

# Low serum testosterone as an indicator of metastatic bronchial carcinoma

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**ABSTRACT** Serum testosterone concentrations were measured preoperatively in 39 men undergoing thoracotomy for histologically proved bronchial carcinoma, in 10 patients with pulmonary opacities that transpired to be non-malignant (benign group) and in 23 men were undergoing minor elective surgical procedures (control group). Thirteen of the 39 patients with known bronchial carcinoma were considered to have had curative surgery and 26 a palliative procedure when operative and pathological findings were taken into consideration. Low serum testosterone concentrations ( $<12$  nmol/l) were detected in four patients in the curative group, in 22 in the palliative group ( $\chi^2$  test:  $p < 0.001$ ), three in the benign group, and in two patients in the control group. A low serum testosterone concentration in patients with bronchial carcinoma may be an indicator of metastatic disease and sequential serum testosterone estimations may prove useful in the follow up of patients thought to have undergone curative surgery.

The difficulties in the accurate assessment of metastatic disease in patients with bronchial carcinoma, with currently available staging techniques, frequently result in a non-curative thoracotomy.<sup>1</sup> Various abnormalities of steroid metabolism have been described in patients with bronchial carcinoma, including low serum testosterone concentrations in men.<sup>2</sup> We have assessed the value of the serum testosterone concentration in identifying men with bronchial carcinoma who are likely to have metastatic disease.

## Methods

The serum concentration of testosterone was measured in 39 men with histologically proved carcinoma, 10 with benign lung lesions and 23 control patients undergoing minor elective surgical operations. Comprehensive staging procedures, including computed tomography, radionuclide imaging, and mediastinoscopy where indicated, were performed in all patients.

All blood samples were withdrawn between 0800 and 0900 hours on the day before surgery and serum

testosterone was estimated by radioimmunoassay. The lower limit of our reference range for serum testosterone in adult males is 12 nmol/l.

Surgery was considered to have been "curative" where the results of all routine blood tests were within normal limits, the primary lesion was completely excised, there was no macroscopic intrathoracic spread, and the mediastinal nodes sampled at operation were histologically free of disease. Statistical analysis was performed with Student's *t* and  $\chi^2$  (with Yates's correction) tests.

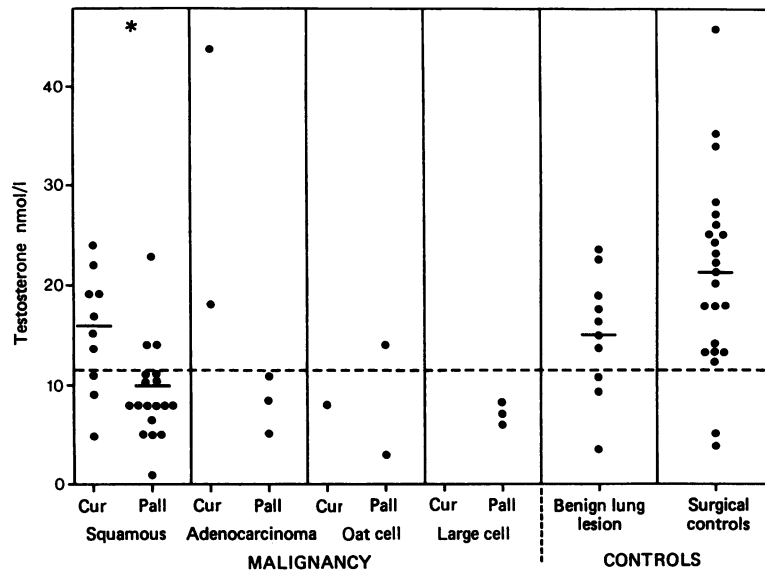
## Results

The radioimmunoassay technique used to measure testosterone concentration used an "in house" <sup>125</sup>I-histamine-3-testosterone label and a sheep anti-serum raised against testosterone-3-CMO-BSA (Dr B Cook, Endocrine Section, Department of Clinical Biochemistry, Glasgow Royal Infirmary). The cost of the assay, including reagents and use of laboratory time for performing measurements, was about £1 a patient.

Thirty nine patients with bronchial carcinoma were submitted to thoracotomy. In 13 patients surgery was considered to be "curative" including 10 with squamous carcinoma, two with adenocarcinoma, and one with an oat cell tumour. Twenty six patients had a palliative procedure (18 with squamous carcinoma,

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*Serum testosterone concentration in various groups of patients. The dotted line is the lower limit of the normal (12 nmol/l) range. The solid bars represent the mean value for each group. \* $p = 0.001$ . Cur—apparently curative surgery; pall—palliative surgery.*

three with adenocarcinoma, two with oat cell carcinoma, and three with large cell carcinoma).

