A Fuzzy-classifier Using a Marker Panel for the Detection of Lung Cancers in Asbestosis Patients

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Abstract. *Background: The aim of this study was to evaluate the diagnostic power of a fuzzy classifier and a marker panel (CYFRA 21-1, NSE, CRP) for the detection of lung cancers in comparison to asbestosis patients at high-risk of developing lung cancer. Patients and Methods: A panel of four tumour markers, i.e. CEA, CYFRA 21-1, NSE, SCC and CRP, was measured in newly diagnosed lung cancer patients of different histological types and stages in comparison to asbestosis patients. In this prospective study, a fuzzy classifier was generated with the data of 216 primary lung cancer patients and 76 patients suffering from asbestosis. The patients and controls were recruited in the clinics of the University in Giessen. Results: At 95%-specificity, it was possible with this tool to detect non-small cell lung cancers in 70% at stage I (n=30), in 95% at stage II (n=22), in 98% at stage III (n=56), in 92% at stage IV (n=50) and small cell lung cancers with limited disease status (n=21) in 90.7% and with extensive disease status (n=37) in 97.3%. In contrast, single markers had a detection rate significantly far below these. The application of the classifier was examined on an independent collective of 38 non-small cell lung cancers and 76 asbestosis patients. The latter underwent stationary rehabilitation in the clinics for occupational diseases in Bad Reichenhall or Falkenstein. The fuzzy classifier showed correct negative classification in 75 out of the 76 cancer-free asbestosis patients, which confirmed a specificity of 97.4%. The overall sensitivity for lung cancer detection in high risk populations was 73.6%. All large cell carcinomas were detected. The positive predictive value was 77.7%. The negative predictive value reached 94.8%. Conclusion: With the fuzzy classifier and a marker panel, a reliable diagnostic tool for the detection of lung cancers in a high risk population is available.*

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The number of compensated occupational cancers in Germany is still rising (1). The most frequent occupational cancers are lung carcinomas (53.8%) and mesotheliomas of the pleura, peritoneum or pericardium (33.7%). Currently, approximately two-thirds (71.9%) of all occupational cancers eligible for compensation are due to asbestos fibers. Because lung cancer occupies such a prominent cause of cancer death in Western industrialized countries, particularly among the male population, early detection of this cancer should be a major focus of secondary preventive interest. Thus a comprehensive primary diagnostic programme is of great importance for successful therapy. Because of their low specificity and sensitivity, tumour markers have not been generally recommended as a tool for detection or screening for lung cancer. For increasing sensitivity and/or specificity in lung cancer diagnosis, a combination of tumour markers would be of great interest.

A new principle is based on the analysis of a panel of different tumour markers and their mathematical processing by means of fuzzy logic. Fuzzy set approaches were found to be superior to the usual sharp cut-off definition in analysis of laboratory data (2). The aim of this study was to improve the diagnostic efficiency of tumour markers in the diagnosis of lung cancer in high risk populations by mathematical evaluation of a tumour marker profile employing fuzzy logic modelling. Neuron-specific enolase (NSE), cytokeratin 19 antibody (CYFRA 21-1), carcinoembryonic antigen (CEA) or squamous cell carcinoma-related antigen (SCC) were associated with lung tumours (3). In addition, C-reactive protein (CRP), also used to indicate inflammatory diseases, is often associated

with neoplasias and correlates with malignancy and tumour size irrespective of histology (4).

Patients and Methods

Patients for generation of the classifier. In this prospective study, a fuzzy classifier was generated using the data of 216 primary lung cancer patients and 76 patients suffering from asbestosis. Two hundred and sixteen consecutive patients (188 male, 28 female) with newly diagnosed, histologically confirmed lung cancer were examined. Histological classification of the primary lung tumour cases yielded 58 patients with small cell carcinoma (SCLC; aged 63±8.7 years) and 158 with non-small cell carcinomas (NSCLC; aged 66±9.3 years). Of the latter, there were 98 patients with squamous cell carcinoma (aged 67±8.2 years) and 60 with adenocarcinoma of the lung (aged 63±10.6 years).

The tumour stages of the NSCLC were separated into four groups according to the UICC recommendations (5). Thirty lung tumours were diagnosed as stage I, 22 as stage II, 56 as stage III and 50 as stage IV. The 58 patients suffering from SCLC were classified as limited (n=28) and as extensive (n=37) disease (6). Exclusion criteria were cancer therapy and relapse, pulmonary metastases of extrapulmonary tumours, mesotheliomas, sarcomas and lymphomas.

The tumour patients were compared with a control group of 76 asbestosis sufferers (75 male, 1 female; aged 64±7.6 years) [criteria for diagnosis: see (7)] without any malignant disease. The patients and the controls were recruited from the clinics of the University in Giessen.

