Eur J Cancer Clin Oncol, Vol. 22, No. 7, pp. 831–835, 1986.
Printed in Great Britain.

0277–5379/86$3.00+0.00
Pergamon Journals Ltd.

Serum Ferritin Levels in Small Cell Lung Cancer

ROBERT COX,* OSCAR H. GYDE and MICHAEL J. LEYLAND
Department of Haematology, East Birmingham Hospital, Birmingham, B9 5ST, U.K.

Abstract—*Serum ferritin levels were measured before treatment, using an immunoradiometric method, in 39 patients with small cell lung cancer. In 11 patients serial estimations were also made.*

The median serum ferritin level for male patients was 660 μg/l (range 13–1329) and for females 306 (range 134–5300), the normal range being 32–501. This increase is significant ($P < 0.001$). Serum ferritin levels were not related to metastatic, haematological or iron status. Serial ferritin levels did not reflect the clinical course of the disease.

Patients with a pre-treatment serum ferritin of < 600 μg/l had a significant prolongation of median survival compared to those with an initial serum ferritin of > 600 μg/l ($P < 0.02$).

Serum ferritin levels are not of value in staging small cell lung cancer nor in monitoring its progress. However, the initial serum ferritin is of prognostic significance.

INTRODUCTION

FERRITINS are a group of proteins with important functions in iron metabolism and storage [1], and raised levels have been reported in conditions of iron overload [2,3]. Elevated serum levels have also been found in patients with a variety of tumours [4,5] and it has been suggested that serum ferritin estimations might be useful as a guide to management in lung cancer [6].

In this study an immunoradiometric assay has been used to measure ferritin levels in patients with small cell lung cancer before treatment. The results have been correlated with tumour stage and the survival and haematological status of the patients. In a small number of patients serial ferritin levels were measured to determine whether these would reflect the clinical course of the disease.

PATIENTS AND METHODS

Serum for ferritin estimations was obtained prior to treatment from 39 patients in whom a histological diagnosis of small cell lung cancer had been made. Twenty-seven patients were male and 12 female. The mean age was 59 yr (range 41–75). Twenty patients (50%) were found to have metastases; extra-thoracic lymph nodes (11 patients) and bone marrow (six patients) being common sites.

All but five patients were assessed (at the time blood was taken for serum ferritin) for Performance Status (PS) according to the following scheme (Eastern Co-operative Oncology Group):

(1) Fully active; no restriction on pre-disease performance
(2) Restricted strenuous activity, ambulatory, can carry out light work
(3) Ambulatory, capable of all self care, capable of light work up to 50% of working hours
(4) Limited self care, confined to bed or chair more than 50% of the day
(5) Completely disabled, incapable of self care, totally confined to bed or chair.

The survival times for these 34 patients were documented.

Eleven patients also had serial ferritin estimations made beginning 6 weeks after the start of any treatment, usually chemotherapy, at a further 6 weeks and then at 12 week intervals. Six of the 11 patients subsequently developed disease progression. The mean follow up period for these 11 patients was 52 weeks (range 12–87).

Ferritin estimations were made using an immuno-radiometric technique previously described [7]. Because the distribution of ferritin levels is approximately normal when expressed as $\log_{10}$ of the actual value, comparisons between groups have been made using statistical tests on $\log_{10}$ transformed results. For the same reason median rather than mean values have been quoted.

Controls were 160 patients (101 male 59 female) who had previously attended the outpatient department and in whom no significant pathology was found. They had normal full blood counts, serum irons and serum transferrin and no evidence of iron overload. The median serum ferritin level for this group was 112 μg/l and the range (log mean ± 2 S.D.) 32–501 μg/l.

Accepted 10 December 1985.
*To whom correspondence should be addressed at: St. Paul's Hospital, Endell Street, London WC2H 9AE, U.K.

All patients underwent routine haematological and biochemical assessment. Estimations of bone marrow iron stores were made on a scale of 0 (no stainable iron at all) to 4 (iron stores markedly increased) in all but one patient.

RESULTS

The median serum ferritin level was 660 μg/l for male patients (range 13–3329) and 306 μg/l for females (range 134–5300), this difference is not significant. The frequency distribution of results is shown in Fig. 1 and it can be seen that ferritin levels were considerably elevated in patients with small cell lung cancer compared with controls ($P < 0.001$). There was no significant difference between serum ferritin levels in patients with detectable metastases (median 668 μg/l range 102–5300) and those without (median 435 μg/l range 13–2926) Fig. 2.

