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

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Objectives: Copious literature shows that in lung cancer many serum markers, especially the cytokeratin degradation products, correlate with the extent of disease. In 1995, we suggested the possibility of predicting the resectability of non-small cell lung cancer by measuring the plasma level of the tissue polypeptide antigen, a marker of the cytokeratin family. This study was designed (1) to confirm the earlier data in a new prospective evaluation, (2) to comparatively assess another classic biomarker (ie, the carcinoembryonic antigen), and (3) to incorporate their results into the preoperative evaluation of non-small cell lung cancer.

Methods: We analyzed the database of a single institution over a 5-year period (1994-1998) in a community-based hospital and second referral level institution for a province of 500,000 people. The database included 124 consecutive patients (105 men) with pathologically documented lung cancer (50% with adenocarcinoma) accurately staged, clinically judged operable or potentially operable, and eventually operated on. Anthropometric, clinical, and laboratory data (including the carcinoembryonic antigen and tissue polypeptide antigen serum levels) and the results of a complex staging workup were prospectively recorded. Receiver-operating characteristic curves and diagnostic formulas were used for data analysis.

Results: Computed tomography of the thorax, upper part of the abdomen, and brain was the most accurate preoperative method to assess tumor resectability (receiver-operating characteristic area: 0.76, 95% confidence intervals: 0.67-0.86, $P = .000$; accuracy rate: 77%, confidence intervals: 69%-84%). Tissue polypeptide antigen was also predictive for tumor resectability (receiver-operating characteristic area: 0.62, 95% confidence intervals: 0.51-0.73, $P = .035$; accuracy rate at a threshold level of 110 U/L: 65%, 95% confidence intervals: 56%-73%). Carcinoembryonic antigen was diagnostic only at the extreme values of its distribution (accuracy rate at a level up to 10 ng/mL: 69%, 95% confidence intervals: 60%-77%). The probability of finding resectable disease at the time of the operation increased from 78% (baseline computed tomography-based probability) to 83% when the concentration of tissue polypeptide antigen was lower than 90 U/L and to 85% when the concentration of carcinoembryonic antigen was below 10 ng/mL. The probability of discovering an advanced disease increased from 68% (baseline computed tomography-based probability) to 89% when tissue polypeptide antigen levels were abnormal and to 100% when carcinoembryonic antigen concentrations were higher

than 10 ng/mL. Conversely, the predictability of computed tomography was diminished by contrasting biomarker results, requiring further clinical investigations.

Conclusions: Computed tomography remains the gold standard for the preoperative evaluation of non-small cell lung cancer, although it may significantly underestimate the real tumor extension. The addition of the easy and inexpensive tissue polypeptide antigen test (with or without carcinoembryonic antigen) is capable of correcting this underestimation and helps to decide whether to completely rely on computed tomography or order additional clinical investigations.

Serum tumor markers are of significance not only to the researcher in developing theories concerning tumor biology, but also to the clinician in treating patients with cancer.¹ In oncology practice, serum tumor markers may be helpful in the diagnosis, pathologic classifications, and evaluation of stage of disease and prognosis. When measured serially after a diagnosis is established, they may aid in assessing the response to treatment, monitoring the spontaneous course of the illness, and surveilling for tumor recurrences.²

Lung cancer is no exception to this rule, and the expression of serum biomarkers in this particular tumor is variable and abundant.³ Lung tumor markers fall into several categories, including oncofetal proteins, structural proteins, enzymes, cell membrane components, secreted peptides, hormones, and other tumor-associated antigens.³ In non-small cell lung cancer (NSCLC), cytokeratin-derived molecules and the carcinoembryonic antigen (CEA) are probably the most helpful markers and certainly the most frequently used.³⁻⁵

In 1995, we suggested that it should be possible to predict the resectability of NSCLC by simply measuring the plasma level of tissue polypeptide antigen (TPA), the oldest marker of the cytokeratin family. We were aware that such evidence was preliminary and needed confirmation. However, the possible equivalence of a blind serum test to the more complex, time-consuming, and expensive multiorgan computed tomography (CT) was a truly exciting perspective. Given the importance of the issue, we decided to continue the preoperative biomarker testing in a new confirmatory study.

In this report, we describe the most recent experience of the Cuneo Lung Cancer Study Group (CuLCaSG) with CEA and TPA obtained in subjects with potentially resectable NSCLC. As already mentioned, this study was done mainly to confirm our earlier data. Secondary aims were (1) the comparative assessment of TPA and the "classic" CEA and (2) the incorporation of marker test results into the conventional preoperative evaluation of NSCLC.

