Prediction of survival and recurrence by serum and cytosolic levels of CEA, CA125 and SCC antigens in resectable non-small-cell lung cancer

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Summary Risk of death and risk of recurrence in 108 potentially curable non-small-cell lung cancer patients were analysed with respect to TNM stage, histological type and carcinoembryonic antigen (CEA), CA125 antigen and squamous cell carcinoma antigen (SCC) levels in serum and cytosol. CA125 and CEA levels were closely related to outcome figures. Multivariate analyses indicated that TNM stage and histological type had the best predictive power, but serum and cytosolic CA125 and serum CEA contained additional, independent prognostic information. Predictive information drawn from serum and cytosolic levels proved mutually complementary. We conclude that CA125 and CEA complement TNM classification and histological type for the purpose of quantifying risk of death or recurrence.

Keywords: carcinoembryonic antigen; CA125; squamous cell carcinoma antigen; lung cancer; prognostic factor; survival

The tumour–node–metastasis (TNM) classification system is the cornerstone for planning therapy options in patients with non-small-cell lung cancer (NSCLC) (Bains, 1991). Such staging of tumour spread is the best available prognostic factor. However, its predictive power is limited. Differences may be seen between expected and actual outcome after curative resection among patients within the same TNM category of risk. Efforts are under way to confirm the possibility that long-term results or response to treatment may be partially based on biological characteristics inherent in tumour cells (Carney, 1991). Methods for the description of biological tumour aggressiveness are rapidly expanding (Carney, 1991; Lee and Hong, 1992).

Owing to their low sensitivity and specificity, tumour markers have, until now, played a less important role in the diagnosis and management of NSCLC than has been the case with most other common cancers (Bergman et al., 1993; Strauss and Skarin, 1994; Jarvisalo et al., 1993). Nevertheless, tumour markers might have a wide range of potential applications within the field of NSCLC as tools for description of tumour biological aggressiveness. Of these tumour markers, carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC) have been two of the most commonly used to date. Their sensitivity for detecting the primary tumour is low, ranging from 30% to 60% (Strauss and Skarin, 1994) depending upon histological type and TNM stage. Several authors have reported that serum CEA and serum SCC assay provide useful information for establishing preoperative diagnosis in patients with localised and resectable disease (GaIl et al., 1984; Sanchez et al., 1994), guiding follow-up after surgical treatment (Diez et al., 1995) and monitoring response to chemotherapy in advanced disease (Shinkai et al., 1986; Spiridonis et al., 1995). CA125 was initially described as an ovarian cancer-associated antigen, and has recently been assayed in NSCLC. In a previous study we reported that serum levels of CA125 provide independent information on survival and tumour relapse in patients undergoing curative surgical treatment for NSCLC (Diez et al., 1994a).

Analysis of tumour marker expression in NSCLC tumour tissue has not been reported as frequently. In a previous study we observed that cytosolic concentration of CEA, SCC and CA125 is a particular and distinctive characteristic of each histological type, something which could aid pathological classification (Picardo et al., 1994). In addition, high CEA plus high CA125 content allows for identification of the large-cell carcinoma histological subtype (Picardo et al., 1994). In our opinion, this kind of study could lead to a better understanding of the relationship between tumour marker and the biological features of the neoplasm.

This study aimed at assessing the ability of preoperative serum and cytosolic levels of CEA, CA125 and SCC antigens to provide information on the risk of death and recurrence in patients who had undergone curative surgical treatment for NSCLC.

Patients and methods

Population

A total of 108 histologically proven NSCLC patients (99 men and nine women; mean age 61 years) (s.d. 9 years) who underwent curative resection of the tumour between October 1989 and October 1993 were included in the study. They were consecutively submitted to our unit for surgical treatment. Patients undergoing chemotherapy or radiation therapy before surgery were not included. Careful, complete sampling of mediastinal lymph node groups was performed routinely before resection of the primary lesion. Patients who died of complications after surgery during this period (operative death) were not included. Histopathological diagnosis was carried out in accordance with the WHO classification of lung tumours (World Health Organization, 1981): 71 patients (65.7%) had squamous carcinoma, 29 (27%) adenocarcinoma and eight (7.3%), large-cell carcinoma. TNM staging (Mountain, 1986) was performed by correlating the operative and histological findings: 55 patients (51%) were in stage I, 12 (11%) in stage II and 41 (38%) in IIIA. Follow-up was conducted prospectively. During this period, two patients died as a result of unrelated causes, 3 and 16 months after surgery respectively. Two patients were lost to follow-up. Tumour recurrence was diagnosed in 51 patients, 45 of whom have since died. Median survival time of patients still living stands at 25 months (range 10–55).
Specimens analysed and tumour marker assay