There was no correlation between serum ferritin levels and Hb, Fig. 3, serum iron Fig. 4 or bone marrow iron grade Fig. 5, apart from in one patient with iron deficiency anaemia (Hb 10.7 g/dl, MCV 74 fl serum iron 5.5 μmol/l, serum total iron binding capacity 81 μmol/l and no stainable iron in the bone marrow) who had a serum ferritin of 13 μg/l.

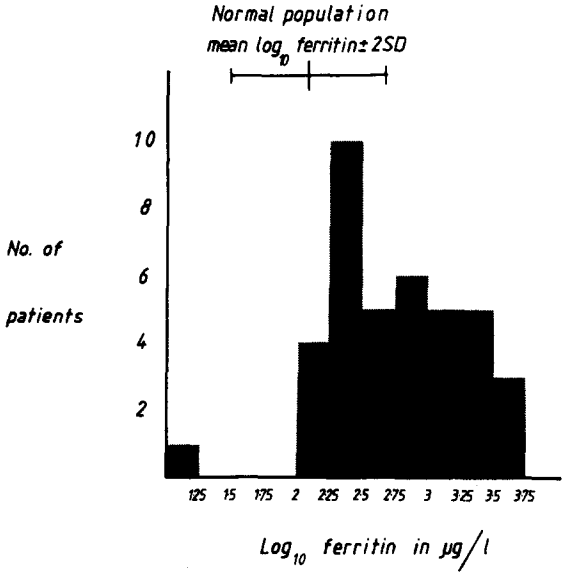

Fig. 1. Distribution of serum ferritin levels, expressed as $\log_{10}$ *of actual concentration in* μg/l *in 39 patients. Range for normal population also indicated.*

Neither was there any obvious relationship between serial ferritin levels and the clinical course of the patient. For the six patients who suffered disease progression the median pre-treatment serum ferritin was 457 g/l compared with 706 μg/l at the time of disease progression, it having increased in three and fallen in three. For the five patients who did not develop disease progression ferritin levels showed no appreciable change in two whilst in the others there was a small rise, a small fall or a gentle fluctuation.

Serum ferritin levels were found to have a predictive value for survival. The 17 patients with a pre-treatment serum ferritin < 600 μg/l had a median survival of 354 days which was significantly greater than for the 17 patients who had serum ferritins > 600 μg/l in whom the median survival was 164 days ($P < 0.02$ log rank test), Fig. 6. These two groups were also compared for the incidence of metastases and for PS (Table 1). Whilst there was no difference in metastatic status significantly more patients with a serum ferritin < 600 μg/l had high PS (ECOG grade 1–3) than did those with a serum ferritin of > 600 μg/l. ($P < 0.02$ $x^2 = 5.4$ with Yates correction for small numbers).

DISCUSSION

In this study serum ferritin levels have been shown to bear no direct relationship to the metastatic status of patients with small cell lung cancer; neither did serial ferritin estimations correspond to the clinical course of the disease in the patients in whom such measurements were made. However, the initial pre-treatment serum ferritin was of prognostic significance. Whilst serum ferri-

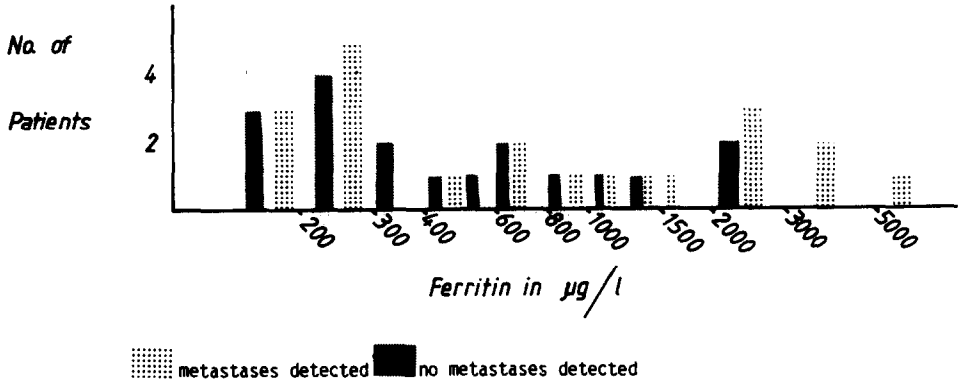

Fig. 2. Serum ferritin levels in patients according to metastatic status. Stippled columns — patients with metastases; diagonally filled columns — patients without metastases. Ferritin in μg/l.