Patients and Methods

Database and Study Design

In the fall of 1982, a group of chest physicians decided to devote their professional activity to the study of lung cancer. The group, which later became known as CuLCaSG, is still active at the Department of Pulmonary Medicine of the "A. Carle" Hospital in the city of Cuneo, Piedmont, Italy. The former "A. Carle" Hospital for Chest Diseases merged with the "S. Croce" General Hospital, and the two hospitals, now named "S. Croce e Carle," were then designated as Hospitals of National Importance. They serve the whole Cuneo Province as a second referral institution. Among the first acts of the CuLCaSG was the creation of a clinical database for patients with carcinoma of the lung, effective in January 1983. All patients with lung cancer referred to a physician of the group were managed uniformly. Data regarding 44 variables were collected for each new patient with a cytologically or pathologically documented diagnosis of lung cancer⁶ and recorded on a computer. This database included anthropometric and clinical characteristics, routine laboratory tests and serum tumor markers, TNM descriptors, and a computer-derived stage of disease. Since 1983, TNM definitions have changed, radically in 1986 and minimally in 1997, because of two consecutive revisions to the International Staging System for Lung Cancer.^{7,8} Therefore, to allow for homogeneous comparisons, we had to review the patients' charts and upgrade their TNM variables. This work was done as soon as the revision of the International Staging System for Lung Cancer was formalized. Every 4 to 5 years, the structure of the database was modified and upgraded to new software, and the number of variables progressively increased to hundreds. However, the core variables of the early database remained unchanged, allowing for careful analyses and time-related comparisons. In particular, of 1296 new patients with lung cancer seen consecutively during the years 1983 to 1998, 1136 underwent a pretreatment CEA test and 1115 had a pretreatment TPA test. A large part of this population has been the object of a number of prior publications concerning mainly TPA.⁹⁻¹³ Updated descriptive statistics of the entire population were obtained during the preparation of this article. This update confirmed prior data, showing that both CEA and TPA levels increased significantly (CEA $R_s = 0.161$, $P = .000$; TPA $R_s = 0.322$, $P = .000$), paralleling the stage of disease.⁸ In the entire sample of the 1115 patients tested, median values of TPA were 70, 120, 70, 115, 114, 130, and 180 U/L, respectively, for the stages Ia, Ib, IIa, IIb, IIIa, IIIb, and IV. Corresponding median values for

TABLE 1. Anthropometric and clinical characteristics of the study population

Characteristic	Median	Range	Frequency	Percent frequency
Sex (male/female)			105/19	84.7/15.3
Age (y)	64	38-77		
Weight loss (no/yes)*			79/45	63.7/36.3
ECOG performance status (0/1/2)			35/73/16	28.2/58.9/12.9
CEA serum levels (ng/mL), No. abnormal	2	0-60	21	16.9
TPA serum levels (U/L), No. abnormal	80	30-790	49	39.5
Tumor cell type (A/S/L/M)			62/49/11/2	50/39.5/8.9/1.6
Pathologic stage of disease (Ia/Ib/IIa/IIb/IIIa/IIIb/IV)†			28/42/5/13/18/15/3	22.6/33.9/4/10.5/14.5/12.1/2.4
T factor (1/2/3/4)			35/59/14/16	28.2/47.6/11.3/12.9
N factor (0/1/2)			8/22/20	66.1/17.7/16.1
M factor (0/1)			120/4	96.8/3.2
Type of operation (ET/SE/LO/BI/PN)			20/5/69/6/24	16.1/4/55.6/4.8/19.4
Postoperative follow-up time (mo)	19.2	1-64		
Status			64/60	51.6/48.4

ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; TPA, tissue polypeptide antigen; A, adenocarcinoma; S, squamous cell carcinoma; L, larger cell carcinoma; M, mixed histologic type; ET, exploratory thoracotomy; SE, segmentectomy; LO, lobectomy; BI, bilobectomy; PN, pneumonectomy.

*In the 6 months preceding the operation.

†1997 Stage classification.

CEA were 2 ng/mL for stages Ia to IIa and 3 ng/mL for more advanced stages.

