

Letter to Editor

Further Comments on *Prognostic Factors of Small-Cell Lung Cancer in Okayama Lung Cancer Study Group Trials*. How About a More Precise Laboratory Technique?

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Key words: preanalytical phase, analytical phase, laboratory expertise, pathology expertise

Most members of the scientific and/or medical community agree that a refinement of the current staging system is necessary for small-cell lung cancer (SCLC) (1-8). I was therefore interested in the article entitled *Prognostic Factors of Small-Cell Lung Cancer in Okayama Lung Cancer Study Group Trials* by Tamura *et al.*, recently published in *Acta Med Okayama* (7). In this paper, in a population of 253 SCLC patients, Tamura *et al.* (7) observe that lactate dehydrogenase (LDH) and albumin concentrations (in serum or in plasma?) have a prognostic significance independent from the usual radio-clinical parameters (1, 3). Although it is obviously an interesting paper, I think that it needs to be examined.

First, I would like to stress that the independent prognostic significance of, not only albumin, but also LDH, is not as clear as might be inferred from the reading of Tamura *et al.*'s article (7). I have reviewed the biomedical literature regarding the independent prognostic significance of laboratory parameters in SCLC (5, 6). I used the method recommended by the International Federation of Clinical Chemistry (IFCC) committee on systematic reviewing in laboratory medicine (9). In order to select studies as close as possible to the one performed by Tamura *et al.* (7), I took into account only those studies in which the prognostic significance of LDH and/or albumin were evaluated through the use of Cox's models (10) in association with recursive partitioning and amalgamation algorithms (RECPAM) analysis (7, 8). To the best of my knowledge, according to much selection

criteria, only seven studies can thus be found in the biomedical literature published over the last 30 years (7, 8, 11-15). In each study reviewed, I chose to consider a parameter as independently significant only if all of the following parameters had been included in the multivariate statistical analysis: patients' performance status, weight loss, age and gender, histology, stage and extent of the disease. In Table 1, the column labelled 'Uncertain significance' indicates parameters which were found significant by authors who had neglected to include at least one of the afore-mentioned radio-clinical and histological parameters in their multivariate analysis.

We can thus see in Table 1 that, of the two laboratory parameters, LDH is the more commonly acknowledged as having prognostic significance. Indeed, the only three studies in Table 1 which seem to reject the prognostic significance of LDH in SCLC are questionable: in De Wet *et al.*'s study, the LDH results were missing in 14 of their 144 patients (11); in Sagman *et al.*'s study, LDH had no prognostic significance with the Cox's model but it had prognostic significance with the RECPAM analysis (15); and in Tamura *et al.*'s study (7), it is just the opposite (Table 1). In the same way, concerning albumin, the results of two of the three studies in Table 1, including Tamura *et al.*'s study (7), suggest that albumin has independent prognostic value in patients suffering from extensive disease but not in patients suffering from limited disease. However, the low number of studies that used Cox's models in combination with RECPAM analysis suggests that further studies using this approach are necessary to more clearly demonstrate

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Table 1 Prognostic significance of plasma or serum concentrations of lactate dehydrogenase (LDH), and albumin in small-cell lung cancer, according to the studies in which Cox's models were used in combination with recursive partitioning and amalgamation algorithms analysis

Parameter	Studies (number of patients included in each study ^a)		
	Not significant	Uncertain significance	Significant
LDH	7(253-ELD), 11(144-ELD), 15(614-ED-LD)	8(2580-ED-LD), 12(286-ELD), 13(1651-ELD), 14(1570-ELD)	7(253-ELD), 15(614-ED-LD)
Albumin	7(253-ELD), 11(144-ELD), 12(286-ELD)		7(124-ED), 11(83-ED)

^a : ED: Extensive-disease patients; LD: Limited-disease patients; ELD: The results observed in LD were not distinguished from the results observed in ED.

that LDH and perhaps albumin have independent prognostic significance in SCLC (Table 1). Incidentally, it might be interesting if such studies also included neuron-specific enolase or sodium in their statistical analyses (6, 16).

More importantly, I would like to express again (5) my serious concern about the fact that not only the study of Tamura *et al.* (7), but also most clinical studies cited in Table 1, as well as many others (2, 5, 6), omitted detailing the analytical and/or preanalytical methodologies used to determine the laboratory parameters included in their statistical analyses. Some authors even specify that laboratory measurements were performed without their having informed the laboratories of their particular scientific purpose. One must therefore seriously question the scientific validity of most of these clinical studies, notably because it is thus impossible for an independent team to try to precisely reproduce their results - a basic principle of good science. I would like to illustrate such potential analytical and/or preanalytical bias in some of these clinical studies with the example of LDH which seems to be the most promising of the two laboratory parameters in Table 1. In this purpose, two preliminary definitions must be recalled: a) preanalytical methodology = materials and methods used for blood sampling, methods and duration of samples' transport to (and storage in) the laboratory before the measurements; b) analytical methodology = measurement technology used in the laboratory.

Indeed LDH measurements are highly influenced by the presence or absence of hemolysis in blood samples (17) and are therefore highly influenced by the methodology used for blood sampling (18, 19). Thus, most doctors know that increased LDH levels without any suitable explanation are probably due to *in vitro* hemolysis. In

contrast, most (if not all) doctors find it difficult to distinguish the blood samples from a) a small-cell lung cancer patient with increased LDH levels due to *in vitro* hemolysis and b) a small-cell lung cancer patient with increased LDH levels due to small-cell lung cancer. Can the possibility be excluded, then, that some of the patients in some of the previously mentioned studies (as is the case in our hospital, particularly for some patients having a poor performance status and whose blood samples may be taken through infusion catheters) had their blood samples taken using material and/or methodology different from the other patients? Have all the blood samples in those studies been assessed for the presence or absence of hemolysis, in order to eliminate the LDH results obtained in hemolyzed samples? Furthermore, inappropriate transport to and/or storage of samples in the laboratory may cause some laboratory parameters (in particular LDH) to increase and/or decrease (18, 20). Transport and storage conditions were almost never indicated in the various studies (5). In the same way, the distinction between plasma and serum was not always made in the various studies (5). Finally, one may think that the analytical bias towards LDH is less likely to occur than the above-mentioned preanalytical bias, unless the measurements are performed in different laboratories using different analytical procedures (21). It must nevertheless be stressed that such is likely to be the case in multicenter studies (5, 8).

My comments thus tend not only to confirm that systematic reviewing in laboratory medicine represents a new challenge for laboratory doctors (9) but also to suggest that a higher degree of multidisciplinary of the teams conducting such clinical studies (including not only clinicians, statisticians and pathologists, but also technicians, nurses...) might be necessary in the future (5, 6).

How about a more precise technique description (and eventually discussion) in medical publications, in particular for the preanalytical phase (5, 9, 18)?

Acknowledgments. The author wishes to express thanks to Jean-Christophe Charet, MD (Respiratory Diseases Department, Hôpital Général, Rodez, France) for his critical readings of this manuscript.

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Received September 9, 1998; accepted October 30, 1998.