

# Overt hypoadrenalism is uncommon in patients with stage 3 and 4 bronchogenic carcinoma

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**Introduction.** Lung cancer is the leading cause of cancer mortality in most countries. The adrenal glands are common sites of metastatic lung cancer as approximately 40% of subjects with stage 4 bronchogenic carcinoma have adrenal metastases. The prevalence of biochemical hypoadrenalism is, however, remarkably poorly documented.

**Objectives.** Our study aimed to determine the prevalence of primary hypoadrenalism, as defined by a subnormal cortisol response to the 250 µg adrenocorticotrophic hormone (ACTH) stimulation test, in patients with stage 3 and 4 lung cancer.

**Methods.** Thirty patients with stage 3 and 4 bronchogenic carcinoma were prospectively recruited from the bronchus clinic. Demographic data and electrolytes were recorded and each patient had a 250 µg ACTH stimulation test to determine the prevalence of overt adrenal insufficiency, defined as a +30 minute cortisol of less than 550 nmol/l.

**Results.** The median age and quartile deviation was 62 (10) years and the median basal cortisol was 429.5 (321) nmol/l.

The median peak cortisol was 828.5 (342) nmol/l (range 536 - 1 675 nmol/l). Twenty-eight patients (93.3%) had an appropriate rise of cortisol to greater than 550 nmol/l following 250 µg ACTH stimulation. Two patients (6.7%) had mild primary adrenal failure with a peak cortisol between 500 and 550 nmol/l associated with a raised plasma ACTH concentration (131.4 and 10.5 pmol/l, normal 2.2 - 10 pmol/l). Twenty-eight patients (92.9%) were normonatremic, while the two hyponatraemic patients had biochemical evidence of the syndrome of inappropriate antidiuretic hormone secretion.

**Conclusion.** In conclusion, despite evidence that the adrenal glands of patients with disseminated bronchogenic carcinoma are frequently affected by metastatic disease, biochemical evidence of clinically significant hypoadrenalism is relatively uncommon and is not accurately predicted by electrolyte abnormalities.

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Lung cancer is the leading cause of cancer mortality in most countries, with the global incidence increasing by 0.5% per year.<sup>1</sup> The adrenal glands are common sites of metastases, as evidenced by a series of 500 consecutive cancer necropsies, where 42% of metastatic lung cancers involved the adrenal glands. This high prevalence of adrenal metastases may reflect the rich sinusoidal blood supply and high local concentration of glucocorticoids, which may promote implantation of metastases.<sup>2</sup>



Despite the plethora of reports confirming the high frequency of adrenal metastases in patients with bronchogenic carcinoma, the prevalence of hypoadrenalism is remarkably poorly documented. One may speculate that hypoadrenalism may be uncommon as the adrenal glands possess large functional reserve, since 90% of both adrenal cortices must be replaced by tumour before adrenocortical insufficiency develops.<sup>3,5</sup> There are, however, several factors that may potentially account for underreporting of hypoadrenalism associated with metastatic carcinoma. Firstly, since the symptoms of adrenal insufficiency are similar to those of extensive metastatic disease, adrenal insufficiency is seldom considered in a patient whose condition is progressively deteriorating with increasing anorexia, malaise and weight loss.<sup>6</sup> Secondly, the treatment of metastatic cancer of the lung with corticosteroids may mask the state of adrenal insufficiency.<sup>7</sup> Finally, since the syndrome of inappropriate antidiuretic hormone (SIADH) is often encountered in small-cell carcinoma, hyponatraemia may be incorrectly attributed to SIADH rather than primary adrenal insufficiency.<sup>7</sup>