Patients for application of the classifier. The application of the classifier was examined on an independent collective of 38 non-small cell lung cancers and 76 asbestosis patients. Thirty-eight consecutive patients (33 male, 5 female; aged 64±8.2 years) with newly diagnosed histological confirmed lung cancer were examined. Histological classification of the primary lung tumour cases yielded 7 patients with large cell carcinoma (aged 63±5.5 years) and 31 with other non-small cell carcinomas (NSCLC; aged 64±8.6 years). Six lung tumours were diagnosed as stage I, 2 as stage II, 13 as stage III and 17 as stage IV. Again exclusion criteria were cancer therapy and relapse, pulmonary metastases of extrapulmonary tumours, mesotheliomas, sarcomas and lymphomas.

The control group comprised 76 asbestosis sufferers (74 male, 2 female) (aged 67±7.3 years) without any malignant diseases. The asbestosis patients underwent stationary rehabilitation in the Clinic for Occupational Diseases in Bad Reichenhall or Falkenstein.

Tumour markers. Blood samples were centrifuged (550 xg, 5 min) within 120 minutes after venipuncture. Sera were kept frozen at –18˚C until analysis was carried out. CEA, CYFRA 21-1 and NSE analyses were performed in sera using reagents from Roche Diagnostics GmbH (Mannheim, Germany) and were measured with an ES® 600 ELISA analyzer (Roche). SCC analysis was performed with a MEIA test system using an IMX®-analyzer (Abbott GmbH, Wiesbaden, Germany). CRP (Roche, Mannheim) was measured with a commercial latex-enhanced turbidimetric immunoassay by means of a Hitachi 917® (Roche).

Mathematical analysis. The panel of lung cancer-associated markers were evaluated by fuzzy logic modelling previously described in Schneider *et al.* (8).

Fuzzy logic draws nearer to realistic answers by replacing the inflexible "yes/no" by a topical adjustment in the form of a "more or less" and by introducing linguistic nuances into the process of decision. This can be done by collecting statistical data and by comparing the probability density functions for the variables. The method of choice for our fuzzy classifier is the rule-based procedure. The substitution of a graded ("fuzzy") function instead of a sharp threshold value of a given "yes-no" decision is an important characteristic: thus the co-ordination of a tumour marker level to the criterion *e.g.* "malignant" would be described in terms of "more...less" and not as a sharp cut-off value. Distinct, sharp values are assessed by so-called membership functions as measures for describing qualitative properties.

Each test result can be correlated to the expression of cancer for a group of persons suffering from a specific disease. Our model uses membership functions of triangular shape describing the relation of each single marker to the term "malignant". Differently applied rules may lead to different results. These intermediate results have to be summarized in the form of a starting figure ("defuzzification"). To achieve the final result, the contributory intermediate results are considered with respect to their individual importance/weight by applying the method of the focal point. The defuzzyfication employed the centre of gravity (COG) method to yield an output variable quantifying the distinctness of malignancy. The membership functions and the rules were defined with reference to the development data.

The result is a multidimensional calculation in the form of specially adapted computer software. The complex information of the tumour marker panel is processed by means of this fuzzy logic modelling to generate an indicator for malignancy. The output variable ranges from 0% to 100% membership for occurrence of cancer. If the value of this "supermarker" was greater than 0.5 (>50% membership) it was said to be "malignant".

The classifier was first generated, then the application of the classifier was examined on an independent collective.

The Chi-square test was used to assess the statistical significance of differences between observed ratios. Since serum levels of the markers did not follow a Gaussian distribution, the significance of differences between the groups was calculated by means of a nonparametric test (Mann-Whitney's *U*-test). Values of $p<0.05$ were considered as significant.

Results

Analysis of single markers – calculation of the stage-dependent sensitivities and the discrimination power (area under the ROC-curves). For this analysis, the 216 lung cancer patients were compared with the 76 asbestosis patients. For analysing the specificity, tumour marker concentrations in 76 asbestosis patients were examined. Table I reports the cut-off values at a specificity of 95% for the total of 76 controls without malignant disease.

Because single markers are dependent on different histological types of lung cancer, the sensitivities of the classification were related to histology and separated into non-small cell lung cancer (n=158) and small cell lung cancer (n=58). Because marker concentrations generally rise with tumour progression, additionally the

Table I. *Cut-off values of analysed parameters. Comparison with manufacturer's data. Manufacturer's cut-off values are understood at a specificity of 95% versus those of healthy persons.*

Marker	CYFRA 21-1 (ng/ml)	CEA (ng/ml)	NSE (ng/ml)	SCC (ng/ml)	CRP (ng/ml)
Cut-off (manufacturer's data)	3.3	5.0	12.5	1.5	5.0
Cut-off (95% specificity for asbestosis patients)	2.7	5.35	9.7	1.2	21.6

Table II. *Sensitivity of CEA, CYFRA 21-1, NSE, SCC and CRP for lung cancer detection stratified by tumour stage at a specificity of 95% asbestosis patients (No. 4103 of the German legal system for occupational diseases, Berufskrankheitenverordnung=BKV).*

Stage	n	CEA [%]	CYFRA 21-1 [%]	NSE [%]	SCC [%]	CRP [%]
I	30	15.0	23.3	20.0	26.7 (30.0*)	33.3
II	22	13.6	54.5	31.8	45.5 (50.0*)	45.5
III	56	37.5	82.1	33.9	39.3 (60.7*)	37.5
IV	50	52.0	88.0	38.0	52.0 (62.0*)	70.0
LD	21	19.0	33.3	66.6	19.0	28.6
ED	37	43.2	54.0	81.1	16.2	51.4

*Squamous carcinoma alone. LD: limited disease; ED: extensive disease.

discrimination of the different tumour stages was of great interest (Table II).

