evaluation including the same tests performed at diagnosis was scheduled in all subjects 6 months after the operation. Recurrence was defined as any unequivocal occurrence of new cancer foci in a disease-free patient. In the few patients with incompletely resected tumors the standard definition of progressive disease was used to define a recurrence. We defined early tumor recurrence tumor relapses that occurred within 1 year of the operation. This cut-off time was clearly an arbitrary one, which we chose based on biological considerations and after a preliminary inspection of our database.

Data Analysis and Statistical Considerations

Diagnostic capability was calculated for CEA and three stage classifications based on (1) the CT reading (three-organ CT stage), (2) the preoperative clinical assessment on the whole (final clinical evaluation), and (3) the postoperative pathologic diagnosis (postoperative pathologic stage). For CEA, three threshold levels (ie, 2 ng/mL, the median; 5 ng/mL, the reference value; and 10 ng/mL, a remarkably abnormal value) were chosen to describe a positive or a negative test. In this study diagnostic capabilities are not intended to show the presence or absence of disease but the presence (or absence) of tumor recurrence within the first 12 months following the operation (early recurrence). Accordingly a CEA level over a given threshold was declared true positive (TP) when the patient had an early recurrence and false positive (FP) when the patient remained disease-free during the first year of observation. A CEA level equal to or below the threshold was considered true negative (TN) when an early tumor recurrence did not occur and false negative (FN) when it did occur.

Statistical analysis was performed using the SPSS package for Windows, Version 9.0 (SPSS, Chicago, IL). Medians and ranges described continuous variables. Sensitivity, specificity, and accuracy rates along with the corresponding predictive values were obtained using standard diagnostic formulas [17]. Diagnostic proportions were given along with their 95% confidence intervals (CI) [18]. To assess the capability to predict tumor recurrence we used the receiver-operating characteristic (ROC) curves [19], whose circumscribed areas (the area under the curve) give an estimate of the test's diagnostic efficiency (in our case, the diagnostic efficiency of future tumor relapses) [20]. ROC curves were used not only for CEA but also for the variable stage of disease as assessed radiologically, clinically, or pathologically. For this type of analysis the seven classes of stage of disease were used to compare overall sensitivity to 1-specificity. Correlation coefficients and differences were tested for statistical significance using the Spearman rank test and the Kruskall-Wallis analysis of variance (ANOVA) [21]. A probability (p) level less than 0.05 was considered statistically significant. All statistical tests were two-sided.

Results

Descriptive Statistics

Table 1 shows summary statistics that describe the anthropometric and clinical characteristics of the study population, for example sex, age, history of weight loss, and performance status (Eastern Oncology Group scale [22]). Also reported are data regarding CEA, tumor cell type, type of surgical treatment, postoperative pathologic stage, TNM descriptors, incidence of tumor recurrences, survival duration, and patients' status at the time of the last scheduled follow-up visit. In December 2000, 62 of the 118 patients (53%) were still alive after a median follow-up of 20 months (range 9 to 64). Most recruited patients had an early stage disease and experienced favorable surgical outcomes. There were 84 postoperative stages Ia/Ib/IIa/IIb, 16 stage IIIa, and 18 stage IIIb/IV. This resulted in 103 pulmonary resections and 15 explorative thoracotomies. Twenty-four patients recurred within the first year of postsurgical observation (probability of recurrence: 20%, CI: 13% to 28%).

As expected for this group of low-risk patients the frequency of abnormal serum concentrations of CEA (values above 5 ng/mL) was quite low (17% of the all sample). In the subgroup of patients with postoperative stage Ia to IIb this rate was even lower (13%, 11 of 84). In the same stages, median values (ranges) of CEA were 2 ng/mL (0 to 60 ng/mL) as compared with the value of 2.5 ng/mL (1 to 22 ng/mL) observed in the stages IIIa to IV. The correlation between serum levels of CEA and the pathologic stage of disease approached the significance level (Rs = 0.162, $p = 0.072$) whereas there was no significant difference in CEA distribution among different histotypes (Kruskall-Wallis statistic).