In 1855 Addison<sup>8</sup> first suggested that adrenal metastases could induce adrenal insufficiency. Several isolated cases supporting this contention have subsequently been reported.<sup>9,10</sup> In addition, there have been reports of adrenal insufficiency as the sole manifestation of cancer and of malignancies initially presenting as an Addisonian crisis.<sup>11,12</sup> There are only two prospective studies examining the prevalence of hypoadrenalism in metastatic bronchogenic carcinoma. Redman and colleagues<sup>13</sup> reported a 33% prevalence of hypoadrenalism in an early study of 15 patients with a variety of metastatic carcinomas and bilateral adrenal enlargement on CT scan. However, the criteria for hypoadrenalism used in this paper (cortisol increment < 150 nmol/l or a peak cortisol concentration < 415 nmol/l) do not accord with validated criteria for primary adrenal insufficiency.<sup>14,15</sup> Lutz and colleagues<sup>16</sup> employed more conventional diagnostic criteria and studied patients with either unilateral ( $N = 8$ ) or bilateral ( $N = 9$ ) adrenal metastases. In this group selected for the presence of adrenal metastases there was no evidence of overt hypoadrenalism. We were interested to determine the prevalence of primary hypoadrenalism prospectively in patients with advanced bronchogenic carcinoma not pre-selected for the presence of adrenal metastases. We therefore designed a prospective study of patients with advanced bronchogenic carcinoma with the following objective, namely to determine the prevalence of primary hypoadrenalism in patients with stage 3 and 4 lung cancer, using validated criteria.

## Materials and methods

Thirty patients were recruited prospectively from the combined bronchus clinic at Groote Schuur Hospital, Cape Town. Patients were considered eligible for the study if they had

histological or cytological proof of primary lung carcinoma with stage 3 or 4 (non-small-cell carcinoma) or advanced disease (small-cell carcinoma) according to the 1997 international TNM (tumour, node, metastasis) staging system for lung cancer.<sup>17</sup> Patients were considered to have metastatic disease if one or more of the following conditions were met: pathological fractures or radiological bony erosions, ultrasound or CT evidence of hepatic metastases, contralateral lung involvement, cutaneous involvement proved by biopsy, CT evidence of brain metastases or extension into pleura, pericardium, diaphragm or mediastinal nodes. Patients were excluded if they had had oral glucocorticoid treatment within the previous 6 months or if the subjects were on therapy that could influence cortisol metabolism, e.g. rifampicin. All patients provided written informed consent and the study was approved by the Research Ethics Committee of the University of Cape Town Medical School.

The nature of metastatic disease, height, weight and body mass index were recorded. Hyperpigmentation and postural hypotension were noted (a fall in systolic blood pressure > 20 mmHg and/or a fall in diastolic blood pressure > 10 mmHg after standing for 3 minutes) and serum, urinary electrolytes and osmolality were measured. SIADH was suggested by the combination of hyponatraemia ( $\text{Na}^+ < 130 \text{ mmol/l}$ ) with low plasma osmolality (< 280 mOsm/kg), inappropriately high urine osmolality and urinary sodium > 20 mmol/l, in the absence of clinical volume depletion or biochemical evidence of hypothyroidism, hypoadrenalism or renal impairment. A standard intravenous 250  $\mu\text{g}$  adrenocorticotrophic hormone (ACTH) test (tetracosactide) was performed and patients were defined as having overt primary hypoadrenalism if the 30-minute cortisol was < 550 nmol/l with increased basal plasma ACTH (normal 2.2 - 10 pmol/l).<sup>18</sup> Compensated hypoadrenalism was defined as a ratio of ACTH/cortisol (pmol/l:nmol/l) > 0.028.<sup>19</sup> Cortisol was measured using the Automated Chemiluminescence System, Cheiron ACS 180 (Beyer Corporation, New York 10591-509). The inter- and intra-assay coefficient of variation was 6.4 - 9.7%. ACTH assay was performed using the Immulite 2000 chemiluminescent immunoassay system and the inter- and intra-assay of coefficient of variation was 6.3 - 8%. Results are expressed as medians and quartile deviation (QD). Since sample sizes were small and variances were generally not homogeneous the Mann-Whitney test was employed for all the comparisons.

## Results

### Baseline demographic data

Baseline demographic data are summarised in Table I. The mean  $\pm$  standard deviation (SD) age was  $60.9 \pm 9.45$  years. Seven patients had proven advanced small-cell carcinoma, whereas 23 patients had non-small-cell carcinoma, of whom 14 had stage 3 (61%) and 9 stage 4 disease (39%).



Table I. Baseline demographic data\*

	Small-cell carcinoma (N = 7)	Non-small-cell carcinoma (N = 23)
Age (yrs)	63.29 (7.11)	60.13 (10.07)
Sex (M:F)	4:3	17:6
BMI	23.32 (1.94)	24.58 (5.09)
Albumin	38.57 (3.46)	35.36 (5.30)
N (%) with Ca <sup>2+</sup>	1 (14.3)	1 (4.3)
N (%) with Na <sup>+</sup>	2 (28.6)	2 (8.7)
N (%) with K <sup>+</sup>	0	3 (13.0)

\* Data expressed as mean (SD) unless otherwise indicated.