All patients seen in 1994 and afterward were eligible for this study if they had a pathologic diagnosis of NSCLC⁶ and had undergone each of the following: (1) complete and accurate evaluation of disease extent that had indicated an almost certain or likely tumor resectability, (2) pretreatment CEA and TPA serum tests, and (3) thoracotomy with curative intent, which had resulted at least in an accurate mediastinal exploration and pathologic confirmation of the T and N status.

Anthropometric and clinical characteristics of the 124 assessable patients are shown in Table 1.

CEA and TPA Assays

Sera for CEA and TPA were stored at -20°C , a temperature that satisfactorily ensures the stability of blood specimens, and were assayed 3 times a week in the central laboratory of the "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 division at the "A. Carle" Hospital. Because we provide no clinical information, biologists have no means of knowing even the disease for which a particular test is required.

Plasma measurements were performed with commercially available radioimmunoassays (CEA test; CIS Bio International, Gif-sur-Yvette, France; Prolifigen R, TPA IRMA; AB Sangtec Medical, Bromma, Sweden), following the manufacturers' instructions. Normal reference values for CEA and TPA were up to 5 ng/mL and 90 U/L, respectively.

CT: Technique and Reading

All patients included in this report were studied with a CT scan of the thorax, upper part of the abdomen, and brain. Up to October 1998, CT scans were performed on a conventional scanner (GE 9800; General Electric, Milwaukee, Wis); since then, a spiral-CT

machine (CT twin flash; Elscint Ltd, Haifa, Israel) has been used. Sections of the brain, 10-mm thick, were obtained at 1-cm intervals during suspended inspiration, as well as sections from the lung apices to the upper part of the abdomen. In selected cases, 5-mm thick sections at 5-mm intervals were acquired through the region of interest. Iodinated intravenous contrast material (150-c³ bolus, plus 100-c³ in slow infusion) was injected before all studies. Appropriate windows were used for viewing both the lungs and soft tissues.

Mediastinal nodes were labeled as abnormal if they were 1.5 cm or larger (transverse diameter). All CT scans were interpreted with no restriction to the clinical information available at the time of the examination.

Other Staging Procedures

Other diagnostic and staging techniques did not vary considerably during the 5 years of recorded data; furthermore, the frequent coexistence of experimental protocols, aimed to optimize diagnostic and staging procedures, ensured an overall accurate clinical assessment. All patients received a technetium 99m methylene diphosphonate bone scan of the entire body. In addition to this, the baseline clinical evaluation also included a 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.¹⁴ Other imaging tests, including radiograms, CT scans, and magnetic resonance imaging of the bones, ultrasonographic studies of the abdomen, and other organ-specific investigations were optional and performed as clinically indicated. Any information obtained in this way was considered part of the final clinical evaluation. The preoperative staging evaluation was particularly reliable in 12 patients (10% of the cohort), who had a pathologic stage assessment made by mediastinoscopy (11 subjects) or CT-guided biopsy of a suspected (and unconfirmed) bone

TABLE 2. Cross-tabulation between major preoperative estimates and pathologic findings

	1997 Pathologic stage							
	Ia	Ib	IIa	IIb	IIIa	IIIb	IV	Total
1997 CT stage								
Ia	21	9	1		3	1		35
Ib	5	25	2	6	4	4		46
IIa	1	2		1				4
IIb		4	2	3	4	6	1	20
IIIa		1		3	7	3		14
IIIb	1					1		2
IV		1					2	3
Total	28	42	5	13	18	15	3	124
Final clinical evaluation*								
	69				10			
Yes	24	34	5	6	5	5		79
No	4	8	0	7	13	10	3	45
	19				26			

*Based on medical history, physical examination, bronchoscopy, 3-organ CT scanning, and any other preoperative available investigation.

TABLE 3. Tumor resectability*: ROC analysis

All patients (n = 124)	AUC	95% CI	P value
CT†	0.763	0.666-0.861	.000
TPA (U/L)	0.621	0.511-0.732	.035 (Figure 1, A)
Average of CEA and TPA‡	0.616	0.507-0.725	.043
CEA (ng/mL)	0.573	0.467-0.680	.201 (Figure 1, B)

AUC, Area under the curve; ROC, receiver-operating characteristic; CI, confidence interval; CT, computed tomography; TPA, tissue polypeptide antigen; CEA, carcinoembryonic antigen.

*Diagnosis of postoperative stage Ia-IIb (pathologically confirmed).

†CT of the thorax, upper part of the abdomen, and brain.