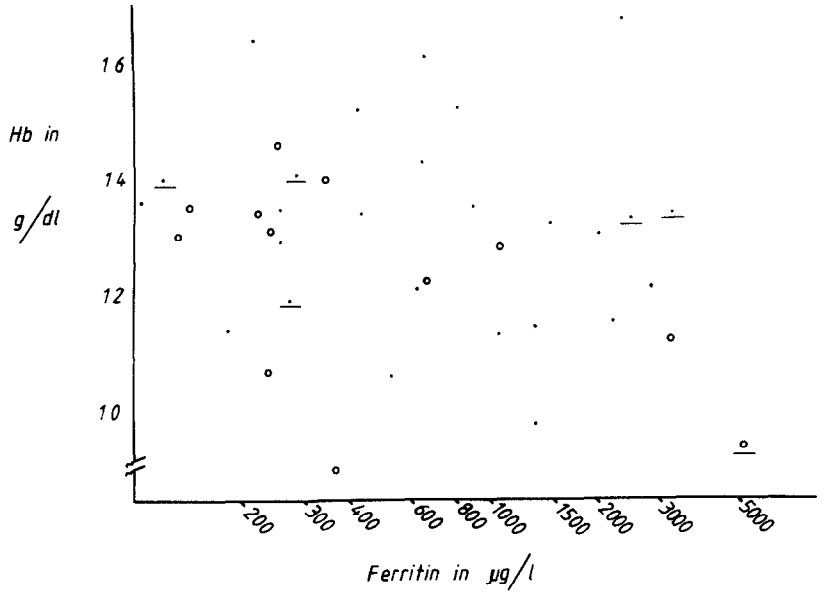

Fig. 3. Relationship between serum ferritin (µg/l) *and Hb* (g/dl) · *male*, ○ *female — infiltrated bone marrow.*

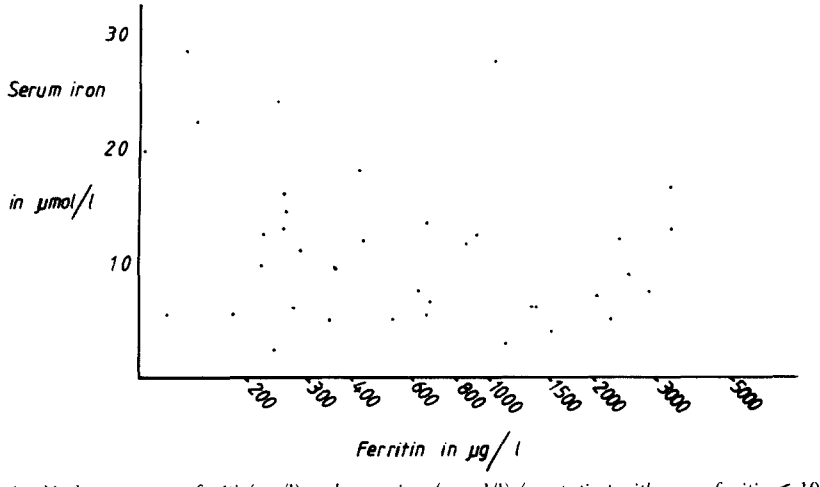

Fig. 4. Relationship between serum ferritin(µg/l) *and serum iron* (µmol/l) (*one patient with serum ferritin* < 100 µg/l *not shown*).

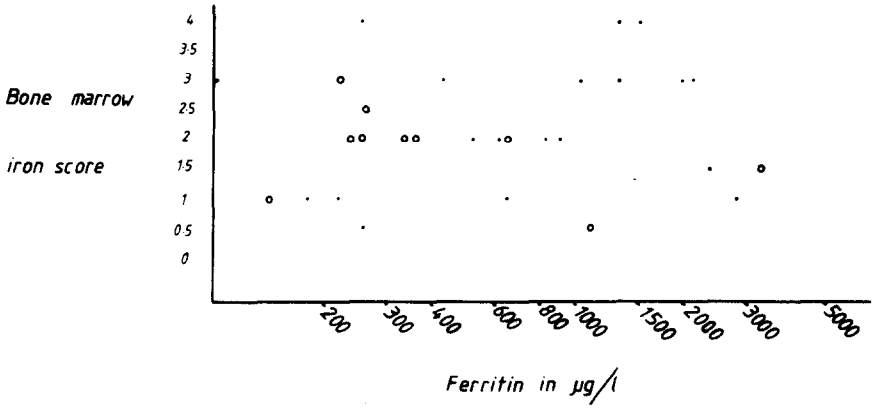

Fig. 5 Relationship between serum feritin (µg/l) *and bone marrow iron grade* (*expressed as* 0, *no iron to* 4 *markedly increased*) *in* 29 *patients.*