Prediction of Postoperative Early Recurrence in Whole Study Sample

Table 2 (first part, cumulative analysis) shows the predictability of CEA as compared with that of both preoperative CT-stage and postoperative pathologic stage. As shown, CEA was among the best methods to predict recurrences. The area under the ROC curve was 0.723 ($p = 0.001$) for CEA (Fig 1), as compared with 0.606 ($p = 0.110$) and 0.679 ($p = 0.007$), respectively, for the two types of disease-stage assessment. For a CEA threshold of 10 ng/mL (the best among the three considered) diagnostic sensitivity was 29% while specificity and accuracy rates were, respectively, 97% and 83% (Table 3). A level of CEA

Table 2. Prediction of Surgical Failure: ROC Analysis

	No. Assessable	Area	95% CI	*p* Value	ROC Curve
Cumulative analysis					
CEA	118	0.72	0.60–0.85	0.001	Fig 1
Postoperative pathological stage	118	0.68	0.56–0.80	0.007	
Three-organ CT[a]	118	0.61	0.47–0.74	0.110	
Subgroup analysis					
CEA in 3-organ CT stage up to IIb[a]	99	0.75	0.61–0.89	0.001	Fig 2A
CEA in final presurgical stage up to IIb	74	0.75	0.58–0.91	0.007	Fig 2B
CEA in postoperative pathological stage up to IIb	84	0.70	0.51–0.88	0.028	Fig 2C

[a] Preoperative staging based on a computed tomography of thorax, upper abdomen, and brain.

CEA = carcinoembryonic antigen; CI = confidence interval; CT = computed tomography; ROC = receiver-operating characteristic.

up to 10 ng/mL was correctly associated with no tumor recurrence in 84% of the patients (95% CI: 77% to 91%). A higher level was diagnostic of an incoming treatment failure in 70% of the cases (95% CI: 42% to 98%). Almost similar results were obtained using the CEA threshold of 5 ng/mL; however, the probability of correctly predicting tumor recurrences was appreciably reduced (55%, CI: 33% to 77%). The threshold level of 2 ng/mL (median value of the CEA distribution) was sensibly inferior to the previous two (Table 3). The clinical characteristics of patients whose CEA test was considered true positive, false positive, or false negative are shown in Table 4. In particular it is remarkable to note that the CEA test identified 4 patients whose disease relapsed soon after the operation in spite of the pathologically confirmed early disease.

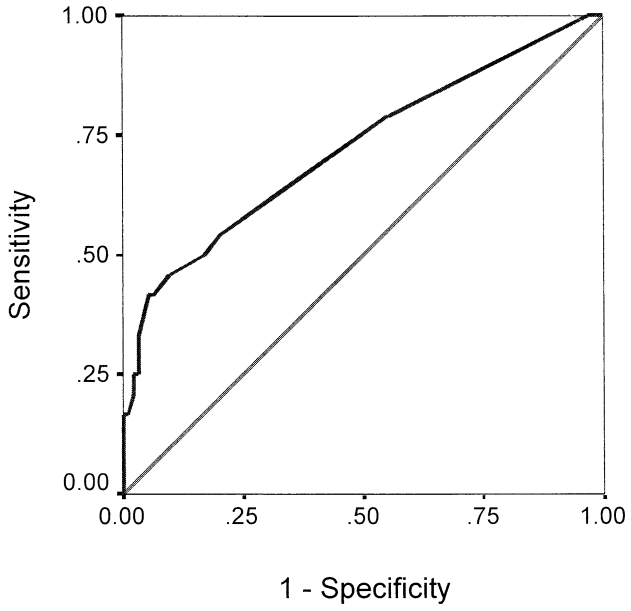

Fig 1. Diagnosis of early postoperative recurrence. Receiver-operating characteristic curves showing the predictive capability of carcinoembryonic antigen. Straight line = *reference line (0 diagnostic efficiency);* curved line = *calculated curve for the diagnostic tool under consideration.*