### Basal cortisol and ACTH

The basal cortisol ranged from 129 to 978 nmol/l in both groups combined, while the median basal cortisol was 432 nmol/l (QD 473) for the non-small-cell carcinoma group and 212 nmol/l (QD 505) for the small-cell carcinoma group ( $p > 0.05$ ). The median basal ACTH was 2.8 pmol/l (QD 2.2) for the non-small-cell carcinoma group and 6.35 pmol/l (QD 9.75) for the small-cell group ( $p > 0.05$ ). Four patients (13.3%) had an abnormally elevated plasma ACTH concentration.

### Cortisol response to 250 µg ACTH stimulation (Fig. 1)

The overall median peak serum cortisol 30 minutes after 250 µg ACTH stimulation was 828.5 nmol/l (QD 345), range 536 - 1 675 nmol/l. When comparing the two histological subgroups, the median peak serum cortisol was 832 nmol/l (QD 336) for the non-small-cell carcinoma group and 792 nmol/l (QD 563) for the small-cell carcinoma group ( $p = 0.86$ ). There was a close correlation between basal and 30-minute cortisol ( $r = 0.78$ ,  $p < 0.0005$ ), while the correlation between basal and incremental cortisol was poor ( $r = -0.07$ ,  $p = 0.9$ ).

Twenty-eight patients (93.3%) had an appropriate rise of cortisol to greater than 550 nmol/l following 250 µg ACTH stimulation. Two patients (6.7%) had definite evidence of adrenal insufficiency, with a peak cortisol of 536 and 545 nmol/l associated with a raised plasma ACTH concentration of 131.4 and 10.5 pmol/l respectively (normal 2.2 - 10 pmol/l). The overall prevalence of adrenal insufficiency was therefore 6.7% in our series (95% confidence interval (CI): 0.8% - 22.1%). Two further subjects had an elevated basal ACTH concentration of 58.9 and 13.4 pmol/l (normal 2.2 - 10 pmol/l) and their peak cortisol levels following ACTH stimulation were 997 and 762 nmol/l respectively. In order to ascertain whether these two subjects had compensated hypoadrenalism we determined the ACTH-to-cortisol ratio, which was 0.059 and 0.017 respectively (ratio  $> 0.028$  suggests compensated hypoadrenalism).<sup>16</sup> Thus we found an additional patient who

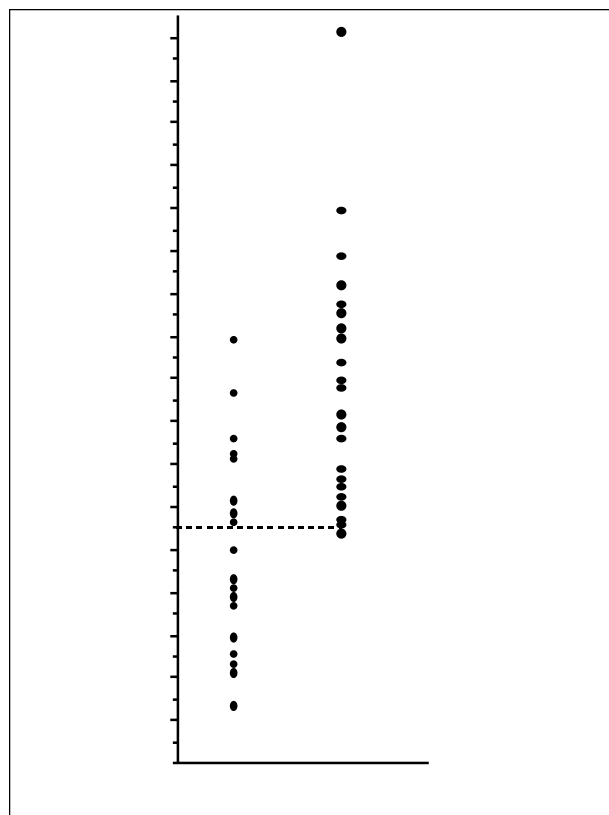


Fig. 1. Basal and 30-minute plasma cortisol concentrations following 250 µg ACTH stimulation. The horizontal line at 550 nmol/l indicates the minimum cortisol value that defines a normal +30 minute response to ACTH stimulation.

had compensated hypoadrenalism (ACTH-to-cortisol ratio 0.059), bringing the overall prevalence of hypoadrenalism in our study to 10%.