The sensitivity and specificity for the 95th percentile levels of the control group (asbestosis patients) were confirmed by receiver-operating characteristics (ROC) curves. To obtain the ROC curves, a new classification procedure is carried out for each data point at a given specificity. These ROC curves were created for every marker in the tumour stages I-IV (NSCLC) as well as in limited and extensive disease status (SCLC). Because of the limited value of single markers in this study, we would like to dispense with the need of presentation for 30 ROC curves.

In Table II, the relevant data of the ROC analyses are given comparing the performance of the single tumour marker measurements in 76 asbestosis patients and in 158 patients suffering from non-small cell lung cancer as well as 58 patients with small cell lung cancer, respectively.

The CEA and CYFRA 21-1 markers showed a good association with tumour stage in NSCLC. This is also true for SCC in squamous carcinomas. As suspected, the best association was observed with NSE in SCLC. Sensitivities in stage IV of the NSCLC were significantly higher than the comparable sensitivities at stage I for the markers CYFRA 21-1, CEA, SCC and CRP. At a 95% specificity, the sensitivity for detection of stage IV non-small cell lung cancer was 88% by the best marker, CYFRA 21-1. For stage IV tumours, CYFRA 21-1 was significantly ($p<0.001$) more sensitive than NSE. CYFRA 21-1, CEA, NSE, SCC and CRP did not differ significantly at 95% specificity in stage I.

At the same specificity (95%), the sensitivities for detection of small cell carcinomas (Table II) were also stage-dependent and reached up to 81.1% for NSE, but only 16.2% for SCC. With limited disease status, corresponding sensitivities were generally lower. NSE and CYFRA 21-1 were significantly more sensitive than CEA (NSE: $p<0.005$, CYFRA 21-1: $p<0.01$), SCC (NSE: $p<0.001$; CYFRA 21-1: $p<0.01$) and CRP (NSE: $p<0.01$; CYFRA 21-1: $p<0.01$) in discriminating small cell lung cancer patients from asbestosis patients. There were no significant differences in sensitivity between NSE and CYFRA 21-1 or between CEA and CRP. As supposed earlier, SCC did not bear any information for the detection of small cell carcinomas.

Table III. *Area under the curve (AUC) of the markers CEA, CYFRA 21-1, NSE, SCC and CRP for lung cancer detection stratified by tumour stage at a specificity of 95% for asbestosis patients (No. 4103 BKV).*

Stage	n	CEA [AUC]	CYFRA 21-1 [AUC]	NSE [AUC]	SCC [AUC]	CRP [AUC]
I	30	0.564	0.803	0.846	0.774 (0.837*)	0.762
II	22	0.617	0.897	0.896	0.801 (0.803*)	0.790
III	56	0.799	0.957	0.890	0.830 (0.892*)	0.760
IV	50	0.820	0.966	0.917	0.878 (0.925*)	0.869
LD	21	0.775	0.826	0.929	0.671	0.677
ED	37	0.763	0.937	0.978	0.714	0.815

*Squamous carcinoma alone. LD: limited disease; ED: extensive disease.

The area under the curves is an indicator of marker quality. The relevant data are presented in Table III.

The area under the curves in stage I of the NSCLC was largest for NSE (0.846) and lowest for CEA (0.564). The best discrimination of the lung cancer patients in comparison to asbestosis patients (No. 4103 BKV) was possible with the CYFRA 21-1 and NSE markers.

Generating the fuzzy classifier for early lung cancer detection. For testing the marker combinations including the fuzzy classification, the parameters with the best malignant-benign discrimination were chosen. For non-small cell carcinomas, as well as for small cell carcinomas, the highest sensitivities were found using CYFRA 21-1, NSE and CRP (8). Further analysis demonstrated that there is no greater benefit for discrimination of malignant *versus* benign lung diseases using other markers (data not shown).