Serum and lung samples were obtained from all these patients. Serum was obtained preoperatively. One sample from the lung tumour was always obtained at the time of surgery. The excised lung specimens were divided, one piece being sent for histological examination and the other for tumour marker assay. This specimen was cleaned of any necrotic tissue, washed with ice-cold saline and immediately frozen in liquid nitrogen. Total time elapsed from removal of specimen to freezing was less than 15 min. Cytosols were analysed immediately or stored at −80°C until assayed. Separation and processing of cytosols was effected by a previously described method (Picardo et al., 1994). Commercially available kits were used and applied according to the manufacturer's instructions: enzyme immunoassay for CEA and CA125 (Hoffmann LaRoche, Basle, Switzerland), radioimmunoassay for SCC (Abbott Laboratories, Wiesbaden-Delkenheim, Germany). Cytosol protein concentration was determined by the Lowry method. Results of CA125 in cytosol are shown as U mg⁻¹ of proteins. Results of CEA and SCC in cytosol are shown as ng mg⁻¹ of proteins.

Performance characteristics of immunometric assays depend upon the matrix of the sample. Commercially available kits are standardised for serum. As a prior step, we therefore had to validate the technique for the cytosol matrix. In order to ascertain the precision and accuracy of the assay, the first ten lung cancer samples were divided into four parts. All the steps of the analysis were repeated in these

### Table I Distribution of the three markers in cytosol and serum

| Variable       | Markers in cytosol | Markers in serum |
|----------------|--------------------|-----------------|
| CEA            | Mean (s.d.) 417.0 (1762.7) | 26.5 (97.2) |
|                | Median (ID) 61.1 (14.0–140.0) | 3.1 (2.2–8.0) |
|                | Range 0.1–4730 | 0.1–874 |
| CA125          | Mean (s.d.) 136.5 (596.4) | 25.5 (95.2) |
|                | Median (ID) 20.0 (4.8–69.0) | 9.5 (2.2–20.0) |
|                | Range 0.1–6006 | 0.1–968 |
| SCC            | Mean (s.d.) 44.4 (61.2) | 3.2 (6.4) |
|                | Median (ID) 19.0 (4.0–55.0) | 1.6 (0.5–3.4) |
|                | Range 0.1–346 | 0.0–48 |

s.d., standard deviation. ID, interquartile distance.