### Clinical and biochemical predictors of hypoadrenalism

Clinical evidence of hyperpigmentation was not predictive of hypoadrenalism since none of the 23.3% of the patients with hyperpigmentation had a subnormal serum cortisol response to ACTH stimulation. Similarly, postural hypotension was of limited utility since 13.3% of patients had postural hypotension and only 1 of these subjects had compensated hypoadrenalism. Twenty-eight patients (93.3%), including the 2 with adrenal insufficiency, were normonatremic, while the 2 hyponatraemic patients (6.7%) had biochemical evidence of SIADH. All patients were normokalaemic and the 2 patients with hypercalcaemia (6.7%) had normal adrenal function, suggesting that the hypercalcaemia was related to the underlying malignancy rather than to cortisol deficiency. Despite convincing evidence in the literature that a basal 08h00 cortisol of less than 100 nmol/l reliably predicts hypoadrenalism, this



cutoff was of limited clinical utility in our study where the subjects with both mild and compensated adrenal failure had basal cortisol levels ranging from 129 nmol/l to 815 nmol/l.<sup>14</sup>

## Discussion

Despite the fact that the adrenal glands are common sites of metastatic spread in patients with bronchogenic carcinoma, our study suggests that clinically relevant hypoadrenalism is distinctly uncommon. However, 2 patients had adrenal insufficiency, with a peak cortisol of between 500 and 550 nmol/l was associated with a raised plasma ACTH concentration. It is relevant to note that these patients had no associated clinical or biochemical features of hypoadrenalism and were not considered to warrant glucocorticoid supplementation. In addition 2 further patients with an elevated basal plasma ACTH of 58.9 and 13.9 pmol/l responded to stimulation with 250 µg ACTH, with a normal cortisol response of 997 and 762 nmol/l. These patients may be considered to have compensated primary adrenal insufficiency and although they would be at increased risk of developing overt primary adrenal insufficiency in the future, there would currently be no benefit in glucocorticoid supplementation.

The 250 µg dose of ACTH used in this study results in markedly supraphysiological concentrations of ACTH, which could potentially limit the ability of the test to detect subtle degrees of cortisol deficiency (false-negative test). The low-dose 1 µg ACTH stimulation test has therefore recently been advocated as a more sensitive test for hypoadrenalism, particularly in the setting of suspected ACTH deficiency. Early enthusiasm for the sensitivity of the 1 µg ACTH stimulation test in the evaluation of patients with pituitary disease has, however, been dampened by several reports indicating that in the setting of partial ACTH deficiency, the low-dose test may, like the standard 250 µg test, produce false-negative results.<sup>20</sup> In the single report exploring the utility of the 1 µg ACTH stimulation test for the diagnosis of primary hypoadrenalism in patients with pre-clinical hypoadrenalism and positive adrenal antibodies there was full concordance between the results of the 250 µg and 1 µg tests, indicating no diagnostic advantage for the low-dose test.<sup>21</sup> This limited sensitivity probably relates to the attainment of supraphysiological concentrations of ACTH following administration of both the 250 µg (60 000 ng/l) and 1 µg (> 100 ng/l) ACTH doses, concentrations which are substantially higher than the plasma ACTH concentration that elicits a maximal cortisol response (70 - 80 ng/l).<sup>22</sup> In light of these data we decided to use the conventional 250 µg ACTH stimulation test for the evaluation of hypoadrenalism in our patient cohort. A crucial characteristic of our patient cohort was that none of our patients was acutely unwell at the time of being evaluated.

