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Clinical Evaluation of Serum Tissue Polypeptide-specific Antigen (TPS) in Non-small Cell Lung Cancer

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M3 is an epitope of the tissue polypeptide antigen detectable in the serum by immunoradiometric assay. This epitope is referred to as tissue polypeptide-specific antigen (TPS). We examined the pretreatment TPS level of 160 non-small cell lung cancer (NSCLC) patients and 71 patients who suffered from non-malignant pulmonary diseases. The upper limit of normal values was 140 U/l. Using this cutoff, the sensitivity and specificity were 36 and 90%, respectively. The TPS was significantly higher in NSCLC patients with an advanced stage, a mediastinal lymph node involvement or a poor performance status. This level was significantly higher in the group of patients for whom the disease proved to progress during chemotherapy. In univariate analysis, patients with a high TPS level proved to have a shorter survival than patients with a TPS ≤ 140 U/l. In Cox's model analysis, performance status, stage of the disease and serum TPS were the only significant prognostic variables. The low sensitivity of TPS precludes its use for diagnosis. However, the pretreatment TPS level adds information to the management of NSCLC inasmuch as it predicts a low sensitivity to chemotherapy and a poor prognosis.

Key words: non-small cell lung cancer, tissue polypeptide-specific antigen, chemotherapy, prognosis
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INTRODUCTION

THE TREATMENT of non-small cell lung cancer (NSCLC) is one of the most important challenges of medical oncology [1]. In patients with local disease, surgery can achieve a high rate of cure [2]. However, the majority of patients present with a more advanced disease for which combined modality treatments, such as radiotherapy and chemotherapy, are the subject of permanent reassessment [3].

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In inoperable NSCLC, seven trials have been conducted to compare the use of chemotherapy with the best supportive care available (for review see [4]). All these studies demonstrate a 10–20-week survival improvement in patients receiving chemotherapy. However, this survival advantage was significant only for trials which included a sufficient number of patients. Thus, the survival improvement induced by chemotherapy in NSCLC is hitherto probably modest. As chemotherapy might be responsible for an impairment of quality of life, particularly in non-responding patients, new markers able to predict prognosis and response to therapy might be useful.

Several serum tumour markers, such as tissue polypeptide antigen (TPA) [5], carcino-embryonic antigen (CEA) [6] or more recently CYFRA 21-1 [7], have been investigated in an attempt to determine their sensitivity, specificity and applicability in NSCLC. One of the most extensive experiences in this field is

the use of TPA. Independent studies suggest that this marker is related to tumour mass and indicates a poor prognosis [5, 8]. Immunological mapping revealed that TPA contains 35 epitopes [9]. One major epitope is recognised by the M3 monoclonal antibody. This epitope, proposed as specific for cell proliferation, is detectable in the serum by an immunoradiometric assay, and is referred to as tissue polypeptide-specific antigen (TPS).

In this prospective study, we examined serum TPS in 160 NSCLC patients and in 71 patients presenting with non-malignant respiratory diseases. The aims were to determine sensitivity, specificity of this new serum marker and to analyse whether a high serum TPS level is correlated with stage of the disease, sensitivity to chemotherapy, tumour response at restaging and prognosis.

MATERIALS AND METHODS

Patients

160 consecutive patients with pathologically-confirmed NSCLC referred to the Montpellier University Hospital between February 1990 and October 1991 were prospectively entered in the study (Table 1). Among them were 99 squamous cell carcinomas (SQC), 40 adenocarcinomas (ADE) and 21 large cell carcinomas (LCC) as defined by the WHO classification [10]. Performance status (PS) was estimated according to the Eastern Cooperative Oncology Group (ECOG) and the percentage of weight loss during the previous 4 months was recorded. Staging was carried out by exhaustive procedures according to the 4th edition of the UICC TNM classification [11], the American Thoracic Society map of regional pulmonary nodes [12] and Mountain's stage grouping [13]. In order to establish the disease stage, the following investigations were applied: clinical examination, standard chest roentgenography, computed tomographic (CT) scan of chest and upper abdomen, fiberoptic bronchoscopy, liver sonography and bone scanning. Mediastinoscopy was used to establish nodal status in patients with non-metastatic disease and evidence of mediastinal lymph node enlargement on chest CT scan. A brain CT scan was carried out if clinically required.

