

SCLC.^{8,14,17-20} The highest CEA sensitivity and serum concentrations are found in adenocarcinomas and large cell lung cancer, with the lowest values being seen in squamous tumours. CEA may provide prognostic information in NSCLC, particularly in lung adenocarcinomas.^{8,21-24} Likewise, as with other tumour markers, the utility of CEA in the early diagnosis of recurrence and in therapy monitoring has been clearly established.^{25,26}

Cytokeratin-19 Fragment

CYFRA 21-1 is a water-soluble cytokeratin-19 fragment. Histopathological studies have demonstrated that cytokeratin-19 is abundant in carcinomas of the lung.^{8,18-22,26,27} Abnormal serum levels (>3.3ng/ml) of this tumour marker have been found in several benign diseases, including liver pathologies and renal failure.⁷⁻⁸ Likewise, CYFRA 21-1 is increased in several malignancies other than lung cancer, including most gynaecological or gastrointestinal tumours, mesotheliomas and urological malignancies.^{8,2} However, the highest CYFRA 21-1 concentrations are found in lung cancer, mainly in NSCLC. On comparing different tumour markers, different authors reported that CYFRA 21-1 is the most sensitive tumour marker in lung cancer, with the highest concentrations in squamous tumours. The sensitivity of CYFRA ranges from 30% to 75% in NSCLC and from 20% to 60% in SCLC.²⁹ Since CYFRA 21-1 determines only fragments of cytokeratin-19, the test shows a higher specificity than tissue-polypeptide antigen (TPA), which determines a mixture of cytokeratins 8, 18 and 19.³⁰⁻³² The utility of CYFRA as an aid in the diagnosis, prognosis (mainly in NSCLC), early diagnosis of recurrence and therapy monitoring has been clearly indicated.^{8,19-22,25-28,30,33-35}

Squamous Cell Carcinoma Antigen

Squamous cell carcinoma antigen (SCC) is a 48kDa protein with strong homology to the serpin family of protease inhibitors. Its main clinical application is in squamous tumours of different origin: uterine cervix, oesophagus, head, neck and lung. The main sources of SCC false positive results are renal failure and dermatological disorders in which very high levels up to 30-40 times higher than the cut-off values may be found.^{16,21} The sensitivity of SCC in lung cancer ranges from 25% to 60% in NSCLC, but is rarely found in SCLC (<5%).^{7-8,17-18,21,27,32} The highest sensitivity of this tumour marker is observed in squamous tumours, but it is possible to find abnormal levels in other NSCLC. One of the most important utilities of SCC in lung cancer is its aid in establishing histological diagnosis.^{7,8,33,17-19,36,37} Several articles have reported the potential utility of

SCC as a prognostic factor in the early diagnosis of recurrence and in the follow-up of NSCLC, mainly in squamous tumours.^{8,36,37}

Clinical Utility of Tumour Markers

Diagnosis and Early Diagnosis

There are no reports on the utility of tumour markers in the early diagnosis of lung cancer in asymptomatic populations. The sensitivity obtained in the early stages of lung cancer clearly suggests that tumour markers are not useful for these purposes. However, tumour markers, alone or in combination, show considerable sensitivity in lung cancer.⁷⁻¹⁰ In the authors' experience, with the use of three tumour markers in NSCLC (CEA, CYFRA 21-1 and SCC) and in SCLC (ProGRP, NSE and CEA or CYFRA 21-1) it is possible to obtain a sensitivity higher than 80% in stage I-III patients or LD and 90% in stage IV or extensive disease (ED).^{7,8} It is known that some benign diseases may produce false positive results in this group of patients.^{7,8,16,21} However, when these pathologies are excluded, the specificity increases significantly (> 90%).⁷⁻¹⁰ In summary, there are no ideal tumour markers in lung cancer, but the sensitivity and specificity obtained with them is higher than that achieved with other tumour markers in other malignancies, such as prostate serum antigen (PSA) in prostate cancer. Tumour markers in lung cancer may be useful as an aid in patients suspected of having this malignancy.^{4,7-8,17-21,26,38,39}

Histological Diagnosis

The most important point in lung cancer is to distinguish NSCLC and SCLC. ProGRP and NSE are useful parameters to suggest SCLC.^{4-11,20} The higher the levels of NSE and/or ProGRP, the higher the probability of SCLC (see *Table 1*). The highest efficiency in the diagnosis of SCLC is obtained using both tumour markers simultaneously (see *Table 1*).^{4-12,33} There are no specific tumour markers for NSCLC, but some of them show a clear relationship with the histological type.^{20,21} Abnormal SCC serum levels suggest a probability higher than 95% of NSCLC (75% probability, squamous). Significantly higher concentrations of CEA and mucins (CA 15.3 and TAG) are found in adenocarcinomas.^{17,18,24,29,40} It is interesting to point out that it is very infrequent to find abnormal levels of some tumour markers such as CEA or CYFRA 21-1 with normal NSE or ProGRP. *Table 2* shows some combinations of tumour markers to help in the histological diagnosis. In summary, pathological evaluation is the gold standard in diagnosis, but the use of tumour markers may be of aid when biopsy is not available or in certain specific situations.