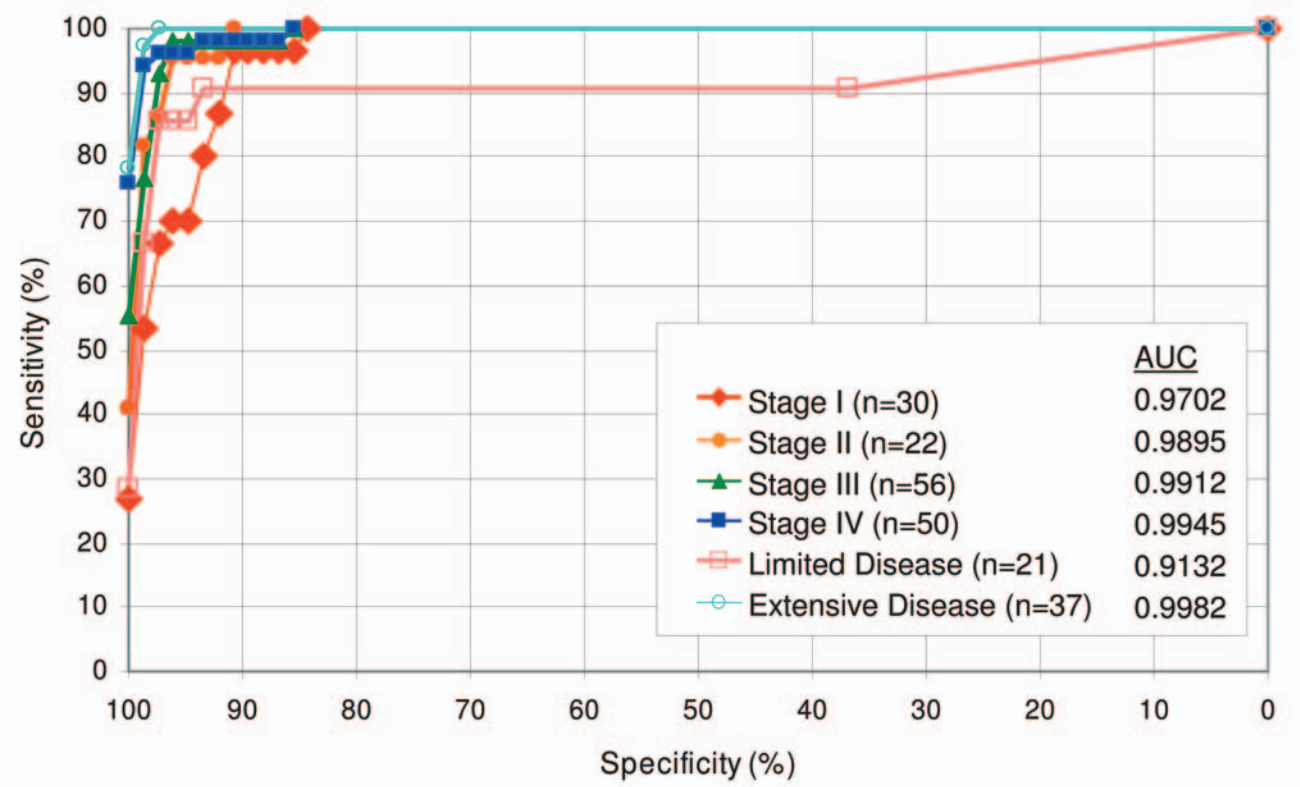

Figure 1. *Receiver operating characteristic (ROC) curves comparing the stage performance with the fuzzy classifier using the CYFRA 21-1, NSE and CRP markers in 216 lung cancer patients and in 76 asbestosis patients (AUC=area under curve).*

At 95% specificity, the fuzzy classifier reached a sensitivity of 93.1% in detection of lung cancers with CYFRA 21-1, NSE and CRP (Figure 1). With the fuzzy classifier, 94.8% of the small cell lung cancers, 91.8% of the squamous and 93.3% of the adenocarcinomas were detected.

The area under the ROC curve (AUC) for the non-small cell lung cancer were calculated and are given in Figure 1. The AUCs using the fuzzy classifier were higher than those calculated using single markers, especially for the early tumour stages: stage I (AUC=0.846), stage II (AUC=0.897), stage III (AUC=0.957), stage IV (AUC=0.966) and extensive disease status (AUC=0.978).

The sensitivities attained using the fuzzy classifier for non-small cell lung cancer and small cell lung cancer are given in Figure 2.

The best single marker was able to detect only 1/3 of the tumours. In progressive lung cancer, CYFRA 21-1 was the best single marker but only reached 88% sensitivity. In small cell lung cancers, NSE was the leading marker, with maximum sensitivity with extensive disease status (81.1%, Table II).

At 95% specificity, the differences in sensitivity were significant: at stage I (p=0.0018), at stage II (p=0.0053), at stage III (p=0.0111) and with extensive disease (p=0.0278). The greatest advantage of the fuzzy classifier was in the early tumour stages.

Application of the fuzzy classifier to an independent collective. In multidimensional calculation, the classification will be between 0 (=0%) and 1.0 (=100%). If the classifier is greater than 0.5 (≥50%), the case is said to be malignant (lung cancer). In contrast, classifications below 0.5 (<50%) are said to be benign.

