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Perspectives and Commentaries

Prognostic and Diagnostic Usefulness of Serum Markers in Lung Cancer

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(A COMMENT ON: Müller T, Marshall RJ, Cooper EH, Watson DA, Walker DA, Mearns AJ. The role of serum tumor markers to aid selection of lung cancer patients for surgery and the assessment of prognosis. *Eur J Cancer Clin Oncol* 1985, **21**, 1461–1466.)

IN A PAPER published in the December 1985 issue of this Journal, T. Müller *et al.* report on the measurement of ten serum proteins, including the tumor marker CEA, acute phase reactants, and a variety of other serum components in patients with suspected or diagnosed lung cancer. They found none of these proteins specific enough to serve as marker for resectability or overall prognosis.

Presumably as part of the process of neoplastic change, lung cancer cells produce and release a variety of substances, some of which have been examined in the clinic in regard to classification of lung cancer, prediction of tumor behavior, and diagnosis.

In vitro studies have documented the production of enzymes (L-Dopa decarboxylase, histaminase, neuron specific enolase, creatine kinase BB), peptide hormones (ADH, ACTH, calcitonin, gastrin-releasing peptide), and other substances (CEA) by human lung cancer cell lines and tumor tissues. In tissue culture, the expression of enzymes and the production of peptide hormones has been associated with small cell carcinoma, but not with other types of lung cancer. It has been suggested, therefore, that examination of these markers *in vivo* would allow to distinguish between small cell and non-small cell carcinoma. Measurement of marker content in surgical specimens and sera of lung cancer patients has confirmed a prevalent expression in small cell carcinoma, however, there was a considerable overlap in marker expression between the two kinds of groups of lung cancer [1]. Thus, so far, no serum marker has yet been identified which would allow one to distinguish between small cell and non-small cell lung cancer with certainty.

The present clinical approach to patients with lung cancer is based on the histological classification. In non-small cell carcinoma, local treatment, mainly surgery, until now has remained the only modality with potential curative impact. The questions asked in clinical studies on tumor markers in non-small cell carcinoma thus have focused on prediction of resectability and survival. The problem is that there are no sensitive serum markers available for non-small cell carcinoma at present. CEA has remained the best characterized tumor marker associated with non-small cell lung cancer, but is found elevated in only a fraction of patients. In one study, CEA was elevated over 6 ng/ml in one third of 149 patients at diagnosis [2]. Elevated CEA at diagnosis might be of prognostic value. Elevated levels over 20 ng/ml before radical surgery has been associated with poor prognosis [3]. Also, persistently elevated values postoperatively have been shown to indicate residual disease and poor prognosis [4].

Small cell carcinoma cells are sensitive to chemotherapy and may release a number of hormone and enzyme markers, as well as CEA into the serum. The focus of clinical studies on tumor markers in this disease has been the monitoring of tumor response and the prediction of prognosis. Serum peptide hormones, including ACTH, ADH,

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and calcitonin were found to be elevated in 29, 33, and 64% of patients with small cell carcinoma, respectively, but were not correlated with stage of disease [5]. Also, these hormones with the possible exception of calcitonin, do not appear to be reliable markers of response [6, 7]. Of the enzymes produced by small cell carcinoma cells, neuron-specific enolase and creatine kinase have been identified as the most promising markers for possible monitoring of disease. Both correlate with stage of disease. Neuron-specific enolase was found elevated in 39% of patients with limited disease and 87% with extensive disease [8]. Preliminary results suggest a good correlation of this marker with response. Serum creatine kinase BB was found elevated in 1% of patients with limited disease and 41% with extensive disease [9]. The value of these two enzyme markers in evaluation of response and their prognostic value needs to be further defined. As in non-small cell carcinoma, CEA was found elevated over 6 ng/ml in one third of the patients [10]. As in another study [11] the level of CEA elevation was found to be related to stage of disease, but also, a strong correlation between complete response and absence of elevated CEA levels were documented.

Despite these advances and recognition of potential useful tumor markers in patients with small cell carcinoma, the question about the role of these serum markers in the clinical decision making and treatment remains unanswered. While some of these serum markers might be a useful adjunct for monitoring response to therapy, major problems in lung cancer such as diagnosis and staging, or, most importantly an improvement of the therapy are not addressed.

Where do we go from here? A possibility would be to go back to the laboratory. By learning about the mechanism responsible for increased production of markers such as gastrin-releasing peptide or other hormones we might learn new ways to control the growth of tumors [12]. Some of these hormones might act in an autocrine fashion on the tumor cells and ways to inhibit this action can be explored. Antibodies to such hormones or their receptors can block such autocrine stimulation and thus may inhibit tumor growth *in vivo* [13]. In addition, it is necessary to identify new markers, such as growth factors or membrane structures, preferentially associated with lung cancer cells. Membrane structures such as GP_{90-135} recognized by LAM8 antibody which is specifically expressed in small cell carcinoma, but not in normal epithelia, might serve as tumor marker not only useful for diagnosis, but also as target for tumor-directed therapy [14]. *In vivo* models have already demonstrated the feasibility of such an approach in adenocarcinoma of the lung [15].

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