

## Short paper

## Gastrin levels in serum and bronchoalveolar lavage fluid of patients with lung cancer: comparison with patients with chronic obstructive pulmonary disease

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### Abstract

**Background** – The gastrin gene is known to be expressed in all classes of bronchogenic carcinomas. Furthermore, high levels of gastrin have been reported in both the bronchoalveolar lavage (BAL) fluid and serum of patients with lung cancer. Based on these preliminary data a study was conducted to evaluate the usefulness of gastrin measurements in the diagnosis and staging of lung cancer.

**Methods** – Thirty five patients with lung cancer (26 non-small cell (NSCLC) and nine small cell (SCLC)) and 25 patients with chronic obstructive pulmonary disease underwent fiberoptic bronchoscopy and BAL. Gastrin levels were determined in both BAL fluid and the serum and compared with each other and with staging.

**Results** – No difference was found between the gastrin levels in the BAL fluid or serum of the study groups. There was no correlation with the stage in NSCLC and no correlation was found between the gastrin levels in the serum and the BAL fluid. A significant difference was seen in gastrin levels in BAL fluid between extensive and limited SCLC ( $p < 0.05$ ).

**Conclusion** – There is no evidence of clinical usefulness for gastrin measurements in lung cancer.

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**Keywords:** lung neoplasms, gastrin, bronchoalveolar lavage.

Recent data suggest that there is an increase in gastrin gene expression in all classes of bronchogenic carcinomas.<sup>1</sup> Studies also indicate that gastrin stimulates mobilisation of calcium ions and clonal growth in small cell lung cancer (SCLC) cells.<sup>2</sup> There has also been a report of increased gastrin levels in serum and bronchoalveolar lavage (BAL) fluid of patients with lung cancer.<sup>3</sup> To test the hypothesis that gastrin measurements might have clinical value in lung cancer we examined gastrin levels in both the serum and BAL fluid of patients with lung

cancer and compared them with a group of patients with smoking related chronic obstructive pulmonary disease (COPD).

### Methods

#### SUBJECTS

Sixty patients were enrolled in the study, 35 with newly diagnosed lung cancer (26 non-small cell lung cancer (NSCLC) and nine small cell lung cancer (SCLC)) of median age 67 years (range 49–76) and a male:female ratio of 6:1, and 25 with COPD of median age 63 (range 41–77) and a male:female ratio of 5:1. Thirty two of the 35 patients with lung cancer were heavy smokers with a mean of 25 pack-years and three were non-smokers. All of the subjects with COPD were heavy smokers with a mean of 24 pack-years. Fiberoptic bronchoscopy was performed in these patients for an episode of pneumonia or infectious bronchitis. The diagnosis of pneumonia or infectious bronchitis was made by response to antibiotic therapy, detection of responsible bacteria on bronchial aspiration, and a 1.4 year follow up showing no cancer. There was no difference between the two groups with regard to age and smoking.

#### STUDY DESIGN

Bronchoalveolar lavage was performed according to the European BAL task group norms.<sup>4</sup> The tip of the fiberoptic bronchoscope was wedged into the affected bronchus of patients with lung cancer and into the lingula or middle lobe of the patients with COPD. Subsequently, 150 ml of 0.9% sterile saline serum was instilled in three aliquots of 50 ml and the fluid was recovered by gentle suction. The total aspirated volume was transferred to the laboratory where the fluid was centrifuged at 500g for 10 minutes to separate the cellular components from the supernatant. Gastrin measurements on the BAL fluid supernatant and serum obtained on the same day were performed based on the immunoradiometric assay technique using a commercial kit (CIS Bio International, Gif-sur-Yvette, France) ac-

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cording to the manufacturer's instructions. Lactate dehydrogenase (LDH) levels were determined by the photometric method using a commercial kit (Merck, Darmstadt, Germany). Results of gastrin levels in BAL fluid were expressed as pg/100 international units (IU) LDH. This was calculated as individual ratio values – that is, the absolute gastrin level in BAL fluid was multiplied by 100 and then divided by the absolute LDH level in BAL fluid of the same patient.<sup>5</sup> This was done in order to compensate for the diluting effect of BAL fluid. TNM staging was made using the Union Internationale Contre le Cancer (UICC) TNM staging system with the following results: T1 (n=5), T2 (n=7), T3 (n=7), T4 (n=7), N0 (n=7), N1 (n=7), N2 (n=5), N3 (n=7), and M1 (n=6). The nine cases of SCLC were categorised as being either localised (n=4) or extensive (n=5) disease.

All data are expressed as median and range with, if relevant, the 95% confidence intervals. The following statistical tests were used when indicated: Mann-Whitney U test, correlation coefficient of Spearman, ANOVA, and Student's *t* test. A probability value of 0.05 was considered significant.