Table 1. Patients' characteristics

	No. of patients
Total no. of patients	160
Male/female	142/18
Mean age, years (S.D., range)	61 (11, 32–88)
Histology	
SQC	99
ADE	40
LCC	21
Performance status	
0	14
1	102
2	34
3	10
Stage of disease	
I and II	20
IIIa	31
IIIb	46
IV	63
Weight loss	
No weight loss	88
Weight loss	72
Treatment	
Surgery	40
Radiotherapy	20
Single drug chemotherapy	24
DDP-containing two-drug chemotherapy	38
DDP-containing three-drug chemotherapy	19
Best supportive care	19

S.D., standard deviation; SQC, squamous cell carcinoma; ADE, adenocarcinoma; LCC, large cell carcinoma; DDP, dichloro-diamino-platinum.

Controls

The serum markers were measured in 71 consecutive patients with non-malignant pulmonary diseases (eight infectious diseases, 55 chronic obstructive pulmonary diseases and eight miscellaneous).

Treatment decision

Each patient was discussed by a medical panel composed of thoracic surgeons, chest physicians, radiologists, radiotherapists and medical oncologists. Patients with stage I or II or resectable IIIa disease underwent surgery in an attempt to achieve complete resection. Other patients with performance status ≤ 2 and distant metastasis (stage IV) or gross mediastinal involvement (stage IIIb and unresectable stage IIIa) were eligible to be entered into one of the chemotherapy trials conducted in the Montpellier University Hospital. The treatment is summarised in Table 1. For these patients, chemotherapy-induced tumour response was analysed using the WHO criteria [14, 15], 10–12 weeks after the beginning of the treatment, by measuring the indicator lesions on CT scan. Best supportive care, including palliative radiation therapy when needed, was given to patients with advanced stage and poor performance status. Treatment was decided upon according to routine clinical and biological findings and without knowledge of the serum TPS level. Hence, treatment was not considered as a prognostic variable in this study.

Biochemical measurements

A blood sample was taken from each patient at presentation, the serum separated and stored at −190°C until tested. 25 patients, among those who underwent chemotherapy, had an additional serum sampling at the time of tumour response evaluation. The per cent increase in serum marker level was calculated as follows:

$$\frac{\text{restaging value} - \text{pretreatment value}}{\text{pretreatment value}} \times 100.$$

TPS (BEKI Diagnostics AB, Bromma, Sweden) is a two-site immunoradiometric assay using two types of antibodies in excess. Polyclonal anti-TPA horse antibodies bound to a plastic bead and 100 µl of ^{125}I-labelled (1.9 µCI/ml) mouse IgG1 kappa anti-M3 monoclonal antibodies were incubated with 100µl of patient serum or standard curve (composed of the following concentrations of TPA: 0, 30, 155, 625 and 2500 U/l). Afterwards, the bead was washed with distilled water in order to remove the unbound labelled reagents. Finally, the bead was transferred to a fresh plastic tube for measurement.

Radioactivity was counted in a well-type gamma counter (Atogamma Packard Instrument Company, Illinois, U.S.A.) and expressed in counts per min (c.p.m.). The M3 concentration of the sample was determined using the results of construction of the standard curve and was expressed in U/l.

CEA was measured using the dissociation-enhanced lantha-

nide fluoroimmunometric assay (DELFIA, Wallac OY, Turku, Finland).

Total lactate dehydrogenase (LDH) assays were carried out following the Deusch Chemical Society recommendations by measuring its activity using pyruvate as a substrate (Bio-Mérieux, France).

The upper limits of normal values were as follows: LDH 330 U/l; alkaline phosphatase 220 U/l; leucocytes 8000/μl. The lower limits of normal values were 32 g/l for albumin and 135 mmol/l for serum sodium.

All sera samples were assayed blind of clinical information.

Statistics

Receiver operating characteristic (ROC) curves were constructed using both patient and control subject serum TPS levels in an attempt to establish a sensitivity–specificity relationship; areas under the ROC curve were calculated [16]. The serum tumour marker was not distributed normally; thus, for each patient subset, results were expressed as median and variation was expressed as interquartile range. Non-parametric statistical analyses were used: differences between two independent groups were determined by means of the Mann–Whitney U-test with the Bonferoni correction for multiple comparisons; differences between more than two groups were determined by means of Kruskal-Wallis one-way analysis of variance; Spearman rank-order correlation coefficients were calculated in order to compare CEA and TPS level; a P level < 0.05 was considered as significant. Survival was defined as the time from the date of sampling to the date of death. Survival data were updated in May 1993 and none of the patients were lost to follow-up. Probability of survival was estimated by the Kaplan–Meier method [17]. Single variable survival analyses were performed by means of Wilcoxon and log-rank tests and multivariate regression was carried out with the Cox's model [18]. Survival was analysed using the SAS software package.