Prediction of Postoperative Early Recurrence in Subgroups With Better Prognosis

Table 2 (second part, subgroup analysis) shows how the predictability of CEA varies in the subgroups of patients with better prognosis. The analysis is limited to patients in stage Ia to IIb, as assessed by the chosen methods of evaluation (ie, the three-organ CT, the final clinical evaluation, and the postoperative pathologic stage). In any subgroup the CEA test was capable of discriminating subjects who were at risk of early recurrence (Fig 2A, B, C). The area under the ROC curve was 0.749 and 0.745 ($p = 0.001$ and 0.007) for patients considered preoperatively in stage Ia to IIb (Fig 2A, B). It was 0.693 ($p = 0.028$) for patients with a pathologically verified stage Ia to IIb (Fig 2C). The CEA test using the threshold of 10 ng/mL was associated with a diagnostic sensitivity for tumor recurrence of 31% to 35%, while specificity and accuracy rates ranged, respectively, 96% to 97% and 86% to 87% (Table 3). A serum level of CEA less than 10 ng/mL correctly excluded a tumor recurrence in about 88% of the cases while a higher value was diagnostic of an incoming treatment failure in 67%. In practice the predictability of the CEA test remains high also in the subgroups of patients for whom such a capability has the greatest clinical importance.

Comment

Serum tumor markers are not only significant to the researcher in developing theories concerning the biology of tumors but also to the clinician in treating patients with cancer [23]. In oncology practice serum tumor markers may be helpful in the diagnosis, pathologic classifications, and evaluation of the stage of disease and prognosis. When measured serially after the diagnosis of cancer is established they may aid in assessing the response to treatment, monitoring the spontaneous course of the illness, and watching for tumor recurrences [24].

Lung cancer does not make exception to this rule and the expression of serum biomarkers in this particular tumor is various and abundant [2]. Lung tumor markers fall into several categories including oncofetal proteins,

Table 3. Prediction of Surgical Failure: Diagnostic Formulas

	TP	TN	FP	FN	total	SE	SE (95% CI)		SP	SP (95% CI)		AC	AC (95% CI)		PPV	PPV (95% CI)		NPV*	NPV (95% CI)	
Cumulative analysis																				
CEA (threshold: 2 ng/mL, median)	15	64	30	9	118	63%	43%	82%	68%	59%	78%	67%	58%	75%	33%	20%	47%	88%	80%	95%
CEA (threshold: 5 ng/mL, reference)	11	85	9	13	118	46%	26%	66%	90%	84%	96%	81%	74%	88%	55%	33%	77%	87%	80%	93%
CEA (threshold: 10 ng/mL)	7	91	3	17	118	29%	11%	47%	97%	93%	100%	83%	76%	90%	70%	42%	98%	84%	77%	91%
Subgroup analysis (CEA threshold: 10 ng/mL)																				
CEA in three-organ CT stage Ia–IIb	6	79	3	11	99	35%	13%	58%	96%	92%	100%	86%	79%	93%	67%	36%	97%	88%	81%	95%
CEA in final clinical presurgical stage Ia–IIb	4	60	2	8	74	33%	7%	60%	97%	92%	101%	86%	79%	94%	67%	29%	104%	88%	81%	96%
CEA in postoperative pathological stage Ia–IIb	4	69	2	9	84	31%	6%	56%	97%	93%	101%	87%	80%	94%	67%	29%	104%	88%	81%	96%

[a] Baseline probability of no failure: 80%.

AC = accuracy; CEA = carcinoembryonic antigen; CI = confidence interval; FN = false negative; FP = false positive; NVP = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.

structural proteins, enzymes, cell membrane components, secreted peptides, hormones, and other tumor-associated antigens [2]. Among them cytokeratin-derived molecules, neuroendocrine markers, and CEA are probably the most used and helpful [1, 2].