The classifications of the 76 asbestosis patients (No. 4103 BKV) were calculated to be between 0.21 and 0.64 (Figure 3) and were ranked according to the score. In two asbestosis patients, the classification was 0.55 and 0.64 respectively favouring diagnosis of lung cancer. In the vast majority of the other patients (n=75) the classification was correctly negative. The rate of correct classification (specificity) was 97.4%.

The results of the classifier in lung cancer patients are presented in Figure 4. At stage I, the fuzzy classifier gives results between 0.42 and 0.57, at stage II between 0.45 and 0.81, at stage III between 0.26 and 0.89 and at stage IV between 0.43 and 1.0. N=3 patients at stage I (=50%), one patient at stage II (=50%), n=10 patients at stage III

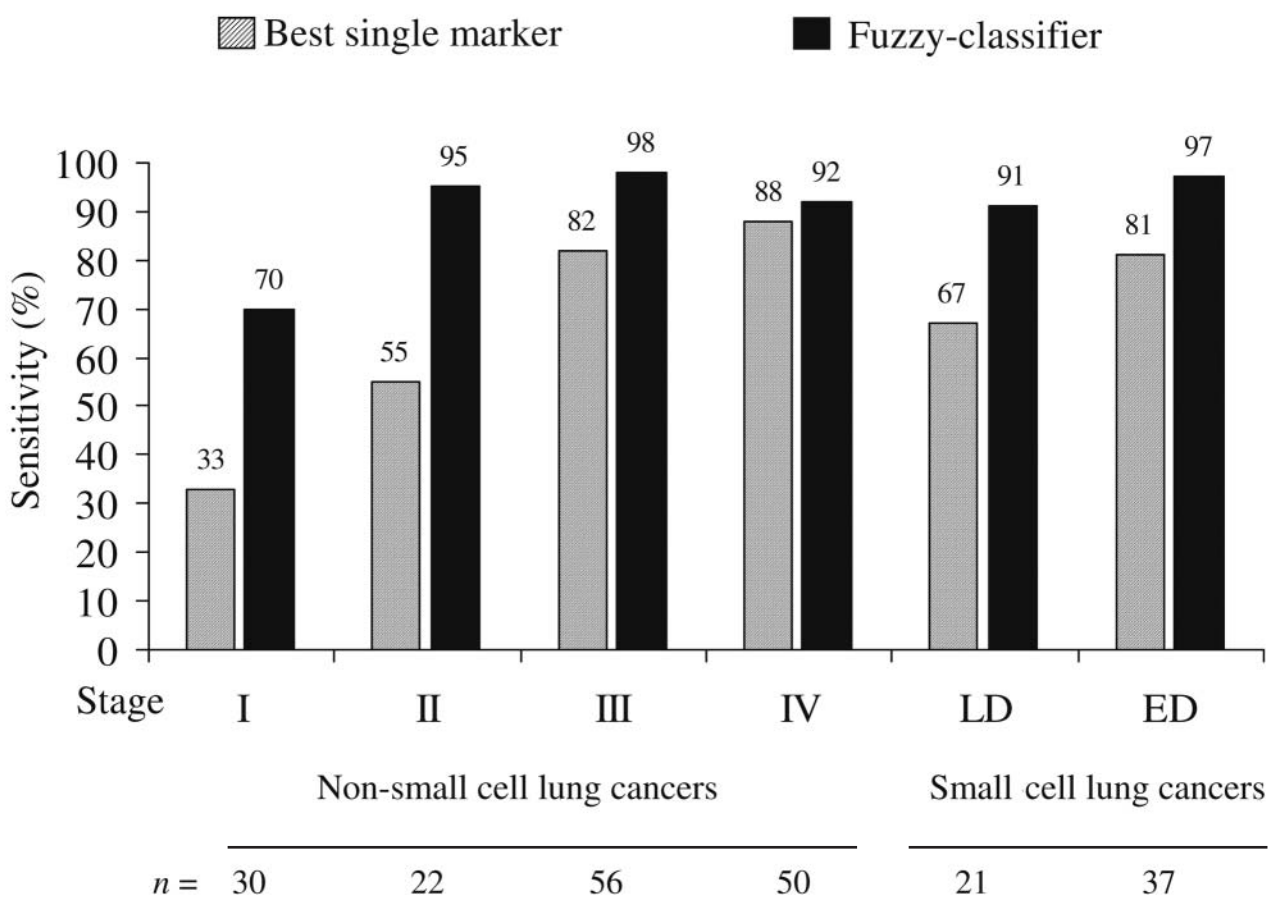

Figure 2. *Sensitivity of the best single marker and the fuzzy classifier, grouped by tumour stage at a specificity of 95%. LD: Limited disease; ED: extensive disease of small-cell lung cancer.*

(=76.9%) and n=14 patients at stage IV (=82.3%) were correctly classified with the diagnosis of lung cancer. The classifier was correct in all patients suffering from large cell lung cancers. The overall sensitivity for lung cancer detection in high-risk populations was 73.6%. The positive predictive value was 77.7% and the negative predictive value was 94.8%.