### Table II Predictors of survival in non-small cell lung cancer according to the univariate analysis

| Variable          | No. of patients | No. of events | 12    | Survival (months) | 24    | 36    | Hazard ratio | 95%CI    | P-value |
|-------------------|-----------------|---------------|-------|-------------------|-------|-------|--------------|----------|---------|
| Histological type |                 |               |       |                   |       |       |              |          |         |
| Squamous          | 71              | 29            | 87    | 66                | 44    | 1     |              |          |         |
| Adenocarcinoma    | 29              | 10            | 86    | 66                | 54    | 0.84  | 0.41–1.73   | 0.642    |         |
| Large-cell carcinoma | 8               | 6             | 38    | 25                | 25    | 3.44  | 1.41–8.38   | 0.007    |         |
| TNM stage         |                 |               |       |                   |       |       |              |          |         |
| I                 | 55              | 18            | 94    | 73                | 51    | 1     |              |          |         |
| II                | 12              | 5             | 83    | 75                | 54    | 1.14  | 0.42–3.07   | 0.799    |         |
| IIA               | 41              | 22            | 67    | 43                | 33    | 2.41  | 1.29–4.50   | 0.006    |         |
| Sex               |                 |               |       |                   |       |       |              |          |         |
| Male              | 99              | 40            | 82    | 65                | 45    | 1     |              |          |         |
| Female            | 9               | 5             | 100   | 44                | 44    | 1.21  | 0.48–3.06   | 0.695    |         |
| Age               |                 |               |       |                   |       |       |              |          |         |
| < 65              | 65              | 23            | 88    | 72                | 53    | 1     |              |          |         |
| ≥ 65              | 37              | 22            | 75    | 47                | 34    | 1.72  | 0.96–3.09   | 0.069    |         |
| CEA in cytosol    |                 |               |       |                   |       |       |              |          |         |
| < 61.1 ng mg⁻¹    | 54              | 19            | 89    | 70                | 49    | 1     |              |          |         |
| ≥ 61.1 ng mg⁻¹    | 54              | 26            | 77    | 56                | 42    | 1.52  | 0.84–2.75   | 0.167    |         |
| CA125 in cytosol  |                 |               |       |                   |       |       |              |          |         |
| < 20 U mg⁻¹       | 54              | 14            | 96    | 79                | 60    | 1     |              |          |         |
| ≥ 20 U mg⁻¹       | 54              | 31            | 69    | 46                | 32    | 2.92  | 1.55–5.50   | <0.001   |         |
| SCC in cytosol    |                 |               |       |                   |       |       |              |          |         |
| < 19 ng mg⁻¹      | 54              | 19            | 85    | 67                | 55    | 1     |              |          |         |
| ≥ 19 ng mg⁻¹      | 54              | 26            | 81    | 57                | 35    | 1.54  | 0.85–2.78   | 0.155    |         |
| CEA in serum      |                 |               |       |                   |       |       |              |          |         |
| < 5 ng ml⁻¹       | 70              | 26            | 85    | 63                | 53    | 1     |              |          |         |
| ≥ 5 ng ml⁻¹       | 38              | 19            | 78    | 62                | 33    | 1.45  | 0.80–2.61   | 0.221    |         |
| CA125 in serum    |                 |               |       |                   |       |       |              |          |         |
| < 15 U ml⁻¹       | 68              | 25            | 88    | 68                | 54    | 1     |              |          |         |
| ≥ 15 U ml⁻¹       | 40              | 20            | 74    | 53                | 29    | 1.92  | 1.06–3.47   | 0.031    |         |
| SCC in serum      |                 |               |       |                   |       |       |              |          |         |
| < 1.5 ng ml⁻¹     | 53              | 25            | 83    | 62                | 40    | 1     |              |          |         |
| ≥ 1.5 ng ml⁻¹     | 55              | 20            | 83    | 63                | 51    | 0.79  | 0.44–1.42   | 0.427    |         |

95% CI, 95% confidence interval.
Serum and cytosolic CEA, CA125, SCC

specimens separately. Variation coefficients of the technique for cytosols were 15% for CEA, 13% for CA125 and 16% for SCC. Intra-assay variation coefficients were 7% in the CEA assay, 6% in CA125 and 8% in SCC. Interassay variation coefficients were 10% in the CEA assay, 9% in CA125 and 11% in SCC.

Statistical analysis

In the statistical analysis, median and interquartile distances were used as summary measures, owing to the asymmetric distribution of marker values. Survival and recurrence rates linked to tumour marker levels were studied using the Kaplan–Meier method, and differences between subgroups of patients were compared using Mantel’s log-rank test.

Survival and disease-free survival were calculated from surgery to last contact or death and from surgery to recurrence respectively. Patients lost to follow-up and deaths due to a different cause were considered as censored. The importance of all prognostic factors considered for both survival and recurrence was estimated using Cox’s proportional hazards regression model. The crude effect of each predictor was evaluated, using unadjusted hazard ratios as an estimate of relative risk. Possible interactions between tumour markers and the other predictors were tested. In the univariate study of survival, the tumour markers were analysed as dichotomous variables. The following cut-offs were used for serum: CEA, 5 ng ml⁻¹; CA125, 15 U ml⁻¹;
SCC, 1.5 ng ml$^{-1}$. These values had been selected in a previous study by our group by studying the receiver operating characteristic curves (Diez et al., 1994a,b). No generally accepted values exist as cut-offs for cytosol, and we therefore decided to use the median value. In the absence of any other reference, this has the advantage of furnishing a balanced distribution of the sample. Accordingly, the cut-offs for cytosol were: CEA, 61.1 ng mg$^{-1}$; CA125, 20 U mg$^{-1}$; SCC, 19 ng mg$^{-1}$. Sample size was not pre-established, but was mainly determined by population incidence and thus by the number of patients attending our hospital.