RESULTS

Tumour marker distributions

The median and interquartile ranges (IR) of serum TPS at presentation were significantly higher in cancer patients (85.5 U/l; IR 29.0–192.3 U/l) when compared with control subjects (50; IR 25.0–94.0; Mann Whitney U-test; $P < 0.002$). The median CEA distribution at presentation was 5.4 ng/ml (IR 2.9–18.3) in cancer patients and 3.4 ng/ml (IR 2.6–4.3) in control subjects. The area under the ROC curve used to assess the ability of serum TPS level to discriminate between lung cancer patients and non-malignant pulmonary disease was 0.58 ± 0.04 (S.D.). This area was significantly smaller than the one constructed with the results of sensitivity and specificity of serum CEA (area: 0.68, S.D. 0.03; $z = 2.3$; $P < 0.01$; Figure 1). For each tumour marker, a threshold was chosen taking the 90% specificity as determined by the distribution in patients with non-malignant pulmonary disease. These upper limits of normal values were 140 U/l and 5.2 ng/ml for serum TPS and serum CEA, respectively. The sensitivities and specificities using these thresholds are shown in Table 2. In lung cancer patients, the comparison of CEA versus TPS level did not demonstrate a statistical correlation ($r_s = 0.18$; non-significant).

Serum TPS level at presentation distribution according to pathology and staging

Serum TPS level did not vary significantly according to histological subtype of NSCLC: the median serum TPS in SQC, ADE and LCC were 85.1 (IR 26.0–191.0), 90.5 (IR 20.5–240.9) and 80.0 (IR 53.0–145.0) U/l, respectively (Kruskal–Wallis test = 0.08 $P = 0.95$). The level of TPS was significantly lower in patients with limited disease (confined to the chest and supraclavicular nodes), being 58.5 (IR 16.8–131.7) in comparison with 158.0 (IR 69.0–380.0) in patients with extensive disease (Mann–Whitney $P < 10^{-4}$). The serum TPS level significantly differed according to stage (Kruskal–Wallis $P < 10^{-4}$; Figure 2), but there was no significant difference when stage IIIa and

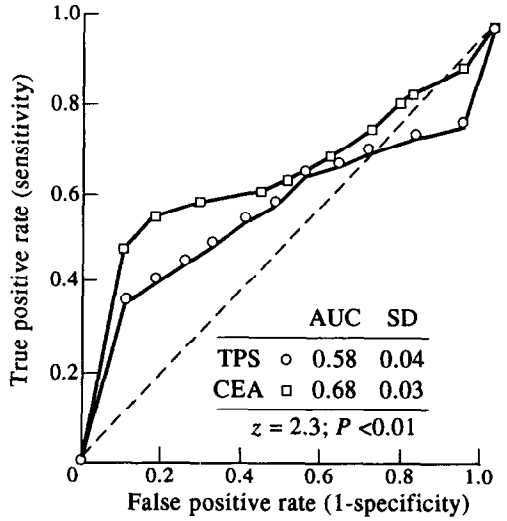


Figure 1. Receiver operating characteristic (ROC) constructed using the sensitivity–specificity relationship of each marker to discriminate lung cancer patients and patients with a non-malignant pulmonary disease. AUC, area under the curve; SD, standard deviation. The diagonal line represents absence of discrimination

Table 2. Sensitivity and specificity of TPS and CEA

Tumour marker	Normal values	Sensitivity	Specificity	Accuracy
TPS (U/l)	≤ 140	0.36	0.90	0.52
CEA (ng/ml)	≤ 5.2	0.51	0.90	0.63

TPS, tissue polypeptide-specific antigen; CEA, carcinoembryonic antigen.