The idea that serum biomarkers are helpful in the management of lung cancer is not uniformly accepted [7, 25, 26]. In 1997 the American Thoracic Society and the European Respiratory Society published jointly their clinical guidelines for pretreatment evaluation of NSCLC [7]. The two medical societies adopted the following statement: "... Unfortunately, none (i.e. no serum tumor marker) appears sufficiently sensitive and has a high enough specificity to add to our ability to reliably detect occult disease or influence disease management. The routine measurement of any of these substances in the screening, staging, or evaluation of disease progression is not recommended" [7].

Nevertheless the role of CEA as a nonspecific marker for lung cancer had been well recognized in the past. A consensus conference held at the National Institutes of Health in 1980 [5] had concluded its work with the following statements:

1. The use of plasma CEA assays in cancer screening of an asymptomatic population is unjustified.
2. In symptomatic patients, grossly raised values, greater than 5 to 10 times the upper limit of the normal range, should be considered strongly suspected for the presence of cancer and should suggest further diagnostic tests.
3. A preoperative plasma CEA value should be obtained in patients with either colorectal or bronchial carcinoma because of its correlation with the stage of disease and the prognosis.
4. The role of regular and sequential assays of plasma CEA in the postoperative and therapeutic monitoring of patients with other cancers is less convincing than it is for colorectal cancer. However, in patients with lung cancer it may be of value in reflecting response to chemotherapy.

The next 20 years added little to this understanding, except for providing more evidence. Abnormally elevated values of CEA were reported in 30% to 70% of patients with bronchogenic carcinoma [8, 9, 27] and more frequently in patients with adenocarcinomas [28]. However, elevated CEA values were observed in any histologic type including in 20% to 60% of all patients with small cell lung cancer (SCLC) [11, 27]. Increased CEA levels occur more frequently in locally advanced or metastatic cancers [8, 29] although reported differences were not always statistically significant [9]. The correlation between plasmatic levels of CEA and the response to treatment was further confirmed in both SCLC [29] and NSCLC [8]. Finally, the prognostic value of CEA is also evident although not always significant especially in studies with limited statistical power [30].