The relatively low prevalence of hypoadrenalism reported in

this study contrasts sharply with previous studies reporting that more than 40% of patients with metastatic bronchogenic carcinoma have adrenal metastases at necropsy.<sup>23</sup> This discrepancy between frequent pathological adrenal involvement and infrequent biochemical hypoadrenalism is well documented and attests to the remarkable functional reserve of the adrenal glands.<sup>34</sup> In light of our findings it is important to evaluate earlier studies of hypoadrenalism in patients with metastatic bronchogenic carcinoma critically. In a study of only 15 patients with metastatic carcinoma and bilateral adrenal enlargement on CT scan Redman and colleagues<sup>13</sup> reported a 33% prevalence of hypoadrenalism. However, the criteria used to define hypoadrenalism in this study, namely failure to increase serum cortisol by at least 150 nmol/l and/or a peak cortisol of less than 415 nmol/l following 250 µg ACTH stimulation, are arbitrary and do not accord with any accepted diagnostic criteria for hypoadrenalism.<sup>14,15</sup> Consensus is now emerging that calculation of the increment in serum cortisol is of limited value in the assessment of the adrenocortical function, as a maximally stressed patient with an intact adrenal axis may have a blunted cortisol response to exogenous ACTH.<sup>24</sup> If one re-examines the study by Redman *et al.*<sup>13</sup> employing validated criteria, namely a peak cortisol response to ACTH of less than 550 nmol/l, then the prevalence of hypoadrenalism is reduced to 20%. A recent study by Lutz and colleagues<sup>16</sup> examined adrenocortical function in patients with either unilateral ( $N = 8$ ) or bilateral ( $N = 9$ ) macrometastases of the adrenal gland. Interestingly, no patient had overt adrenal insufficiency (defined as a serum cortisol response to ACTH stimulation below 560 nmol/l, while only 2 of 9 patients (22%) with bilateral macrometastases had subclinical hypoadrenalism (defined as an elevated basal ACTH/cortisol ratio).<sup>16</sup> The reported prevalence of overt hypoadrenalism of 20 - 22% from studies that selected patients for the presence of adrenal metastases is in accordance with our study, which documented a combined prevalence of hypoadrenalism (overt and compensated) of 10% in a group of patients with advanced bronchogenic carcinoma who were not selected for CT evidence of adrenal metastases.

The predictive value of clinical and biochemical markers of hypoadrenalism in our study was poor since none of the patients considered to have hyperpigmentation had biochemical hypoadrenalism. Conversely, the 2 patients with mild adrenal insufficiency and elevated plasma ACTH concentration were not hyperpigmented. We propose that hyperpigmentation reflects longstanding ACTH excess which is not typically a feature in patients with adrenal metastases. Similarly, there was no correlation between postural hypotension and hypoadrenalism. Although hyponatraemia and hyperkalaemia had a prevalence of 78% and 52% respectively in our previous series of 50 patients with Addison's disease, neither of the 2 patients with mild



hypoadrenalism in this study had any electrolyte disturbance.<sup>25</sup> This likely reflects the mild cortisol deficiency with preservation of mineralocorticoid function in this group of patients. Finally, basal cortisol cannot be used as a predictor for overt or compensated hypoadrenalism.

There are several potential criticisms of our study. Firstly the limited number of enrolled subjects may have resulted in a falsely low prevalence of hypoadrenalism. This uncertainty is reflected in the wide CIs for the prevalence of overt hypoadrenalism of 0.8 - 22.1% and can only be addressed by increasing the number of patients recruited in future studies. In addition, although the patients had advanced bronchogenic carcinoma according to conventional staging, serum albumin and body mass index were remarkably well preserved (Table I). It is therefore possible that patients with clinically more advanced bronchogenic carcinoma would have a higher prevalence of primary hypoadrenalism. Finally, patients were not selected for the presence of adrenal metastases on CT imaging as in previous studies. We were, however, interested in answering a clinically relevant question, namely the prevalence of hypoadrenalism in unselected patients with advanced bronchogenic carcinoma as this is the problem frequently faced by clinicians, who typically do not have CT data available when assessing a patient with advanced malignancy and possible hypoadrenalism. It would, however, have been interesting to verify the presence of adrenal metastases in our small group of patients with overt and compensated adrenal failure.

In conclusion, despite frequent pathological adrenal involvement in patients with metastatic bronchogenic carcinoma, clinically relevant hypoadrenalism is distinctly uncommon. Furthermore, electrolyte disturbances and basal cortisol concentration are of limited use in identifying the occasional patient with mild hypoadrenalism.

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