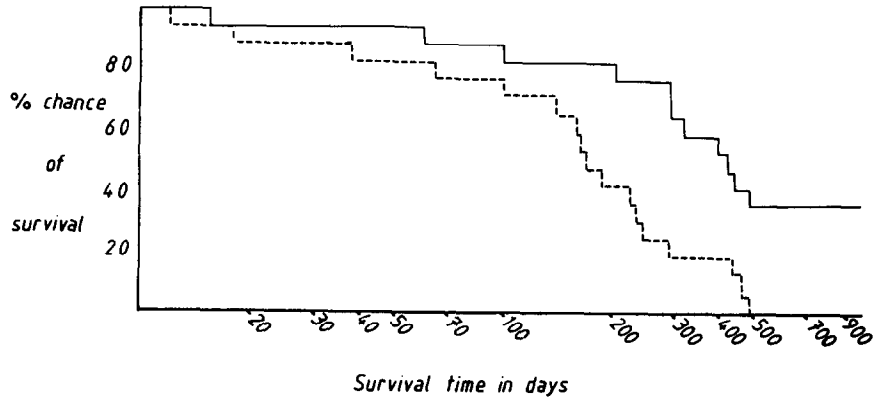

Fig. 6. Difference in survival for 17 patients with a pretreatment serum ferritin of < 600 g/l — solid line, compared with 17 patients with a pretreatment serum ferritin of > 600 g/l — broken line.

Table 1. Comparisons for metastatic status and performance status according to serum ferritin levels

	Serum ferritin	
	< 600 μg/l (n = 17)	> 600 μg/l (n = 17)
Metastases present	8	9
Performance status		
1–3	16	9

tins were not proportional to parameters of haematological or iron status they were related to performance status.

The results found in the present study are, to a certain extent, contradictory. Much of the interest in raised serum ferritin levels in malignant disease is based on the hypothesis that the degree of ferritinaemia is related quantitatively to tumour bulk. If this is so, then serum ferritin levels might be expected to be higher in patients with metastases compared to those without; to rise with progressive tumour growth and to fall during remission. Similarly, a high pre-treatment ferritin level might be expected to predict a poorer prognosis than a low initial ferritin because in small cell lung cancer, detectable metastases, implying a relatively large tumour bulk, confer reduced survival compared with undetectable metastases implying a smaller tumour burden.

Previous work has shown that serum ferritin levels are proportional to tumour stage, not only in lung cancer [6] but in Hodgkins' disease [5] and probably in breast cancer [8]. However, in the present study, although the median serum ferritin level (668 μg/l) was higher for patients with detectable metastases than for those without (435 μg/l) this difference is not significant. This failure to achieve a clear distinction between patients with and without metastases may, in part, be due to the high metastatic potential of small cell cancer. It is known that less than 5% of patients are cured by surgery alone [9], thus 95% of patients must have metastases at presentation, yet current routinely used techniques detect spread in only about half of all patients [10]. This raises the possibility that these undetected metastases could be the source of ferritin. Again this argument is based on the hypothesis that the ferritin is derived quantitatively from tumour tissue. However, there is data indicating that there is no difference between the amount of ferritin in normal lung and cancerous lung [11]. Hence the raised ferritin levels may be secondary to the presence of tumour but not actually produced by it.

Serial ferritin levels were not of value in predicting the course of the disease. This is perhaps not surprising in view of their lack of relationship to metastatic status. Others have found serial ferritin levels to be useless in the prediction of the course of acute lymphatic leukaemia [12]. On the other hand Gropp *et al.* [6] found a rise in serial ferritin coincided with progressive tumour growth in the small number of patients they studied.

The pre-treatment serum ferritin level was found to be of prognostic significance in this study. This may be related to the influence of PS on survival. Significantly more patients with a serum ferritin of < 600 μg/l had high PS (grade 1–3) than those with serum ferritins >600 μg/l. Performance status is known to be a prognostic variable in small cell lung cancer [10]. Further work is required to determine the precise relationship between serum ferritin and PS, not only in small cell lung cancer, but in other cancers and furthermore, to determine whether they are independent or related prognostic variables. Whilst others have found serum ferritin levels to predict early recurrence in breast cancer [13], this observation does not appear to have been made in patients with lung cancer. If it is confirmed it may be of importance in the design and analysis of

future studies of survival amongst patients with small cell lung cancer.