There are, however, several other uses of CEA that is possible to explore. A potentially useful one is the preoperative prediction of the real, postsurgical, pathologic stage of disease. We have recently investigated this area,

Table 4. Clinical Characteristics of Patients Showing Preoperative Serum CEA in Excess of 10 mg/mL or Early Surgical Failure or Both

Patient	Sex (m/f)	Age (yrs)	ECOG PS	WL (y/n)	Maximum Tumor Diameter (cm)	Cell Type (A/L/S)	CT Stage	Post-operative TNM	Type of Resection	CEA (ng/mL)	Follow-up Time (mo)	Time to Recurrence	Site of Tumor Recurrence/ Disease Progression
AG	m	67	0	n	2.5	A	Ia	T1N0M0	LO	18	33.1+		
PB	f	56	1	y	8.0	L	IIIa	T4N1M1 (lung)	ET	14	6.4	1.2	Lung
AL	f	76	1	y	0.4	L	Ia	T1N0M0	LO	18	45.3	28.0	Kidney
BC	f	68	1	y	3.3	A	IIb	T2N2M0	PN	22	54.0+		
GA	m	58	1	n	5.0	S	IIb	T4N0M0	ET	11	8.9	6.4	Supraclavicular nodes, lung
DG	m	57	0	n	6.0	A	Ib	T2N2M0	LO	18	19.0	11.4	Brain
LL	m	60	0	n	2.0	A	Ia	T1N0M0	LO	34	7.9	2.5	Liver, bones
BM	m	56	0	y	4.0	A	Ib	T2N1M0	PN	42	7.6	2.1	Lung, liver, adrenal gland
MA	m	72	2	n	3.0	L	Ia	T1N0M0	LO	46	27.7	11.8	Lung, adrenal gland
MG	m	72	2	y	5.0	S	Ib	T2N0M0	LO	60	14.9+	9.0	Brain
AL	m	60	0	n	2.5	A	Ia	T1N0M0	LO	1	14.8	8.7	Bones
BM	f	57	1	y	3.3	L	IV	T2N0M0	PN	1	4.0	2.9	Bones, adrenal gland
BG	m	65	0	n	3.5	A	Ib	T2N0M0	LO	1	6.0	5.0	Lung, adrenal gland
FG	m	72	1	n	4.5	L	IIb	T3N0M0	LO	1	21.3+	5.4	Brain
GF	m	74	1	y	5.0	A	IIIa	T2N2M0	PN	1	10.4	5.9	Lung
CC	m	74	1	y	6.0	S	Ib	T3N0M0	LO	2	4.0	2.9	Lung, bones
DG	m	72	1	y	3.2	S	IIIa	T2N1M0	LO	2	7.0	2.5	Bones
GF	m	72	1	y	3.5	A	Ia	T3N1M0	LO	2	12+	11.0	Brain
MG	m	53	0	n	3.0	A	Ia	T1N2M0	LO	2	14.5	11.5	Supraclavicular nodes, lung
GG	m	59	1	n	7.0	S	IIb	T2N2M0	LO	3	13.8	9.3	Bones
GG	m	63	0	y	4.0	S	Ib	T4N0M0	ET	1	35.4	12.0	Bones
EF	m	64	1	y	3.0	A	IIIa	T4N2M0	ET	4	17.0	11.2	Lung
CR	m	50	0	n	8.5	A	IIIa	T2N2M0	LO	5	6.4	4.2	Bones
GG	m	72	1	y	7.5	S	Ib	T2N1M0	LO	6	27.4+	10.7	Lung
CG	m	60	1	n	3.0	A	Ib	T1N1M0	LO	8	12.4+	9.3	Brain
CM	f	56	1	n	6.5	A	IV	T4N1M1 (lung)	ET	8	14.4+	9.3	Supraclavicular nodes
MA	m	57	2	n	3.8	A	IIb	T2N1M0	PN	9	3.9	2.3	Brain