‡Values of TPA and CEA are expressed as a percent of their reference values (90 U/L and 5 ng/mL, respectively), added up, and divided by 2.

metastasis (1 subject). Because we considered both anti-CEA immunoscintigraphy and the marker assay to be investigative, no clinical decision was made on the sole basis of their results.

All 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.

Data Analysis and Statistical Considerations

Diagnostic capabilities were calculated for the final clinical assessment, CT reading, CEA, TPA, and CEA-TPA combined variable (mean of the two marker values expressed in percentage of their reference of 5 ng/mL [CEA] and 90 U/L [TPA]). For CEA, TPA, and CEA-TPA, one or multiple threshold levels were chosen to describe a positive or negative test result. In this study, diagnostic capabilities are not intended to show the presence or absence of disease, but the presence (or absence) of the condition of full resectability, that is, the pathologic postoperative documentation

of stage Ia through IIb disease. Accordingly, a marker level below a given threshold or a CT result suggestive of stage Ia-IIb was declared *true positive* when the actual pathologic stage was Ia to IIb and *false positive* when the latter was IIIa or more. Markers over the considered threshold or more advanced CT stages were considered *true negative* or *false negative* when the corresponding pathologic stage was, respectively, IIIa-IV or Ia-IIb.

Statistical analysis was performed with the use of the SPSS package for Windows, version 9.0 (SPSS, Inc, Chicago, Ill). Continuous variables were described by medians and ranges because in many instances, such as in the case of CEA and TPA, their distribution was not gaussian.¹⁵ Sensitivity, specificity, and accuracy, along with predictive positive and negative values, were obtained by means of standard diagnostic formulas.¹⁶ Diagnostic proportions were given along with their 95% confidence intervals (CI).¹⁷ To compare diagnostic capabilities, we used the receiver-operating characteristic curves,¹⁸ whose circumscribed areas (the

Figure 1. Receiver-operating characteristic curves showing the predictive capability of TPA (A) and CEA (B). The preoperative diagnosis was postoperative pathologic stage Ia-IIb.

Figure 2. Receiver-operating characteristic curves showing the predictive capability of TPA for the T factor (A) and the N factor (B). The preoperative diagnosis was postoperative pathologic factors T1-2 N0-1.

area under the curve) give an estimate of the diagnostic efficiency.¹⁹ Correlations and differences were tested for statistical significance by means of the Spearman rank test and the Kruskal-Wallis analysis of variance.¹⁵ All statistical tests were 2-sided.

Results

Descriptive Statistics

Table 1 shows the anthropometric and clinical characteristics of the patient population, with descriptive statistics on sex, age, history of weight loss, performance status (Eastern Oncology Group scale²⁰), and CEA and TPA serum levels.

Also reported are tumor cell type, the postoperative pathologic stage of disease, the correlated parameters of disease extension, the type of surgical treatment, the survival duration, and the patients' status at the last follow-up reassessment. As of May 1999, 64 of 124 patients (52%) were still alive after a median follow-up of 19 months (range 1-64 months). Most recruited patients had an early stage of disease and had favorable surgical outcomes. A total of 88 patients had completely operable disease (postoperative stages Ia, Ib, IIa, or IIb), another 18 subjects might have benefited from the

TABLE 4. Tumor resectability*: Diagnostic formulas

	TP	TN	FP	FN	Total	SE (%)	SE (CI) (%)
<i>Single test evaluations:</i>							
CT†	82	13	23	6	124	93	88-98
Final clinical evaluation‡	69	26	10	19	124	78	70-87
TPA (up to 80 U/L, median)	50	21	15	38	124	57	46-67
TPA (up to 90 U/L, RF)	59	20	16	29	124	67	57-77
TPA (up to 110 U/L)	67	13	23	21	124	76	67-85
CEA (up to 2 ng/mL, median)	58	18	18	30	124	66	56-76
CEA (up to 5 ng/mL, RF)	72	5	31	16	124	82	74-90
CEA (up to 10 ng/mL)	81	4	32	7	124	92	86-98
Average of CEA and TPAS	61	16	20	27	124	69	60-79
<i>CT evaluations stratified by:</i>							
TPA (≤90)	54	5	11	5	75	92	84-99
TPA (>90)	28	8	12	1	49	97	90-103
CEA (≤10)	75	12	20	6	113	93	87-98
CEA (>10)	7	1	3	0	11	100	100-100

TP, True positive; TN, true negative; FP, false positive; FN, false negative; SE, sensitivity; SP, specificity; AC, accuracy; PPV, positive predictive value; NPV, negative predictive value; CI, 95% confidence interval; CT, computed tomography; TPA, tissue polypeptide antigen; CEA, carcinoembryonic antigen; RF, reference value; NC, noncalculable.