Prognostic Value

Numerous studies have been published regarding the utility of tumour markers in the prognosis in SCLC (CEA, CYFRA 21-1, NSE and ProGRP), as well as in NSCLC (CEA, CYFRA 21-1, NSE, SCC, CA 125).^{4-8,17-26,34,35,40,41} The authors' group compared the most important clinical and pathological prognostic factors and tumour markers in a prospective evaluation of 211 NSCLC patients and, on multivariate analysis, found that some clinical (stage, histology, Karnofsky Index, thoracic pain), therapeutical (surgery, chemotherapy) and biological (CA 125 or CEA, NSE or LDH and SCC) parameters were independent prognostic factors. However, as occurs with most prognostic factors, the clinical utility remains to be demonstrated. Moreover, serum tumour markers have potential advantages, as they are readily performed and can be standardised and quality controlled. NSE has also been suggested as a prognostic factor in NSCLC.^{22,33,42,43} The hypothesis to explain these results may be that NSE is a predictive factor, selecting the patients with neuroendocrine differentiation and with higher response to chemotherapy. The use of NSE and other parameters such as LDH or chromogranin A as predictive factors in SCLC has also been suggested.³⁻¹⁰

Early Diagnosis of Recurrence

Following curative resection, tumour markers, depending on the half-life of each tumour marker, may decrease, reaching normal values within a short period of time. Patients with an elevated plateau or with increased tumour marker levels in serial determinations are indicative of the presence of residual tumour cells.⁴⁴ However, to suspect recurrence, possible sources of false positive results such as in liver diseases or renal failure must be excluded. Tumour marker sensitivity, as well as the lead time, are related to the tumour marker used. Increasing serial SCC levels have been reported as the first sign of recurrence in 79% of squamous tumours.²⁶ The sensitivity of CYFRA 21-1 was found to be similar in NSCLC with a lead time of between two and 15 months.^{26,45,46} CEA and TPS have also been reported as relevant tumour markers for detecting recurrent disease.^{24,25,45-47} The simultaneous use of ProGRP and NSE is useful in the early diagnosis of recurrence in more than 80% of patients with SCLC recurrence.^{3-8,10,15}

Therapy Monitoring

The main interest of tumour marker evaluation in serum is in patient follow-up, mainly in those with abnormal values.^{7-15,21,28,34,40-43} Patients in remission

Table 1: Probability of SCLC According to Tumour Stage and NSE and/or ProGRP Serum Levels in 533 Patients with Lung Cancer

Criteria	SCLC/total lung cancer	LD/total stage I-III	ED/total stage IV
NSE >25ng/ml	98/135 (72.6%)	38/57 (66.7%)	60/78 (76.9%)
NSE >35ng/ml	76/79 (96.2%)	24/24 (100%)	52/55 (94.5%)
NSE >40ng/ml	68/70 (97.1%)	20/20 (100%)	48/50 (96%)
ProGRP >100pg/ml	95/113 (84.1%)	36/44 (81.8%)	59/69 (85.5%)
ProGRP >150pg/ml	87/95 (91.6%)	31/32 (96.8%)	56/63 (88.9%)
ProGRP >200pg/ml	82/86 (95.3%)	29/29 (100%)	53/57 (93%)
NSE >40ng/ml and/or ProGRP >200pg/ml	109/114 (95.6%)	40/40 (100%)	69/74 (93.2%)
NSE >35ng/ml and/or ProGRP >150pg/ml	116/126 (92%)	44/45 (97.8%)	72/81 (87.7%)

Table 2: Probability of NSCLC According to Tumour Extension and Tumour Markers in 384 Patients with Lung Cancer

Criteria	NSCLC/total lung cancer	Stage I-III/total lung cancer Mo	Stage IV/total lung cancer MI
SCC >2ng/ml	84/85 (98.8%)	47/48 (97.9%)	36/36 (100%)
CEA >5ng/ml, NSE <26ng/ml and ProGRP <50pg/ml	157/161 (97.5%)	70/71 (98.6%)	87/90 96.7%
CYFRA >3.3ng/ml and NSE <36ng/ml	223/231 (96.5%)	118/121 (97.5%)	105/110 (95.5%)
PROgrp <150pg/ml	76/80 (95%)	22/23 (95.7%)	54/57 (94.7%)
CA 125 >100U/ml and NSE <36ng/ml and ProGRP <150pg/ml			

usually have a substantial reduction in marker levels, while those with progressive disease generally have increased levels. Tumour markers in patients treated with chemotherapy should be determined before every chemotherapy course, since certain treatments may cause transient increases in serum marker levels. ProGRP is the most sensitive tumour marker in SCLC but the addition of NSE as complementary tumour marker, mainly in patients with LD, provides additional information.^{3-6,15}

The tumour marker used in NSCLC differs according to the histological type. CYFRA 21-1 is the most sensitive tumour marker in NSCLC and its use in therapy evaluation, mainly in the detection of progression, has been reported.^{26,32,43} In our experience, the best combination of tumour markers in disease monitoring is CYFRA 21-1 and CEA in all NSCLC, also including SCC in squamous tumours and one mucin (CA 15.3, TAG) in adenocarcinoma or SCLC.

Conclusion

Tumour markers are not habitually used in patients with lung cancer because the clinical advantages of their use are not clear. In this review it is shown that the sensitivity and specificity of tumour markers in lung cancer are high or are at least

similar to the values obtained in other malignancies. The use of tumour markers is closely related to treatment and lung cancer is habitually diagnosed late with short curative possibilities. Nevertheless, tumour markers may provide very helpful aid in diagnosis, prognosis, early diagnosis of recurrence and therapy monitoring. ■

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