Low values of serum testosterone (<12 nmol/l) were detected in four of 13 patients in the "curative" group and in 22 of 26 patients in the palliative group ( $\chi^2$ :  $p < 0.001$ ), as shown in the figure. The mean value of serum testosterone in 10 patients with squamous carcinoma undergoing "curative" surgery was 16 (SD 6) nmol/l compared with 10 (4) nmol/l in the 18 patients with squamous carcinoma whose surgery was palliative ( $p < 0.001$ ). The small numbers of patients in the other histological subgroups precluded statistical comparisons between "curative" and palliative groups.

Seven patients with low serum testosterone concentrations but a normal superior mediastinum on the computed tomography scan were subsequently found to have diseased mediastinal nodes. Four patients with macroscopically normal but histologically affected mediastinal nodes had serum concentrations of testosterone within the normal range (mean 14 nmol/l).

At four months' follow up overt metastatic disease has appeared in two of the four patients with low serum testosterone concentrations who underwent "curative" surgery. Of the other nine patients from the same group, with normal concentrations of serum testosterone, whose mean follow up was six months (range 3–8 months), none has evidence of metastatic disease.

In this study 10 patients undergoing thoracotomy for pulmonary opacities were found to have non-malignant lesions. Three of these patients had low concentrations of serum testosterone (including two with histological inflammation of uncertain, but non-malignant, aetiology and one with sarcoidosis) and showed substantial pneumonic changes on chest radiographs, a feature not observed in seven patients whose opacities were not associated with widespread inflammatory changes and who had normal testosterone concentrations.

Low values of serum testosterone were detected in two control patients (aged 76 and 82 years) who were undergoing minor general surgical procedures.

Follow up data at four months for the 49 patients undergoing surgery showed a low serum testosterone concentration to have a sensitivity of 86% and a specificity of 76% in predicting metastatic disease. The predictive value of a positive result (that is, a low serum testosterone concentration) in identifying patients with metastases was 83% and the predictive value of a negative result (that is, a normal testosterone concentration) 80%, with an overall accuracy of 82%.

## Discussion

Accurate preoperative assessment of metastatic disease in patients with bronchial carcinoma, particularly where mediastinal lymph nodes are affected

remains difficult. Consequently, thoracotomy undertaken for apparently localised primary bronchial carcinoma may bring to light previously unsuspected metastases, particularly when macroscopically normal mediastinal lymph nodes are submitted for histological examination. Enlarged mediastinal lymph nodes detected by computed tomography either may represent metastatic disease or may be reactive and their value remains uncertain<sup>3</sup> unless they are accessible to biopsy at mediastinoscopy. Systemic markers of tumour activity, including carcinoembryonic antigen,  $\alpha$  fetoprotein, and peptide hormones, have been of little benefit in diagnosis or follow up of most patients with bronchial carcinoma.<sup>4</sup>

Abnormalities of serum testosterone concentration have been described in various malignancies, including bronchial carcinoma. No previous study, however, has used a low serum testosterone concentration to indicate the likelihood of metastatic disease in men with bronchial carcinoma. When tumour status was reassessed in patients four months after surgery, the sensitivity of a low serum testosterone concentration at the time of operation in predicting metastatic disease was 86%, the specificity 76%, and the accuracy 82%.

The cause of a depressed serum testosterone concentration in patients with metastatic bronchial carcinoma is unknown but may result either from reduced production or increased utilisation of testosterone. Testosterone production could be attenuated directly at the gonadal level or through suppression of its controlling hormones at the pituitary level as a consequence of metastatic disease. Alternatively, normal lung tissue has the capacity to metabolise testosterone<sup>5</sup> and a low serum testosterone concentration in patients with malignancies may reflect an acceleration of this process, either within normal lung parenchyma or within malignant cells, with further accentuation in the presence of metastases. A further possibility is that malignant cells may in some way interfere with hepatic degradation of testosterone. A low serum testosterone concentration is likely to be a specific marker of malignancy rather than a non-specific marker of ill health in the patient with cancer because, although various non-malignant debilitating conditions may cause a reduction in the concentration of testosterone metabolites, the concentration of serum testosterone itself is unaffected.<sup>6</sup>

Despite these encouraging early observations the finding of a low serum testosterone concentration, in isolation from other data, is unlikely to become sufficient justification for denying a patient thoracotomy. Serum testosterone concentration is, however, relatively cheap to estimate and may prove useful, in conjunction with the results of other investigations, as an early indicator of recurrent disease in patients thought to have undergone "curative" surgery. Caution must be exercised in the interpretation of a low serum testosterone concentration where there are obvious pneumonic changes on chest radiographs or in patients over the age of 70 years, when testosterone concentrations are known to decline.<sup>7</sup>

We are currently carrying out a prospective trial to evaluate the aforementioned possibilities and to define further the relationship of a low serum concentration of testosterone and its protein binding activity to the integrity of the pituitary-gonadal axis.

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