*Diagnosis of postoperative stage Ia-IIb, confirmed pathologically.

†CT of the thorax, upper part of the abdomen, and brain.

‡Based on the results of physical examination, routine laboratory tests, bronchoscopy, 3-organ CT, and any other preoperative available investigation.

§Values of TPA and CEA are expressed in percent of their reference values (90 U/L and 5 ng/mL, respectively), added up, and divided by 2.

operation (stage IIIa), and 18 others had a nonoperative condition (stage IIIb or IV). This resulted in 104 pulmonary resections and 20 exploratory thoracotomies.

Median values (ranges) of CEA and TPA in the postoperative pathologic stage Ia-IIb were, respectively, 2 ng/mL (0-60 ng/mL) and 70 U/L (30-360 U/L). Corresponding values for postoperative stages IIIa-IV were 2.5 ng/mL (1-22 ng/mL) and 100 U/L (40-790 U/L). The correlation between serum levels of TPA and the pathologic stage of disease was statistically significant (Spearman $R = 0.3$, $P = .001$), whereas that of CEA did not reach the significance level ($R_s = 0.162$, $P = .072$). No significant difference in the distribution of the serum markers' concentration among different histotypes was observed (Kruskal-Wallis statistic).

Diagnosis of Postoperative Pathologic Stage by Means of a 3-Organ CT and the Best Clinical Assessment

Table 2 shows a cross-tabulation between the 3-organ CT stage and the best clinical assessment on the one hand and the postoperative pathologic stage on the other. On the basis of CT, the preoperative classification was stage Ia-IIb in 105 patients. Stage Ia-IIb disease was confirmed postoperatively in only 88 of them. By contrast, there were 19 patients with CT-diagnosed stage IIIa-IV disease and 36 patients with truly inoperable disease. This means a considerable CT underestimation of the real extent of disease, partially corrected by the completion of the full staging workup. The final and best clinical assessment, however, showed no

greater diagnostic accuracy, because of an increased overestimation of the real disease (Table 2).

Diagnosis of Resectable Disease (Postoperative Pathologic Stage Ia-IIb), 3-Organ CT Findings, and CEA and TPA Serum Levels

TPA and CEA differed remarkably in their capability to disclose early stages of disease. In particular, the diagnosis of postoperative stage Ia-IIb was only partially correct with TPA and inaccurate with CEA (Figure 1). The area under the receiver-operating characteristic curve was 0.621 ($P = .035$) for TPA and 0.57 ($P = .201$) for CEA (Table 3). Three-organ CT was the most accurate method for the preoperative diagnosis of resectability (Table 4). For a TPA of 90 U/L or less, the diagnostic sensitivity was 67%, and the specificity and accuracy rates were, respectively, 56% and 64% (Table 4). A normal level of TPA was properly associated with resectable disease in 79% of the patients (95% CI: 69%-88%), and a higher level was diagnostic of advanced disease in 41% (95% CI: 27%-55%). TPA was also capable of diagnosing resectability when the T or the N factors alone were taken into consideration (Figure 2). For a CEA level up to 5 ng/mL, sensitivity, specificity, and accuracy rates were, respectively, 82%, 14%, and 62%, whereas the probability of properly diagnosing a condition of resectability was 70% (CI: 61%-79%). The combination of CEA and TPA (CEA-TPA combined variable) was unable to increase the overall diagnostic accuracy of TPA alone (Table 4).