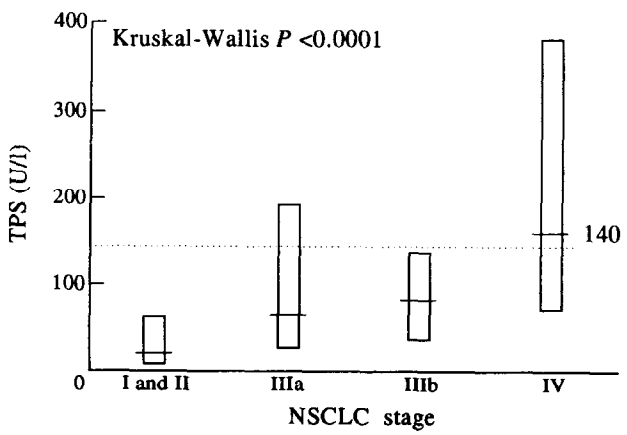


Figure 2. TPS distribution according to stage grouping in non-small cell lung cancer. Horizontal bar, median value; columns, interquartile range.

stage IIIb were compared. The TPS level was analysed according to the presence (N2–3) or absence (N0–1) of mediastinal lymph node metastases: in patients with a N2–3 nodal status, the serum TPS was significantly higher (median 930; IR 41.0–220.0) in comparison with patients for whom staging procedure resulted in a N0-1 status (median 62.0; IR 13.2–152.0, Mann–Whitney U-test $P = 0.03$). These aforementioned results indicate that the TPS level at presentation was significantly lower in patients for whom surgery was possible (median 38.2; IR 0.9–110.0) in comparison with patients with unresectable disease (median 104.0; IR 46.0–229.0; Mann–Whitney U-test $P < 10^{-3}$).

The TPS level differed significantly according to PS: patients with a PS < 2 had a significantly lower TPS level (median 74.0; IR 24.6–153.0) when compared to patients with a PS ≥ 2 (median 163.8; IR 49.6–335.8; Mann–Whitney U-test $P = 0.002$).

TPS distribution at presentation in chemotherapy-treated patients

Among the 81 patients who received chemotherapy, 4 did not complete the induction programme and were not evaluable for tumour response measurement (3 early treatment stops for toxicity and 1 patient refusal to continue). The distributions of pretreatment serum TPS and serum CEA levels were fully analysed in the 77 remaining patients. There was a partial response in 28 patients, a complete response in 4 and stabilisation in 19, whereas the disease progressed in the 26 others. The median serum TPS level at presentation was significantly higher in the group of patients for whom the disease proved to have progressed during chemotherapy when compared with complete response, partial response or stabilisation groups (Kruskal–Wallis; $P < 0.02$, Figure 3). The pretreatment CEA level did not significantly differ according to response to chemotherapy: responders: median 8.1; IR 3.2–30.0; stabilised: median 9.0 (IR 2.7–57.9); progressive disease: median 5.5 (IR 2.7–41); Kruskal–Wallis NS.

Taking into account the observation of a higher pretreatment serum TPS level in patients with progressive disease, we analysed the sensitivity–specificity relationship of TPS by constructing a ROC curve among two subgroups of chemotherapy-treated patients: patients with progressive disease and patients with non-progressive disease (responder and stabilised patients). The area under the TPS ROC curve was significantly greater when compared with that of CEA suggesting that a high TPS level predicted a poor response to chemotherapy more accurately than CEA (Figure 4).

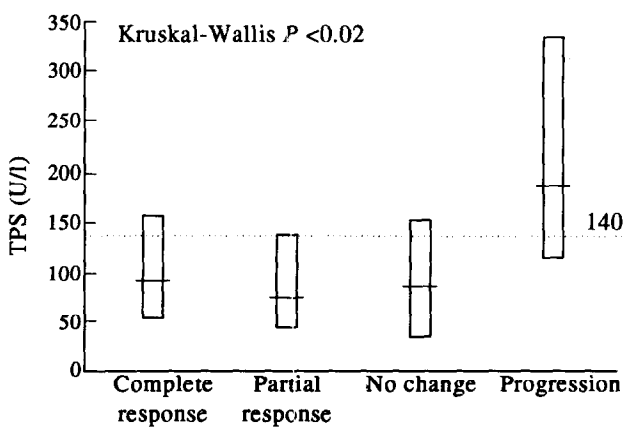


Figure 3. Pretreatment serum TPS distribution according to response to chemotherapy. Horizontal bar, median value; columns, interquartile range.