A = adenocarcinoma; CEA = carcinoembryonic antigen; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = exploratory thoracotomy; L = large cell carcinoma; LO = lobectomy; PN = pneumonectomy; WL = weight loss (10% or more in 6 months); S = squamous cell carcinoma.

showing that the addition of an easy to perform and inexpensive marker test such as CEA is capable of correcting the underestimation of clinical staging and helps to decide whether to completely rely on computed tomography or order additional clinical investigations [12]. Another useful application might be the preoperative prediction of surgical radicalness. This information is even more important than the former, surgical radicalness being the ultimate reference for a curative intervention. We decided to explore this field, stimulated by the discovery of a surprisingly high correlation observed in our patient database between CEA and the variable postoperative treatment failure. The study was based on a new patient population and fully maintained the promises. We can summarize our current findings as follows: (1) the preoperative prediction of postsurgical treatment failure based on a CT scan of brain, thorax and upper abdomen is not particularly accurate; (2) better results are obtained using the pathologic perioperative findings; but surprisingly (3) a single blind preoperative serum assay of CEA was comparable with the pathologic stage of disease; (4) very elevated levels of CEA (above 10 ng/mL) are predictive of postoperative recurrences also in early stage completely resected cancers (accuracy rate 87%).

In conclusion, evidence from this study reemphasizes

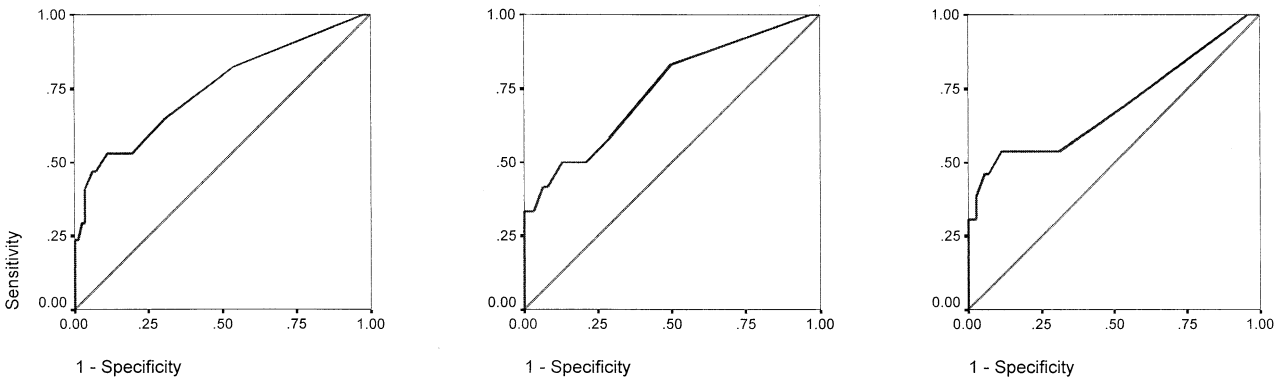

Fig 2. Diagnosis of early postoperative recurrence. Receiver-operating characteristic curves showing the predictive capability of carcinoembryonic antigen in subgroups of patients with a stage of disease up to IIb as diagnosed by three different techniques: three-organ computed tomography (left), the final clinical assessment (center), and postoperative pathologic stage (right). Straight lines = *reference line (0 diagnostic efficiency);* curved lines = *calculated curve for the diagnostic tool under consideration.*

the need of obtaining a routine CEA test in any potentially operable patient with NSCLC. This allows with very little cost the identification of a significant proportion of patients who are at high risk of developing an early tumor relapse. Of course the number of subjects at risk being globally low, many patients will receive a useless—but inexpensive—blood test while few will obtain critical information. Computed tomography remains the gold standard for the preoperative evaluation of NSCLC. However, it may significantly underestimate the real extension of the tumor, giving no insight into the possible presence of micrometastases. This limitation is shared by the perioperative pathologic staging, at least for the micrometastases growing out of the surgical field. The CEA test may correct such an underestimation (in our study this happened in about 4% of the sample) and may help to decide the next steps. We believe that a three-organ CT showing a resectable tumor (stages Ia through IIb) and a normal serum concentration of CEA in a nonsymptomatic patient are a clear indication to proceed with the operation. After resection there will be a very low risk of tumor recurrence in this subject. On the other hand high preoperative CEA values (especially if higher than 10 ng/mL) are an indication to intensify the routine preoperative staging. This could be obtained by performing a mediastinoscopy or a positron emission tomography (PET) scan even in the absence of symptoms and signs. Then after an apparently successful resection the risk of developing an early tumor relapse will remain high. For these patients the postoperative surveillance should be intensified and adjuvant treatments considered.