### Results

As the limit of detection of gastrin by this assay was 10 pg/ml, it was undetectable in the BAL fluid of some of the patients. Twenty eight of the 35 patients (80%) with cancer and 17 of the 25 (68%) with COPD had BAL fluid gastrin levels above 10 pg/ml. There was no significant difference in the concentration of LDH in the BAL fluid of the two groups (Student's *t* test,  $p=0.9$ , data not shown), thus allowing us to make accurate comparisons of gastrin in BAL fluid. Furthermore, no correlation was found between the LDH concentrations in the serum and BAL fluid ( $p=0.4$ , data not shown). No statistical difference was seen in the gastrin level in BAL fluid, expressed as absolute values, between the three groups ( $p=0.6$ ): NSCLC (median 17.5, range 11.1–39.6), SCLC (median 22.8, range 11–27.8), and COPD (median 17.3, range 10.7–33.3). There was no difference in the gastrin level in the BAL fluid expressed as pg/100 IU LDH (Mann-Whitney U test, fig 1) between patients with NSCLC (median 32.7, range 5.3–115) and those with COPD (median 27, range 2–72.5) ( $p=0.2$ ) nor between patients with SCLC (median 29.9, range 1.9–152) and those with COPD ( $p=0.8$ ). Furthermore, there was no difference in BAL fluid gastrin levels between patients with SCLC and those with NSCLC ( $p=0.9$ ). No correlation was found between BAL fluid or serum gastrin levels and tumour size, nodal status, or the presence of metastases. In patients with SCLC there was a significant difference in BAL fluid gastrin levels between those with extensive (median 2.9, range 1.9–35.2, 95% CI –6.6 to 28.8) and those with limited disease (median 88.1, range 24.6–152, 95% CI –18.5 to 194.9;  $p<0.05$ ). No difference was seen in serum gastrin levels between patients with COPD (median 50.5, range 31–419) and those

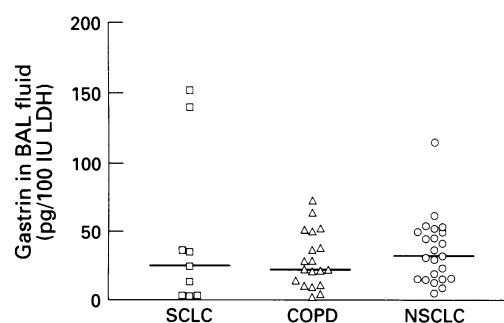


Figure 1 Scattergram of gastrin levels in bronchoalveolar lavage (BAL) fluid expressed as pg/100 IU lactate dehydrogenase (LDH) in patients with small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), and chronic obstructive pulmonary disease (COPD). No differences were seen between the three groups.

with cancer (median 58, range 29–472) group ( $p=0.6$ ). There was no relation between serum and BAL fluid gastrin levels ( $r = -0.027$ ,  $p=0.9$ ).

### Discussion

Bronchogenic carcinomas frequently synthesise neurohormonal peptides of which adrenocorticotrophic hormone, calcitonin, gastrin releasing peptide, and vasopressin are of particular interest. It has also been shown that gastrin is synthesised in all bronchogenic carcinomas irrespective of histological class, whereas the related cholecystokinin is not detectable.<sup>1</sup> In the same study the authors showed that the concentration of the biosynthetic precursor, progastrin, is higher than that of mature gastrins, suggesting that the post-translational processing in lung cancer tissue is incomplete.

In view of the easy access to gastrin assays during the last 15 years, surprisingly few studies have been performed in lung cancer with very conflicting results. Two studies reported in 1974 found that gastrin was undetectable in lung tumour extracts.<sup>6,7</sup> These first negative results were explained by the insufficient sensitivity of the early gastrin radioimmunoassays. Moreover, previously used gastrin assays measured only bioactive amidated gastrins and not the biosynthetic precursors which occur in higher concentrations.

Two recent studies by Zhou *et al* showed higher gastrin levels in both the BAL fluid and serum of patients with lung cancer than of those with non-cancerous pulmonary disease using a radioimmunoassay,<sup>3</sup> and serum gastrin levels were found to be correlated with disease extension with a significant fall in postoperative gastrin levels implying a better prognosis in 58 patients with lung cancer studied before and after surgery.<sup>8</sup>

Our study does not confirm these results. This discrepancy might relate to the fact that in our study we compensated for the diluting effect of BAL fluid by expressing the results of gastrin as pg/100 IU LDH while Zhou *et al* made no such compensation. Our study shows that the gastrin levels in BAL fluid are higher in limited than in extensive SCLC. However, these results should be interpreted with caution

because of the small numbers of patients in each subgroup. A possible explanation for the lower levels of gastrin in BAL fluid of patients with extensive disease is the finding of Rehfeld *et al* that post-transcriptional defects exist in gastrin production in lung cancer.<sup>1</sup> It is possible that, as SCLC progresses, the production of gastrin decreases due to increased genetic damage. Hansen *et al* have shown that serum calcitonin and gastrin levels have an inverse relation in patients with SCLC.<sup>9</sup>

In conclusion, our study shows no clinical usefulness for gastrin measurements in either BAL fluid or the serum for the diagnosis or staging of lung cancer.

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