**Results**

Distribution of serum and cytosolic concentration of CEA, CA125 and SCC are depicted in Table I. Concentrations of these markers were far higher in cytosol than in serum; likewise, the degree of dispersion was comparatively greater in the cytosol-based results.

**Survival**

The cumulative probability of survival over 36 month follow-up was 45%. In the univariate analysis this result was significantly related to histological type, TNM stage and CA125 levels in serum and cytosol (Table II). Patients with large cell carcinoma showed significantly lower probability of survival than patients with squamous carcinoma and adenocarcinoma ($P=0.007$), but no significant differences were detected between the latter two histological types ($P=0.642$). Whereas stage IIIa patients showed significantly lower probability of survival than patients in stages I and II ($P=0.006$), no differences were detected between the latter two ($P=0.799$). High CA125 cytosolic levels were associated with a significantly lower probability of survival (32% vs 60%) ($P<0.001$), as were high CA125 serum levels (29% vs 54%) ($P=0.031$). When survival estimates for histological type and TNM stage were classified according to results of CA125 in cytosol, patients with high levels of the marker exhibited a significantly worse outcome (Figures 1 and 2). Likewise, within adenocarcinoma, patients with high serum CEA levels exhibited significantly lower survival than those with low serum CEA (Figure 3).

Table III sets out the results of the multivariate analysis. Shown in this table are: a first model, including the results of cytosolic measurements after adjustment for histological type, TNM stage and age; a second model, including serum measurements after adjustment for the same three factors; and a third model, including only those variables showing significant influence in the first two models. Interaction terms did not significantly improve any of these models. The likelihood ratios indicate that the partial models were significantly poorer predictors than the final combined model. In this final model, TNM stage and histological type proved to be the most important predictors of survival. Cytosolic and serum levels of CA125, and serum CEA, once adjusted for other prognostic variables, revealed themselves to be independent predictive factors. Table III shows that the risk of death increases in direct proportion to a rise in cytosolic CA125, serum CA125 and serum CEA.

**Recurrence**

The 36 month disease-free survival rate was 47%. In the univariate analysis, this result was related to histological type, TNM stage, age, cytosolic CEA and serum and cytosolic CA125 (Table IV). High CA125 cytosolic and CEA serum levels were associated with a significantly lower probability of disease-free survival.

Table V sets out the results of the multivariate analysis. In the final model, TNM stage and histological type again proved to be the most important predictors. Cytosolic CA125 and serum CEA revealed themselves to be independent predictive factors. Table V illustrates that risk of recurrence increases in direct proportion to a rise in cytosolic CA125 and serum CEA.

**Discussion**

Preoperative serum CA125, cytosolic CA125 and preoperative serum CEA were observed to be closely related to outcome figures in NSCLC. These markers provided prognostic information not taken into account by TNM stage or histological type. The data indicate that CA125 and CEA levels do not simply reflect tumour load but are
Table III Predictors of survival in non-small-cell lung cancer according to the multivariate analysis