References

1. Ferrigno D, Buccheri G, Biggi A. Serum tumour markers in lung cancer: history, biology and clinical applications. Eur Respir J 1994;7:186–97.
2. Buccheri G. Tumor markers: clinical meaning and use. In: Brambilla C, Brambilla E, eds. Lung tumors. New York: Marcel Dekker, 1999:435–52.
3. Concannon JP, Dalbow MH, Hodgson SE, et al. Prognostic value of preoperative carcinoembryonic antigen (CEA) plasma levels in patients with bronchogenic carcinoma. Cancer 1978;42:1477–83.
4. Gold P, Freedman SO. Demonstration of tumor-specific antigen in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 1965;121: 439–62.
5. N.H.I.. Carcinoembryonic antigen: its role as a marker in the management of cancer. BMJ 1981;1:282–373.
6. Ebert W, Muley T, Drings P. Does the assessment of serum markers in patients with lung cancer aid in the clinical decision making process. Anticancer Res 1996;16:2161–8.
7. American Thoracic Society, European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. Am J Respir Crit Care Med 1998;156:320–32.
8. Buccheri GF, Violante B, Sartoris AM, Ferrigno D, Curcio A, Vola F. Clinical value of a multiple biomarker assay in patients with bronchogenic carcinoma. Cancer 1986;57:2389–96.
9. Buccheri GF, Ferrigno D, Sartoris AM, Violante B, Vola F, Curcio A. Tumor markers in bronchogenic carcinoma. Superiority of tissue polypeptide antigen to carcinoembryonic antigen and carbohydrate antigenic determinant 19–9. Cancer 1987;60:42–50.
10. Buccheri G, Ferrigno D, Vola F. Carcinoembryonic antigen (CEA), tissue polyptide antigen (TPA), and other prognostic indicators in the squamous cell carcinoma of the lung. Lung Cancer 1993;10:21–33.
11. Buccheri G, Ferrigno D. Serum biomarkers of non-neuron-endocrine origin in small-cell lung cancer: a 16-year study on carcinoembryonic antigen, tissue polypeptide antigen and lactate dehydrogenase. Lung Cancer 2000;30:37–49.
12. Buccheri G, Ferrigno D. Serum biomarkers facilitate the recognition of early- stage cancer and may guide the selection of surgical candidates: a study of carcinoembryonic antigen and tissue polypeptide antigen in patients with operable non-small cell lung cancer. J Thorac Cardiovasc Surg 2001;122:891–9.
13. World Health Organization. International histological classification of tumours. Berlin: Springer-Verlag, 1991.
14. Mountain CF. Revisions in the international system for staging lung cancer [see comments]. Chest 1997;111:1710–17.
15. Buccheri G, Biggi A, Ferrigno D, et al. Anti-CEA immunoscintigraphy and computed tomographic scanning in the preoperative evaluation of mediastinal lymph nodes in lung cancer. Thorax 1996;51:359–63.
16. American Joint Committee on Cancer. Purposes and principles of staging. In: Beahrs OH, Earl Henson D, Hutter RVP, Myers MH, eds. Manual for staging of cancer. Philadelphia: Lippincott, 1988:3–10.

17. Galen RS. Predictive values of laboratory tests. Am J Cardiol 1975;36:536–8.
18. Bulpitt CJ. Confidence intervals. Lancet 1987;1:494–7.
19. McNeil BJ, Keeler E, Adelstein SJ. Primer on certain elements of decision making. N Engl J Med 1975;293:211–15.
20. Hanley JA, McNeil BJ. The meaning and use of the area under receiving operating characteristic (ROC) curve. Radiology 1982;43:29–36.
21. Siegel S. Nonparametric statistics for the behavioural sciences. New York: McGraw Hill, 1956.
22. Zubrod CG, Scheiderman MA, Frei E, et al. Appraisal of methods for the study of chemotherapy in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. J Chron Dis 1960;11:7–33.
23. Pamies RJ, Crawford DR. Tumor markers—an update. Med Clin North Am 1996;80:185–99.
24. Coombes RC, Powels TJ. Tumour markers in the management of human cancer. In: Deeley TJ, ed. Topical reviews in radiotherapy and oncology. Bristol: Wright PGS, 1982:39.
25. Watine J, Charet JC. Are the ATS (American Thoracic Society) and the ERS (European Respiratory Society) correct in not recommending routine tumor marker assays screening, staging, or evaluation of non-small cell lung cancer? [Translation.]. Rev Mal Respir 1999;16:139–49.
26. Cooper EH. Tumor markers. In: Bennet JC, Plum F, eds. Cecil textbook of medicine. Philadelphia: WB Saunders, 1996:1133–6.
27. Jorgensen LGM, Hansen HH, Cooper EH. Neuron specific enolase, carcinoembryonic antigen and lactate dehydrogenase as indicators of disease activity in small cell lung cancer. Eur J Cancer Clin Oncol 1989;1:123–8.
28. Bergman B, Brezicka F-T, Engström C-P, et al. Clinical usefulness of serum assays of neuron-specific enolase, carcinoembryonic antigen and CA-50 antigen in the diagnosis of lung cancer. Eur J Cancer 1993;29A:198–202.
29. Laberge F, Fritsche HA, Umsawasdi T, et al. Use of carcinoembryonic antigen in small cell lung cancer. Prognostic value and relation to the clinical course 1. Cancer 1987;59: 2047–52.
30. Buccheri G, Ferrigno D. Prognostic factors in lung cancer: tables and comments. Eur Respir J 1994;7:1350–64.