SP (%)	SP (CI) (%)	AC (%)	AC (CI) (%)	PPV (%)	PPV (CI) (%)	NPV (%)	NPV (CI) (%)
36	20-52	77	69-84	78	70-86	68	48-89
72	58-87	77	69-84	87	80-95	58	43-72
58	42-74	57	49-66	77	67-87	36	23-48
56	39-72	64	55-72	79	69-88	41	27-55
36	20-52	65	56-73	74	65-83	38	22-55
50	34-66	61	53-70	76	67-86	38	24-51
14	3-25	62	54-71	70	61-79	24	6-42
11	1-21	69	60-77	72	63-80	36	8-65
44	28-61	62	54-71	75	66-85	37	23-52
31	9-54	79	69-88	83	74-92	50	19-81
40	19-61	73	61-86	70	56-84	89	68-109
38	21-54	77	69-85	79	71-87	67	45-88
25	-17-67	73	46-99	70	42-98	100	100-100

Stratifying the CT-based stage of disease by marker results (Table 4) identified two different situations. The first was the presence of concordant findings (which increased both positive and negative predictive values of CT); the second was the occurrence of bidirectional discordant data (this lowered CT predictability). The TPA-stratified CT stage was the best possible combination of CT and any one single marker (Table 4). As shown, the presence of a normal TPA level increased the chance, based on CT, of correctly predicting tumor resectability from 78% (CI: 70%-86%) to 83% (CI: 74%-92%). The opposite situation was associated to a diagnostic improvement of 21%, from the 68% rate of negative predictability of a sole CT suggesting nonresectability (CI: 48%-89%) to 89% (CI: 68%-109%). In the area of uncertainty of an abnormal TPA and tumor resectability suggested by CT (or vice versa, conversely, of normal TPA and presence of advanced disease on CT), the CT diagnosis of resectable disease was correct in about 50% to 70% of the cases (Table 4).

Discussion

This study aimed to assess, in resectable NSCLC, the exact diagnostic capability of two serum biomarkers, CEA and TPA, that are commonly measured in many European countries²¹ but are still ignored by important medical societies.^{22,23}

CEA is an oncofetal protein found normally in the embryonic and fetal gut, produced sometimes by malignant cells. It was discovered in 1965 by Gold and Freedman²⁴ in the sera of subjects with adenocarcinoma of the colon. Raised CEA concentrations may be detected in persons who smoke, in patients with benign tumors, and in 15% to 20% of subjects with inflammatory disorders such as ulcerative colitis, pancreatitis, liver disease, and pulmonary infec-

tions.²⁵ Abnormally elevated concentrations of CEA can be found in 30% to 70% of patients with lung cancer.^{11,13,26-28} Raised levels of CEA are particularly common in those with adenocarcinoma^{28,29}; however, they can be present in any histologic type.^{26,27} Studies have shown that increased concentrations of CEA occur more frequently in advanced cancers,^{12,27} although reported differences are not always statistically significant.¹¹

Nearly half a century ago, Björklund³⁰ discovered a new antigen by mixing many different tumors and producing an immune serum against the mixture. He called it TPA. TPA has been subsequently identified as a degradation product of the cytoskeleton, formed by the cytokeratins 8, 18, and 19.³¹ The cytoskeleton is a complex network that influences the dynamic structure of all eukaryotic cells in their tissue environment.³² It is composed of microfilaments (7-9.5 nm in diameter), microtubules (25 nm), and intermediate filaments (10-12 nm).³² Cytokeratins are the major components of the intermediate filaments.³³ Cytokeratins may be divided into 20 different types, according to molecular weight and isoelectric point.³⁴ The expression of a single cytokeratin or a combination of certain cytokeratins is typical of a specific tissue. Elevated serum concentrations of TPA (ie, of cytokeratins 8, 18, and 19) have been observed in different types of epithelial cancers.³⁵ In lung cancer, pretreatment levels of TPA are often elevated, particularly in the later stages of disease.^{9-13,36-38}

As already mentioned, this is not our first attempt to define a clinical strategy capable of exploiting the widely known correlation between tumor burden and serum marker concentration. In 1995, in this Journal, we³⁶ reported a study specifically designed to investigate the use of TPA as a common test of preoperative assessment. We considered 104 patients with NSCLC who had undergone thoracotomy,

mediastinoscopy, or biopsy of suspected metastatic deposits in addition to an extensive noninvasive evaluation of the stage of disease. We made several retrospective evaluations, but the two most pertinent to this study were those regarding TPA and the readings of a CT of the brain, thorax, and upper portion of the abdomen. Among the 20 threshold values considered, ranging from 45 U/L to 450 U/L, we identified two thresholds for detecting the postoperative stage of disease with the highest rate of success. Then, on the basis of the pathologic reference, we determined the sensitivity, specificity, accuracy, and predictive capabilities of both CT and TPA at the thresholds of 110 U/L and 160 U/L. We found that CT and TPA had a diagnostic accuracy of, respectively, 79% and 68% for stages I and II; 69% and 77% for stage IIIa; and 77% and 76% for stages IIIb and IV (1987 International Union Against Cancer [UICC] classification). Impressed by those results, we postulated the equivalence of TPA and CT in predicting surgical resectability. This study starts from that premise, but it limits the focus to what we think is the most clinically important information. Is the patient under assessment a surgical candidate or does he or she have a condition that is partially or completely inoperable? We can summarize our current findings as follows:

1. The preoperative assessment of tumor resectability, based on a CT scan of brain, thorax, and upper part of the abdomen, is acceptably accurate (accuracy rate: 77%).