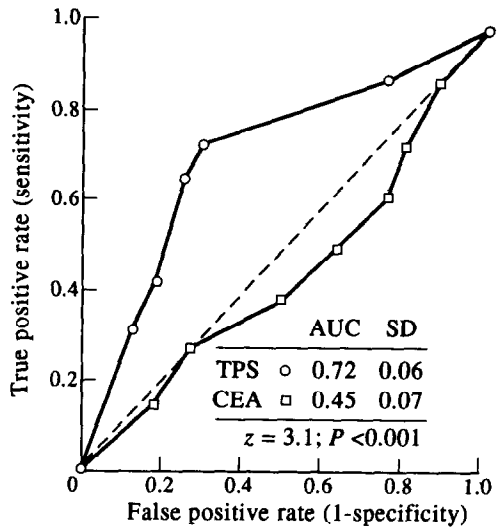


Figure 4. Receiver operating characteristic (ROC) curve constructed using the sensitivity–specificity relationship of tumour marker among two subgroups of chemotherapy-treated patients: patients with progressive disease and patients with non-progressive disease (responder and stabilised patients). The highest TPS values corresponded to patients with progressive disease. AUC, area under the curve; SD, standard deviation.

Follow-up of serum TPS at time of tumour response assessment

Among the 25 patients for whom a TPS titration was performed at the time of tumour response assessment, 14 had a partial response and 11 did not respond. The per cent increase in TPS level was higher in non-responders when compared with responders, although this difference did not reach a statistical significance (Figure 5). In 4 of the 14 (29%) responder patients, the marker increased despite the fact that tumour response was concomitantly demonstrated. Conversely, the marker decreased in 4/11 (36%) who experienced a progression during chemotherapy.

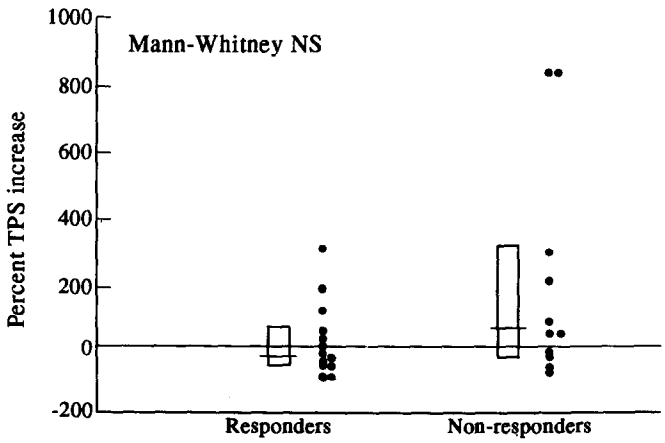


Figure 5. Percentage increase of serum TPS at restaging in 25 of the 77 patients receiving chemotherapy. The calculation of this variable is described in the Materials and Methods. A negative value indicates a decrease in marker level. Horizontal bar, median value; columns, interquartile range.

Survival

Patients with a serum TPS level over 140 U/l proved to have a shorter survival than patients with a TPS less than or equal to this value (log-rank test and Wilcoxon test; $P < 0.0001$; Figure 6). Separate survival analyses showed a significant negative effect of an advanced stage, a poor performance status, involvement of mediastinal nodes, weight loss, a serum albumin level lower than 32 g/l, a serum LDH over 330 U/l and a serum sodium lower than 135 mmol/l (Table 3). No difference in overall survival was seen when histological subgroup, age, sex, leucocytes, alkaline phosphatase and serum CEA (Figure 7) were considered.

Cox's model analysis was written after a Boolean codage of the following variables: sex, age, performance status, histology, nodal status, stage of the disease, weight loss, serum sodium, alkaline phosphatase, albumin, leucocytes, serum TPS and serum CEA. For each variable, the proportional hazard assumption was tested graphically. With Cox's model analysis, performance status, stage of the disease and serum TPS were the only significant determinants of survival (Table 4).

DISCUSSION

The results of chemotherapy studies in NSCLC are analysed taking into account two main factors: PS and stage of the disease. These two important features influence the prognosis and response to therapy [19]. However, they are insufficient to predict precisely the outcome inasmuch as a great heterogeneity of clinical behaviour appears within a subgroup of patients.