| Variable                        | Including only cytosolic measures | Including only seric measures | Final model |
|---------------------------------|----------------------------------|-------------------------------|-------------|
|                                 | Hazard ratio 95% CI               | Hazard ratio 95% CI            | Hazard ratio 95% CI   | P-value |
| Histological type               |                                  |                               |                          |         |
| Squamous + adenocarcinoma       | 4.327 1.738–10.770 0.002         | 3.748 1.436–9.779 0.007       | 4.308 1.642–11.300 0.003 |         |
| Large-cell carcinoma            | 2.448 1.327–4.516 0.004          | 2.304 1.253–4.238 0.007       | 2.609 1.398–4.870 0.003 |         |
| TNM stage                       |                                  |                               |                          |         |
| I–II                            | 1                                | 1                             | 1                        |         |
| IIIA                            | 1.752 0.961–3.194 0.067          | 1.656 0.898–3.053 0.106       | 1.697 0.918–3.138 0.091 |         |
| Age                             |                                  |                               |                          |         |
| <65                             | 1                                | 1                             | 1                        |         |
| ≥65                             | 1.051 1.014–1.090 0.007          | 1.056 1.018–1.095 0.004       | 1.056 1.018–1.095 0.004 |         |
| CEA in cytosol (for every 100 ng mg⁻¹) | Not included owing to lack of statistical significance | 1.056 1.018–1.095 0.004 | 1.056 1.018–1.095 0.004 |         |
| CA125 in cytosol (for every 100 U mg⁻¹) | 1.038 0.989–1.088 0.131 | 1.067 1.019–1.117 0.006 | 1.068 1.022–1.116 0.004 |         |
| SCC in cytosol (for every 10 ng mg⁻¹) | 1.021 1.001–1.041 0.041 | 1.024 1.003–1.045 0.025 | 1.024 1.003–1.045 0.025 |         |
| CEA in serum (for every 10 ng ml⁻¹) |                                  |                               |                          |         |
| CA125 in serum (for every 10 U ml⁻¹) |                                  |                               |                          |         |
| SCC in serum (for every 10 ng ml⁻¹) |                                  |                               |                          |         |
| Comparison with the final model | Likelihood ratio (degrees of freedom) 12.09 (2) | 6.53 (2) | 6.53 (2) |         |
| P-value                         | 0.002                            | 0.038                          | 0.038                    |         |

Table IV Predictors of disease-free survival in non-small-cell lung cancer according to the univariate analysis

| Variable                        | No. of patients | No. of events | Survival (months) 12 24 36 | Hazard ratio 95% CI | P-value |
|---------------------------------|-----------------|---------------|-----------------------------|---------------------|---------|
| Histological type               | Squamous        | 71            | 33                          | 74                  | 51      | 51   | 1    | 1    |
| Adenocarcinoma                  | 29              | 12            | 79                          | 52                  | 52      | 0.94 | 0.49–1.83 | 0.862 |
| Large cell carcinoma            | 8               | 6             | 25                          | 25                  | 25      | 3.26 | 1.36–7.84 | 0.008 |
| TNM stage                       | I               | 55            | 21                          | 85                  | 58      | 58   | 1    |       |
| II                              | 12              | 5             | 75                          | 58                  | 58      | 1.11 | 0.42–2.94 | 0.835 |
| IIIA                            | 41              | 25            | 51                          | 34                  | 34      | 2.28 | 1.27–4.08 | 0.006 |
| Sex                             | Male            | 99            | 46                          | 71                  | 50      | 50   | 1    |       |
| Female                          | 9               | 5             | 78                          | 44                  | 44      | 1.04 | 0.41–2.62 | 0.935 |
| Age                             | <65             | 65            | 26                          | 75                  | 58      | 58   | 1    |       |
| ≥65                             | 37              | 25            | 65                          | 36                  | 36      | 1.75 | 1.01–3.04 | 0.046 |
| CEA in cytosol (≥61.1 ng mg⁻¹)  | 54              | 21            | 80                          | 60                  | 60      | 1    |       |
| CA125 in cytosol (≥20 U mg⁻¹)   | 54              | 18            | 87                          | 64                  | 64      | 1    |       |
| SCC in cytosol (≥19 ng mg⁻¹)    | 54              | 33            | 56                          | 35                  | 35      | 2.59 | 1.45–4.61 | 0.001 |
| CEA in serum (≥5 ng ml⁻¹)       | 70              | 29            | 74                          | 55                  | 55      | 1    |       |
| CA125 in serum (≥15 U ml⁻¹)     | 68              | 28            | 78                          | 57                  | 57      | 1    |       |
| SCC in serum (≥1.5 ng ml⁻¹)     | 53              | 27            | 70                          | 47                  | 47      | 1    |       |

