Clearly our two methods of analysis are not entirely compatible and results of cosinor analysis will give more conservative estimates of amplitude since it takes a balanced view of all the data points whereas calculation from the highest observed daily values is biased towards extremes of variation in the raw data. Moreover, patients in Dr Connolly’s study achieved a lower overall PEFR (mean values 182 l min⁻¹ for males and 127 l min⁻¹ in females). At these lower levels the noise to signal ratio is high and amplitude is liable to overestimation in comparison with our subjects with PEFR in the predicted normal range. Unfortunately, these differences between normal subjects and patients constitute an insuperable obstacle to comparison of their PEFR rhythms. Amplitude measured as percentage of the highest daily reading also relies heavily on the accuracy of these few readings whereas cosinor analysis attaches equal weight to all observations.

We, therefore, maintain that an amplitude of >20% of the mean value in the PEFR rhythm is a valid threshold above which the diagnosis of asthma should be considered. As a corollary to this, we have previously found that only some 20% of asthma patients in hospital had amplitudes of >25% measured from raw data as percentages of the highest daily reading. Thus the threshold for a diagnosis of asthma appears to lie in the range 20–25%. This view is supported by the work of Dawkins and Muers who have used cosinor analysis to study PEFR rhythms in chronic bronchitis and obtained similar results to our normal data.

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References


What is the best treatment for early operable small cell carcinoma of the bronchus?

Sir,—We wish to take issue with much of the factual data presented by Dr Levison in his editorial and to suggest that the proposed national study is not practical and will fail to determine the role of surgery in operable small cell carcinoma of the bronchus (SCCB).

SCCB does not behave in a uniform manner; there is a considerable variability of response to chemotherapy which does not correlate with any obvious histological subtyping. The statement that 95% of SCCB occurs in men is no longer true; more recent reports contain ratios of three or four men to one woman and in the last 300 cases treated by our group 40% were women. The overall incidence is not 36% of all lung cancers, but nearer to 20–25%.

Much of the data presented in the editorial come from studies in patients with “limited” disease but it is important to make clear what this term means. It is usually used to describe a category of patients where the disease is confined to one hemithorax and in whom there is no detectable metastatic spread. These patients are rarely “operable”. In our study sequential staging using CT scanning of thorax and abdomen in 50 consecutive patients showed that all patients were inoperable, 74% having T3 tumours including the three patients who, on chest x-ray, were thought to have T1 tumours. In our last 315 patients we have seen one operable case. There is now a considerable body of evidence to show that the median survival of even “limited” disease does not exceed nine months when a local treatment, such as radiotherapy, is used alone. Better results with chemotherapy are achieved in this category of patients, and it is not yet clear if radiotherapy has any part to play in management other than as a palliative procedure. Early results from randomised trials, including our own, suggest that it does not prolong survival in patients treated adequately with drugs.

After high dose radiation relapse in the chest is common, indicating that local control is rarely achieved and that the suggested preoperative low dose radiotherapy would not render patients operable. It is not appropriate to draw an analogy between “debulking” surgery in ovarian cancer and small cell carcinoma. Ovarian cancer often remains localised in the abdomen and is a slowly growing adenocarcinoma. Small cell carcinoma usually spreads early and grows rapidly. Local surgery is unlikely to influence mortality in this situation.

Cranial irradiation is of no proven benefit for survival in small cell carcinoma and it is not logical to include it in randomised studies until longer survival is achieved than that currently being obtained.

Dr Levison’s proposed study therefore concerns a tiny minority of patients with small cell carcinoma in whom the tumour is operable. Adequate investigation of these patients will probably reveal more extensive disease in many. Furthermore by having four arms to the study, all of which include surgery, it is certain that the investigation will take many years to complete and that the role of surgery will not have been evaluated. The study design as proposed will assess the role of preoperative low dose radiotherapy and brain irradiation. At the present time neither of these aims seems worthwhile.

If a trial of surgery in the rare operable cases is to be mounted this should include careful preoperative
staging and be a straightforward comparison of surgery alone, surgery plus chemotherapy, and chemotherapy alone. Only in this way will the role of surgery be decided.

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Sir,—Thank you for allowing me to see the letter from Dr Souhami and his colleagues. May I take their various points as they arise?

1 I agree that SCCB does not behave in a uniform manner, and that it is not possible to predict the response to chemotherapy from any histological subtyping. This statement is equally applicable to many malignant tumours currently being treated with drugs. The majority of patients with macroscopic SCCB do however respond, albeit temporarily, to chemotherapy and it is therefore logical to attempt the destruction of micrometastases by the same method.

2 I accept their updated figures from the American Cancer Society relating to both overall and sex incidence of SCCB.

3 It has not been our experience at the North Middlesex Hospital (NMH) that these patients with apparently limited disease are rarely operable. In our first series1 reported in 1974 treated by radiotherapy and surgery five of 29 (24%) were alive and well at four years. Further support for the true operability of early SCCB is shown by a recent paper reporting 40 curative resections in 63 patients with SCCB between 1959 and 1974, 10 (25%) surviving five years or more.2 I do however agree that intensive investigation of the clinically early, localised and apparently operable patient with SCCB will reveal a high proportion to have disseminated disease, precluding surgery.

4 I accept the point regarding the different behaviour of ovarian cancer and SCCB. It is open to question that the removal of a large tumour mass—"debulking"—is of no benefit to the patient with SCCB. It is well recognised by radiotherapists and chemotherapists that in general the response of large tumour masses is much less than that of small deposits. If chemotherapy is to be effective and kill the micrometastases it is surely more likely to do so if it has to deal with small groups of cells only, and not a large primary tumour in addition.

5 I agree cranial irradiation is not of proven benefit in SCCB. It might prove to be so were its use to be adequately tested in combination with other treatments.

6 It has never been the intention of my colleagues and myself at NMH to advocate the use of radiotherapy to render a tumour operable, the implication being that it is inoperable without the preoperative radiotherapy. The treatment combination of preoperative radiotherapy and surgery is suggested only for those patients who are accepted by the surgeons as early, localised, and operable even were no preoperative radiotherapy to be given.

7 The penultimate paragraph is surely a contradiction in terms. If a tumour is operable this is because adequate investigation has shown it to be so. If these investigations reveal "more extensive disease," the growth is not by definition operable.

8 Nobody dealing with SCCB would dispute that early operable disease is unusual, if not rare. From 1966-76 90 such patients were seen at NMH, only 73 undergoing surgery.

Chemotherapy alone produces good palliation and short-term remission, but long-term survival is very unusual.3 Moreover, my surgical colleagues would not be agreeable to treating this small but in our opinion potentially curable group in this fashion.

The poor results of treating SCCB by surgery alone in the MRC trial1 have now been called into question.2 It may well be that the 24% 4 year survival figure from the NMH owes nothing to the preoperative radiotherapy but is entirely the result of the surgery.
I cannot agree that it is not worthwhile to assess the value of preoperative low dose radiotherapy; only a trial can prove or disprove this.

If it could be agreed that the mainstay of a study to ascertain the best treatment for early operable SCCB was surgery, it is surely correct to add to this radiotherapy or chemotherapy or both, which offer the most optimistic approach based on current knowledge; perhaps the use of cranial irradiation could be left open to discussion.

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