2. The 20% to 25% margin of error is not appreciably reduced by the addition of any other preoperative investigation.

3. In patients considered for surgery, a blind single serum test of TPA is diagnostic of full resectability (postoperative stage Ia-IIb) at an overall accuracy rate of 65%.

4. Very elevated levels of CEA (above 10 ng/mL) are also capable of recognizing a postoperative resectable disease (accuracy rate: 69%).

5. The stratification of CT readings by TPA (serum test results up to 90 U/L or more) allowed us to identify a group of 9 patients, among the 19 with supposedly inoperable disease, who had a particularly high risk of unresectable disease (89%) and another 65, among the 105 judged operable, whose tumors were more often resectable (83%). The remaining 50 subjects were left in an area of uncertainty that required further clinical testing.

6. In slightly smaller groups, the stratification of CT data by both CEA (cutoff: 10 ng/mL) and TPA (cutoff: 90 U/L) made it possible to accurately discriminate between resectability and nonresectability, increasing the negative predictive efficiency to 85% to 100%.

Conclusions

Evidence from this study suggests obtaining a routine TPA test (and possibly a CEA test) in all patients with potentially operable NSCLC. CT remains the gold standard for the preoperative evaluation of NSCLC. However, it may signifi-

cantly underestimate the real extension of tumor. The TPA test is capable of correcting such an underestimation and helps to determine the next steps. We believe that a 3-organ CT showing a resectable tumor (stage Ia-IIb) and a TPA level up to 90 U/L in an asymptomatic subject are clear indications for immediate operation. On the other hand, a higher TPA value (or a very high level of CEA) associated with CT findings of nonresectability (stage IIIa-IV) virtually eliminates any surgical approach. In case of conflicting data, the patient is still a surgical candidate, but an intensification of the preoperative evaluation is mandatory. This could be obtained by ordering a bone scan or performing a mediastinoscopy, even in the absence of symptoms and signs.

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References

1. Pamies RJ, Crawford DR. Tumor markers—An update. *Med Clin North Am.* 1996;80:185-99.
2. Coombes RC, Powels TJ. Tumour markers in the management of human cancer. In: Deeley TJ, editor. Topical reviews in radiotherapy and oncology. Bristol: Wright PGS; 1982. p. 39.
3. Buccheri G. Tumor markers: clinical meaning and use. In: Brambilla C, Brambilla E, editors. Lung tumors. New York: Marcel Dekker, Inc; 1999. p. 435-52.
4. Ferrigno D, Buccheri G. Clinical applications of serum markers for lung cancer. *Respir Med.* 1995;89:587-97.
5. Ferrigno D, Buccheri G, Biggi A. Serum tumour markers in lung cancer: history, biology and clinical applications. *Eur Respir J.* 1994;7:186-97.
6. World Health Organization. International histological classification of tumours. Berlin: Springer-Verlag; 1991.
7. Mountain CF. A new international staging system for lung cancer. *Chest.* 1986;89(Suppl):225S-33S.
8. Mountain CF. Revisions in the International System for Staging Lung Cancer [see comments]. *Chest.* 1997;111:1710-7.
9. Buccheri G, Ferrigno D. Usefulness of tissue polypeptide antigen in staging, monitoring, and prognosis of lung cancer. *Chest.* 1988;93:565-9.
10. Buccheri G, Ferrigno D. Prognostic value of the tissue polypeptide antigen in lung cancer. *Chest.* 1992;101:1287-92.
11. Buccheri G, 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.
12. Buccheri G, Ferrigno D, Vola F. Carcinoembryonic antigen (CEA), tissue polypeptide antigen (TPA), and other prognostic indicators in the squamous cell carcinoma of the lung. *Lung Cancer.* 1993;10:21-33.
13. Buccheri G, 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.
14. Buccheri G, Biggi A, Ferrigno D, Quaranta M, Leone A, Vassallo G, 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.
15. Siegel S. Nonparametric statistics for the behavioural sciences. New York: McGraw Hill; 1956.
16. Galen RS. Predictive values of laboratory tests. *Am J Cardiol.* 1975;36:536-8.
17. Bulpitt CJ. Confidence intervals. *Lancet.* 1987;1:494-7.
18. McNeil BJ, Keeler E, Adelstein SJ. Primer on certain elements of decision making. *N Engl J Med.* 1975;293:211-5.
19. Hanley JA, McNeil BJ. The meaning and use of the area under receiving operating characteristic (ROC) curve. *Radiology.* 1982;43:29-36.