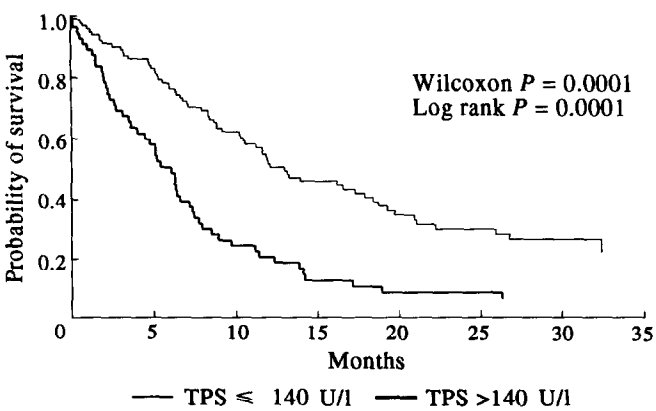
Biological properties of NSCLC have been investigated as putative indicators of prognosis. In different multivariate studies, aneuploidy [20], lack of expression of blood group A antigen [21] or expression of the neural cell adhesion molecule [22] have been independently demonstrated as prognostic factors; however, correlations and interactions between these variables are not known. Moreover, this information is difficult to obtain and there is, therefore, a place for serum tumour markers.

Several markers have been proposed to help the management of NSCLC. None of them can be proposed in a diagnostic setting owing to a low ability to discriminate lung cancer from non-malignant pulmonary diseases. This weakness did not rule out a role as an aid for treatment decision, follow-up and prediction of outcome. CEA is one of the first tumour markers extensively studied in lung cancer [6, 8, 23, 24]. Most of the studies have

Table 3. Significant variables in univariate analysis

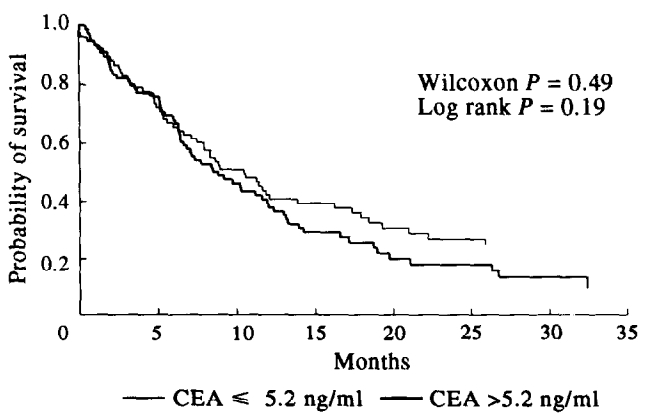
Factor and level	Median survival (months)	*P* value Wilcoxon	*P* value Log rank
TPS			
≤ 140 U/l	12.9	0.0001	0.0001
> 140 U/l	6.0		
Stage			
I and II	*	0.0001	0.0001
IIIa	13.8		
IIIb	8.8		
IV	5.1		
Nodal status			
N0	18.7	0.001	0.0001
N1	17.3		
N2	10.5		
N3	6.2		
Performance status			
0–1	13.2	0.0001	0.0001
2–4	4.8		
Weight loss			
No weight loss	10.5	0.02	0.02
0–5%	10.2		
> 5%	5.2		
Albumin (g/l)			
≥ 32	10.5	0.004	0.01
< 32	6.5		
Lactate dehydrogenase (U/l)			
≤ 330	13.8	0.0001	0.0001
> 330	7.1		
Serum sodium (mmol/l)			
≥ 135	10.4	0.03	0.04
< 135	6.5		

*Median survival not reached in this subgroup.



	n	Median survival	% censored
≤ 140 U/l	103	12.9	35
> 140 U/l	57	6.0	12

Figure 6. Probability of survival of patients with normal and elevated pretreatment serum TPS level.



	n	Median survival	% censored
≤ 5.2 ng/ml	77	10.4	31
> 5.2 ng/ml	81	8.8	22

Figure 7. Probability of survival of patients with normal and elevated pretreatment serum CEA level.

Table 4. Regression analysis results: estimated relative risk for significant variables

Variable	Regression coefficient β ± S.E.	P	Relative risk
Performance index	1.05 ± 0.23	< 0.0001	2.85
Disease stage	1.23 ± 0.25	< 0.0001	3.41
Serum TPS	0.47 ± 0.21	0.0275	1.60

TPS, tissue polypeptide-specific antigen.

demonstrated that serum CEA level correlated with tumour mass, although a low serum CEA level is not a proof of operability. Conflicting results have been published regarding the effect of CEA level on survival. The former studies concluded a negative effect of a high pretreatment serum CEA level on survival [23, 24]. However, more recent studies concluded a lack of survival effect of CEA level [6, 25]. In our present study, CEA was not a prognostic factor. This negative result might be regarded as a true negative one inasmuch as the survival of our patients was significantly influenced by known prognostic factors such as stage of the disease, performance status, lymph node status, serum albumin, weight loss, etc.