Ferritin is known to be closely related to iron storage [14] although the raised levels of ferritin encountered in inflammatory and neoplastic diseases are usually acidic isoferritins and different in type to those elevated in disorders of iron storage [4]. It is thus perhaps not surprising that serum ferritin levels were unrelated to other parameters of iron status. Some have obtained similar results [12], but others have found serum ferritin to be proportional to bone marrow iron stores [5].

Possibly the marked rise in serum levels of ferritin due to the underlying malignancy swamped any small rise associated with the increase in marrow storage iron and thus obscured the normal relationship between serum ferritin and marrow iron. A further factor tending to elevate serum ferritin levels is the presence of inflammation secondary to the tumour. No attempt was made to quantify the degree of inflammatory changes in the patients studied. However, it is known that inflammatory disease itself can cause a rise in serum ferritin levels [15].

There is no doubt that serum ferritin levels are considerably elevated in patients with small cell lung cancer and may well be of prognostic significance. However, much further work is required for a complete understanding of the manner in which serum ferritin levels vary with the severity of the underlying disease process in small cell lung cancer.

REFERENCES

1. Crichton RR. Ferritin: structure, synthesis and function. *N Engl J Med* 1971, **284**, 1413–1422.
2. Prieto J, Barry M, Sherlock S. Serum ferritin in patients with iron overload and with acute and chronic liver disease. *Gastroenterology* 1975, **68**, 525–533.
3. Hoffbrand AV, Gorman A, Laulicht M, Garidi M, Economidou J, Georgipoulou P, Hossain MAM, Flynn DM. Improvement in iron status and liver function in patients with transfusional iron overload with long term subcutaneous desferrioxamine. *Lancet* 1979, **i**, 947–949.
4. Marcus DM, Zinberg N. Measurement of serum ferritin by radio-immunoassay: results in normal individuals and patients with breast cancer. *J Nat Cancer Inst* 1975, **55**, 791–795.
5. Jakobsen E, Engeset A, Sandstad B, Aas M. Serum ferritin and bone marrow haemosderin in patients with malignancies and in healthy controls. *Scand J Haematol* 1982, **28**, 261–271.
6. Gropp C, Lehmann FG, Bauer HW, Haveman K. Carcinoembryonic antigen, α1 fetoprotein, ferritin and α2 pregnancy associated glycoprotein in the serum of lung cancer patients and its demonstration in lung tumour tissues. *Oncology* 1977, **54**, 267–272.
7. Leyland MJ, Ganguli PC, Blower D, Delamore IW. Immunoradiometric assay for ferritin in human serum. *Scand J Haematol* 1975, **14**, 385–392.
8. Coombes RC, Gazet JC, Sloane JP, Powles TJ, Ford HT, Laurence DJR, Neville AM. Biochemical markers in human breast cancer. *Lancet* 1977, **1**, 132–134.
9. Arnold MA, Williams CJ. Small cell lung cancer: a curable disease. *Br J Dis Chest* 1979, **73**, 327–348.
10. Hansen HH, Dombernowsky P, Hirsch FR. Staging procedures and prognostic features in small cell anaplastic bronchogenic carcinoma. *Semin Oncol* 1978, **5**, 280–286.
11. Linder MC, Wright K, Madara J. Concentration, structure and iron saturation of ferritins from normal human lung and lung tumours with graded histopathology. *Enzyme* 1982, **27**, 189–198.
12. Parry DH, Ricketts C, Jacobs A. Serum ferritin during unmaintained remission in acute lymphoblastic leukaemia. *Br Med J* 1978, **ii**, 1341–1342.
13. Jacobs A, Jones B, Ricketts C, Bulbrook RD, Wang DY. Serum ferritin concentration in early breast cancer. *Br J Cancer* 1976, **34**, 286–290.
14. Walters GO, Miller FM, Worwood M. Serum ferritin concentration and iron stores in normal subjects. *J Clin Pathol* 1973, **26**, 770–772.
15. Bentley DP, Williams P. Serum ferritin concentration as an index of storage iron in rheumatoid arthritis. *J Clin Pathol* 1974, **27**, 786–788.