In asbestosis patients, the highest classification result (0.64) was observed in a patient suffering from severe lung asbestosis (ILO: s/t 2/2) with cor pulmonale and liver insufficiency. All other results were far below 0.60. Fuzzy classification above 0.65 is only seen in lung cancer patients. So classifier results greater than 0.65 lead to the diagnosis of lung cancer with certainly. In 19 out of the 38 lung cancer patients, classification was >0.65. In no lung cancer patient was the classification below 0.42.

To detect all lung cancer patients at stage I (sensitivity: 100%), fuzzy classification should be >0.42. But this will result in a higher rate of false-positive classifications in asbestosis patients: 7 out of the 76 asbestosis patients would then be said to have malignancies, relating to a specificity of 90.0%.

Generally the fuzzy classifier is able to detect a higher rate of the malignant diseases than the use of a single marker. With the fuzzy classifier and a marker panel, a reliable diagnostic tool for the detection of lung cancers in a high-risk population is available.

Discussion

Lung cancer is one of the most prominent causes of cancer death in Western industrialized countries, particular among the male population. Thus, a comprehensive primary diagnostic program is of great importance for successful therapy.

Patients with lung cancer often do not exhibit specific symptoms, particularly in the early stages. Dyspnea, cough and thoracic pain are considered as nonspecific early signs, hemoptysis may already indicate advanced stages of lung cancer. Relapsing infectious diseases of the respiratory system in combination with a smoking history or occupational exposures to lung carcinogens might be a hint for further

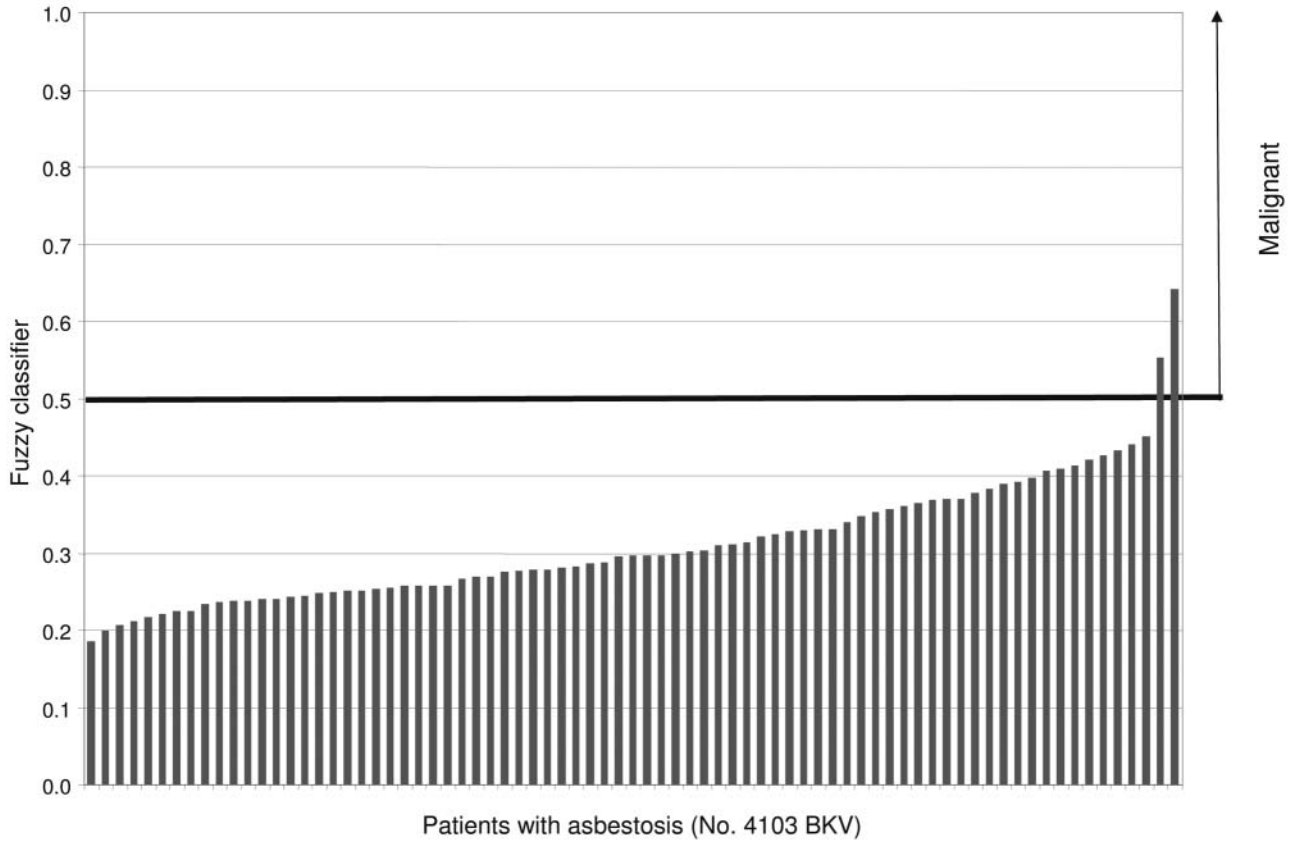

Figure 3. *Results of the fuzzy classifier in 76 asbestosis patients (No. 4103 BKV). If the classifier is greater than 0.5 (≥50%) it is said to be indicative of lung cancer.*