TPA has been described as a human antigenic protein released immediately after mitosis [9]. Both sensitivity and specificity of TPA in NSCLC are higher than those of serum CEA, and patients with an elevated serum TPA level have a worse prognosis on univariate analysis [5, 8, 24]. The immunological mapping of TPA relealed that, among the 35 epitopes shared by the molecule, only two are specific for cell proliferation [9]. M3 is a new monoclonal antibody referred to as TPS, which detects one of these two major epitopes. Its clinical usefulness has been suggested in various human malignancies [26–28]. *In vitro* studies demonstrated that expression of TPS by various tumour cell lines is enhanced during cell proliferation. (B. Björklund, personal communication). In addition, serum TPS level was correlated with *in situ*-evaluated tumour labelling index in 32 women with breast cancer (G. Valenti, personal communication). Thus, serum TPS might be tested as a putative marker of proliferation in human malignancies.

In our study, we analysed the sensitivity, specificity and clinical applicability of serum TPS in NSCLC. The ROC curve analysis demonstrated clearly that this marker is not a tumour marker *per se* since its accuracy to discriminate between cancer patients and patients presenting with a non-malignant pulmonary disease is very poor and significantly lower than that of CEA. This result indicated that TPS is not a diagnostic test of NSCLC. Using the 140 U/l cutoff, the sensitivity of TPS was very low. However, the upper limit of normal values for the CEA was 5.2 ng/ml. The sensitivity and specificity of CEA at this cutoff were similar to those already extensively published by several independent groups [6, 8]. The remaining analysis of this study tried to determine (i) the clinical behaviour of patients for whom a high pretreatment TPS level has been detected and (ii) whether TPS is a putative marker of proliferation in NSCLC rather than a classical tumour marker.

Our study demonstrated a correlation between serum TPS and stage of the disease. Moreover, the marker varied significantly according to nodal status. These results reproduced other observations with various tumour markers such as CYFRA 21-1 [7]. Although the distribution of TPS varied significantly according to the stage of the disease, it must be emphasised that determining the operability of a patient with this marker is not possible. As shown in Figure 2, there was an overlap of the TPS distribution between stage IIIa and stage IIIb which are, respectively, considered as marginally resectable and unresectable stages. Nevertheless, a high serum level of TPS seems to be an indicator of the presence of metastases, and might indicate the need for a careful investigation of all putative metastatic sites.

The serum TPS level at presentation was significantly higher in the group of patients for whom the disease proved to progress during chemotherapy. In this setting, TPS level was more accurate than CEA in predicting a poor tumour response. A possible explanation for this result may be that a high serum TPS indicated a higher growth fraction, which is a feature usually linked to very aggressive clinical behaviour. Alternatively, it must be stressed that a high pretreatment serum TPS was also associated with poor performance status and metastatic stage. These clinical features are well-known indicators of the poorest response to chemotherapy in NSCLC [19]. Thus, the ability of a high serum TPS level to predict progression during chemotherapy is only a clue but not proof of its proliferative nature. In our small longitudinal experience of TPS, its level seemed to be poorly correlated with tumour shrinkage or tumour growth during chemotherapy.

The univariate survival analysis found a significant negative effect of a variety of previously-published prognostic variables, such as stage of the disease and performance status [29, 30]. These variables have been tested in order to ascertain that the outcome of our population complies with established factors. As the serum TPS distribution correlated with both disease extent and performance status, it was not surprising that patients with a high TPS level proved to have the shortest survival. However, in multivariate analysis, the prognostic significance brought by TPS was independent, and adds information to the well-known prognostic factors, namely performance index and disease stage. This independent prognostic information might be considered as an additional argument in favour of the hypothesis that TPS is a marker of proliferation. However, the present results are quite similar to those which we observed in a different lung cancer patient population in which we analysed CYFRA 21-1, a marker able to detect in the serum a cytokeratin 19 fragment [7]. These data might be analysed with regard to the information that CYFRA 21-1, TPS and TPA have in common a 40% homology [31].

We conclude that various evidence exists in favour of the hypothesis that TPS is a marker of proliferation in NSCLC, although this cannot be firmly established by our study. Moreover, a larger study design to compare this marker with TPA and CYFRA 21-1 is needed in order to clearly define the role of each marker in the management of this disease.

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