20. Zubrod CG, Scheiderman MA, Frei E, Brindley E, Gold LG, Shnider B, et al. Appraisal of methods for the study of chemotherapy in man: comparative therapeutic trial of nitrogen mustard and triethylene thio-phosphoramide. *J Crohn Dis.* 1960;11:7-33.
21. Watine J, Charet JC. [Are the ATS (American Thoracic Society) and the ERS (European Respiratory Society) correct in not recommending routine tumor marker assays for screening, staging, or evaluation of non-small cell lung cancer]? *Rev Mal Respir.* 1999;16:139-49.
22. American Society of Clinical Oncology. Clinical practice guidelines for treatment of unresectable non-small-cell lung cancer. *J Clin Oncol.* 1998;15:2996-3018.
23. Lynch T. Treatment of stage III non-small-cell lung cancer: 1998. In: Perry MC, editor. ASCO educational book—34th annual meeting. Alexandria: American Society of Clinical Oncology; 1998. p. 265-75.
24. 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.
25. N.H.I. Carcinoembryonic antigen: its role as a marker in the management of cancer. *BMJ.* 1981;282-373.
26. 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.
27. Laberge F, Fritsche HA, Umsawasdi T, Carr DT, Welch S, Murphy WK, 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.
28. Mizushima Y, Hirata H, Izumi S, Hoshino K, Konishi K, Morikage T, et al. Clinical significance of the number of positive tumor markers in assisting the diagnosis of lung cancer with multiple tumor marker assay. *Oncology.* 1990;47:43-8.
29. Niklinski J, Furman M, Laudanski J, Kozlowski M. Prognostic value of pretreatment CEA, SCC-Ag and CA 19-9 levels in sera of patients with non-small cell lung cancer. *Eur J Cancer Prev.* 1992;1:401-6.
30. Björklund B. Serological analysis of human cancer antigen. In: Anonymous proceedings: VI Internat Congres Microbiol Rome: 1953; 344.
31. Björklund B. Tissue polypeptide antigen (TPA): biology, biochemistry, improved assay methodology, clinical significance in cancer and other conditions, and future outlook. In: Schonfeld H, editor. Laboratory testing for cancer. Basel: Karger; 1978. p. 16-31.
32. Luna EJ, Hitt AL. Cytoskeleton-plasma membrane interactions. *Science.* 1992;258:955-63.
33. Lazarides E. Intermediate filaments as mechanical integrators of cellular space. *Nature.* 1980;283:249-56.
34. Debus E, Moll R, Franke WW, Weber K, Osborn M. Immunohistochemical distinction of human carcinomas by cytokeratin typing with monoclonal antibodies. *Am J Pathol.* 1984;114:121-30.
35. Gronowitz JS, Bergstrom R, Nou E, Pahlman S, Brodin O, Nilsson S, et al. Clinical and serologic markers of stage and prognosis in small cell lung cancer. *Cancer.* 1990;66:722-32.
36. Buccheri G, Ferrigno D. The tissue polypeptide antigen serum test in the preoperative evaluation of non-small cell lung cancer: diagnostic yield and comparison with conventional staging methods. *Chest.* 1995;107:471-6.
37. Ferrigno D, Buccheri G, Rendine S. The prognostic value of CEA and TPA in the initial evaluation of lung cancer: results of a multivariate analysis of 312 patients. In: Motta G, editor. Lung cancer: advanced concepts and present status. Genova: IASLG; 1989; p. 179-88.
38. Luthgens M, Schlegel M. Verlaufskontrolle bei Bronchialkarzinomen mit Tissue Polypeptide Antigen und Carcinoembryonalem Antigen [summary in English]. *Tumor Diagn Ther.* 1985;6:1-7.

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