exams. Diagnostics for lung cancer include medical history and physical examination, clinical laboratory tests, chest radiography, computed tomography or magnetic resonance imaging of the chest, abdomen and the brain, bronchoscopy, sputum cytology, biopsy, bone scan, preoperative pulmonary function studies, and eventually positron emission tomography, bone marrow biopsy and thoracentesis (9-14).

Ideally, diagnostic procedures should be conducted rapidly, costs for staff and equipment should be kept low and moreover there should not be any complications for the patient. These are the reasons why examinations for tumour markers could be a promising tool, because these necessitate only a blood test (15). Because of their low sensitivity, tumour markers have not generally been recommended as a tool for early detection or screening for lung cancer (15, 16).

The sensitivities reported in the literature for single tumour markers are comparable with our results (17-20).

In order to improve the sensitivities of detection of primary lung cancers, combinations of the different tumour markers were utilised (21). By combining CEA, SCC and NSE the sensitivity for detecting lung cancer was improved to a maximum of 65% (22). In other reports, NSE and CYFRA 21-1 (23, 24) or CEA and CYFRA 21-1 (25), respectively, showed the highest sensitivity. The multiple marker panel proved to be more sensitive and specific than any single marker, but it was of limited value in discriminating malignant from benign lung diseases (26). The combination of NSE and CYFRA 21-1 achieved the highest sensitivity for patients with small cell lung cancers (22). With non-small cell lung cancers the combination of NSE and CYFRA 21-1 did not show any superiority (23). Combining CYFRA 21-1 (sensitivity: 57.7%) and CEA (sensitivity: 45.3%) increased the sensitivity for non-small cell lung cancers to a total of 75.4% – a gain in sensitivity of 17.7%. Unfortunately this was accompanied by a loss in specificity, down to 86.5% (25). Other studies also confirmed that marker panels were more sensitive than single marker examinations (20). As regards discrimination between malignant and non-malignant pulmonary diseases, a marker panel showed limited utility, because there was always a loss in specificity involved (21, 22, 25-27). Methods of logistical regression analysis only slightly improved the diagnostic capabilities (27, 28). Therefore marker combinations were not assessed as being useful tools for lung cancer screening