95% CI, 95% confidence interval.
Table V Predictors of disease-free survival in non-small-cell lung cancer according to the multivariate analysis

| Variable                      | Including only cytosalic measures | Including only serum measures | Hazard ratio | P-value | Hazard ratio | P-value | Hazard ratio | P-value |
|-------------------------------|-----------------------------------|------------------------------|--------------|---------|--------------|---------|--------------|---------|
| Histological type            |                                   |                              |              |         |              |         |              |         |
| Squamous + Adenocarcinoma    | 4.468                             | 1                            | 1.824–10.950 | 0.001   | 3.417        | 0.009   | 4.344        | 0.002   |
| Large Cell Carcinoma         |                                   |                              |              |         |              |         |              |         |
| TNM stage                    |                                   |                              |              |         |              |         |              |         |
| I–II                         | 2.382                             | 1                            | 1.348–4.211  | 0.003   | 2.301        | 0.004   | 2.538        | 0.002   |
| IIIA                         |                                   |                              |              |         |              |         |              |         |
| Age                          |                                   |                              |              |         |              |         |              |         |
| <65                          | 1.624                             | 1                            | 0.920–2.867  | 0.095   | 1.555        | 0.129   | 1.565        | 0.131   |
| ≥65                          |                                   |                              |              |         |              |         |              |         |
| CEA in cytosol (for every 100 ng ml⁻¹) | 1.015                        | 1                            | 1.000–1.031  | 0.050   | 1.014        | 0.077   | 1.018        | 0.003   |
| CA125 in cytosol (for every 100 U ml⁻¹) | 1.053                        | 1                            | 1.016–1.091  | 0.005   | 1.056        | 0.003   | 1.018–1.095  | 0.003   |
| SCC in cytosol (for every 10 ng ml⁻¹) | 1.039                        | 1                            | 0.997–1.083  | 0.068   | 1.041        | 0.062   | 0.998–1.086  | 0.062   |
| CEA in serum (for every 10 ng ml⁻¹) | 1.037                        | 1                            | 1.009–1.066  | 0.010   | 1.036        | 0.014   | 1.007–1.066  | 0.014   |
| CA125 in serum (for every 10 U ml⁻¹) | 1.015                        | 1                            | 0.996–1.034  | 0.121   | 1.018        | 0.064   | 0.999–1.038  | 0.064   |
| SCC in serum (for every 1 ng ml⁻¹) | Not included owing to lack of statistical significance |  |  |  |  |  |  |  |
| Comparison with the final model | Likelihood ratio (degrees of freedom) | 6.53                        | 9.22 (3)     | 0.038   | 0.027        |  |  |  |
levels in the two compartments is weak and may be determined by factors other than the rate of production (e.g., delivery into the bloodstream, necrosis, metabolism, hepatic and renal excretion, production at other sites).

For a biological parameter to be used as a prognostic factor in clinical medicine, it is essential that the assay be cheap, simple, objective, comparable, reproducible and that the result be available in a short space of time to the doctor (Fielding et al., 1992). In our opinion, serum and cytosolic quantification of CEA and CA125 clearly meets these requirements. From a theoretical standpoint, these factors offer some advantages over other predictive parameters. Histological features (tumour grade, mitotic index, vascular invasion) and immunohistochemical evaluation of onco-gene-encoded protein expression, furnish qualitative and semi-quantitative information, and are subject to a certain degree of interobserver variation. Direct genetic studies (DNA sequencing, polymerase chain reaction single-strand conformation polymorphism), although very useful for research purposes, are at present, unsuitable for application in daily clinical practice. However, no accurate determination of the practical importance of our findings can be made without first ascertaining the exact relationship between the predictive value of serum and cytosolic quantification of CEA and CA125 in tandem with other factors, for assessment of biological aggressiveness.

Serum CA125, cytosolic CA125 and serum CEA are closely linked to outcome figures in NSCLC patients operated on with curative intent and provide prognostic information independent of TNM stage and histological type. Serum and cytosol furnish mutually complementary information. These biomarkers enhance current ability to quantify risk of recurrence or death on an individualised, patient-by-patient basis.

Acknowledgements
This study was supported in part by grant 94/1556 from Spain’s Fondo de Investigaciones Sanitarias (Health Research Fund).

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