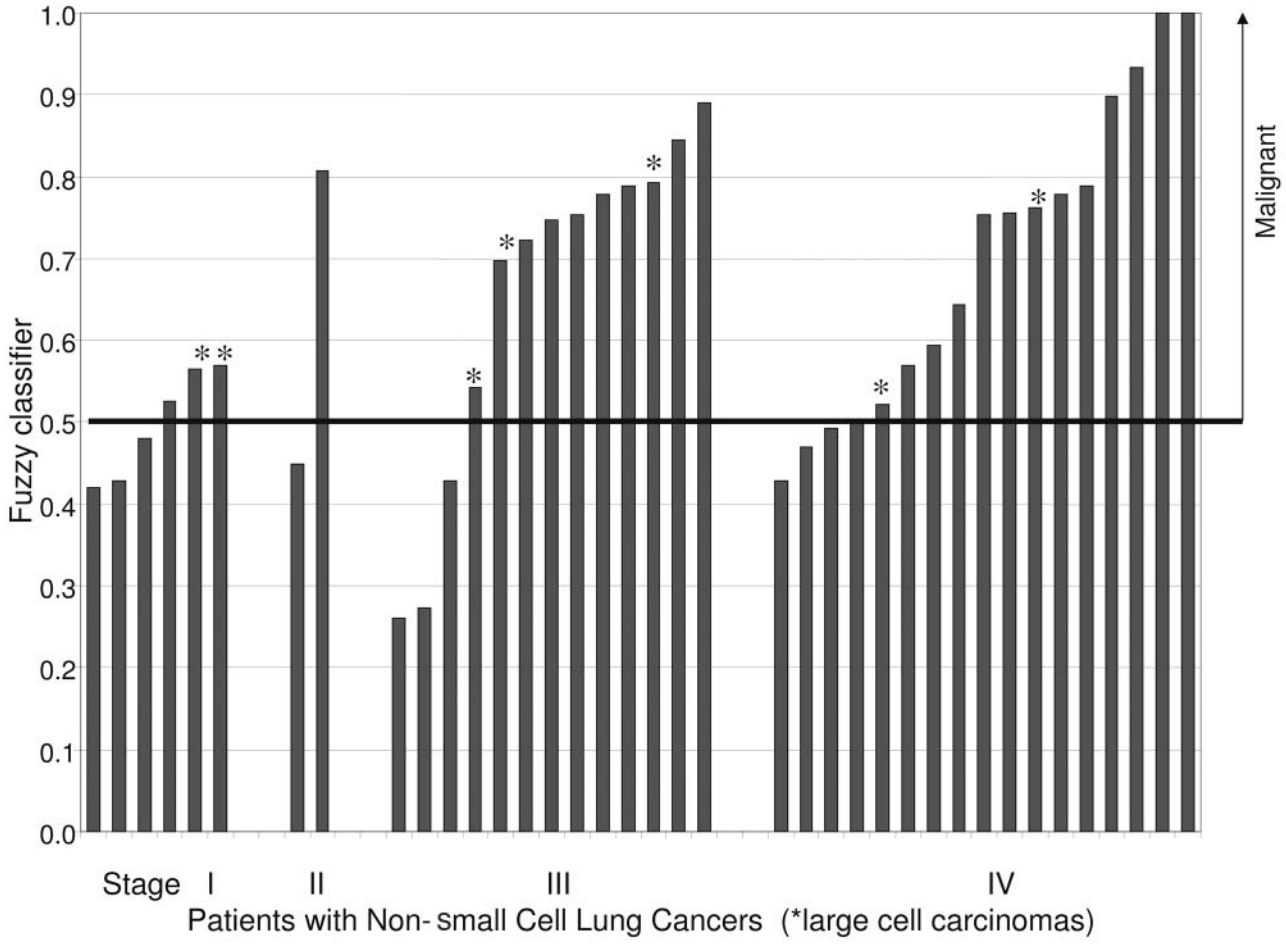

Figure 4. *Results of the fuzzy classifier 38 patients suffering from non-small cell lung cancer, grouped by tumour stage.*

(29). Even the powerful and widely used logistic regression and recursive partitioning methods for discrimination sometimes did not prove to be superior (27, 28). The results of the available serum bank studies indicated a need to develop a better individual marker or marker combination especially for achieving detection of localized lung cancers.

With a tumour marker panel and the fuzzy logic techniques, we were able to improve diagnostic procedures in the detection of lung cancer (8) and in gastro-intestinal cancers (29) at a high specificity of 95%. Fuzzy logic techniques were also effective in the early detection of recurrent diseases (30).

In this study we generated a test for lung cancer detection with respect to asbestosis patients at a high risk of developing lung cancers. The fuzzy techniques provide more information concerning the occurrence of lung cancer. In our study, we tested a panel of established tumour markers and CRP. Only use of a combination of the CYFRA 21-1, NSE and CRP markers led to an increase in sensitivity for all histological types (8).

The best single marker CYFRA 21-1 was able to detect only about 1/3 of the cancers at stage I. Significantly higher sensitivities were reached by fuzzy classifier for non-small cell lung cancers at stage I in 70%, and also at stage II in 95% (best single marker: 55%) (Figure 2).

To evaluate the fuzzy classifier, the application was examined on an independent collective consisting of 38 non-small cell lung cancers and 76 asbestosis patients. The fuzzy classifier showed correct negative classification in 75 of the 76 cancer free asbestosis patients, which confirmed a high specificity of 97.4%. The overall sensitivity for lung cancer detection in high-risk populations was 73.6%. All large cell carcinomas were detected. The positive predictive value was 77.7%. The negative predictive value reached 94.8%.

These characteristics may be of certain interest in monitoring localized and possibly curable lung cancers. Fuzzy classification is a non-invasive analytical method. We were able to demonstrate that this method is practicable also in high risk collectives. The confirmation of the data in other clinics will lead to a broader indication of the methods.

To improve early detection of (occupational) lung cancers computed tomography or sputum cytology were used in larger populations (9-13). A comparison with tumour marker analyses is possible regarding the sensitivity and specificity of the methods in lung cancer detection. The sensitivity in the computed tomography studies was reported as 100% (31), 90% (11) and in sputum analyses as 87.5% (12). The corresponding specificity in the computed tomography studies were reported as 90% (31), 79% (11) and the sputum cytology analyses as 92.7% (12). The specificity in our study reached up to 97.4%. With computed tomography it was possible to detect all peripheral squamous or adenocarcinoma of the lung, but there was a lack in detection of small cell lung cancers or central localised tumours (11, 31). Because of the rapid growth of small cell lung cancers, these histological tumour types were diagnosed in the interval between two intended computed tomography examinations (9). Thus computed tomography is a good method for the detection of peripheral slowly growing cancers. It is of great interest that a tumour marker panel with fuzzy technics are able to detect small cell lung cancers even in limited disease status with a sensitivity of 91%.

The fuzzy classifier with a marker panel provides a reliable diagnostic tool for the detection of lung cancer in a high-risk population.

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