

## Letters

## Population screening for lung cancer using CT

We read with interest the paper by Black and colleagues<sup>1</sup> which outlines the current status of CT screening, and value the authors' cautious interpretation of the relatively few well conducted studies regarding this controversial topic. However, when using reduction in lung cancer mortality as proof of screening efficacy with CT due to early intervention, one has to be careful in interpreting the calculation of the potential reduction in mortality. This is because the denominator used for calculating disease-specific mortality is also affected and is thus biased by the proportion of early cancers detected, especially when overdiagnosis is likely to be encountered.

We would like to highlight the recent ELCAP study to illustrate this.<sup>2</sup> Screening of 27 456 participants led to the detection of 74 early lung cancers which translated to an annual incidence of 269/100 000 persons at risk (100 000/27 456×74). The reported cure rate was 80% and mortality was 20%. Although we acknowledge that the study included participants from several countries, Centers for Disease Control and Prevention have reported annual lung cancer mortality of 83.3/100 000 men and 53.7/100 000 women.<sup>3</sup> Assuming equal gender distribution, lung cancer mortality of 68.5/100 000 is obtained. When this figure is compared with the ELCAP study, an overdiagnosis of 200/100 000 persons could be implied by CT screening alone. Considering the generally quoted dismal cure rate of 15% for 69/100 000 persons, overdiagnosis and overtreatment of such a magnitude would automatically result in a higher cure rate of 78.5% (69×15% + 200×100%) and 21.5% mortality.

It would therefore appear premature to associate the effectiveness of lung screening with a higher cure rate or reduction in mortality. Instead, a significant reduction in annual lung cancer mortality following the start of any screening method will be the proof of clinical significance. In our opinion, it should decrease lung cancer mortality statistics year after year.

**P Lee, T G Sutedja**

Department of Pulmonary Diseases, VU Medical Center, Amsterdam, The Netherlands

**Correspondence to:** Dr P Lee, Department of Pulmonary Diseases, VU Medical Center, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands; P.Lee@vumc.nl

**Competing interests:** None.

## REFERENCES

1. **Black C**, de Verteuil R, Walker S, *et al*. Population screening for lung cancer using computed tomography, is there evidence of clinical effectiveness? A systematic review of the literature. *Thorax* 2007;**62**:131–8.

2. **Henschke CI**, Yankelevitz DF, Libby DM, *et al*. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;**355**:1763–71.
3. **Centers of Disease Control and Prevention**. *Lung cancer: statistics*. Atlanta: Centers of Disease Control and Prevention, 2007.

## Authors' reply

We thank Drs Grigoriu and Scherpereel for commenting on our recent publication examining the diagnostic value of soluble mesothelin in malignant pleural mesothelioma.<sup>1</sup> We agree with their comments that the numbers in our study may not have been sufficient to address the question of the prognostic value of this marker. While we have found that mesothelin levels reflect tumour burden and would therefore be expected to have prognostic value, the patients did not receive a standardised treatment regime. At our centre, patients are offered a range of surgery, chemotherapy, radiotherapy, novel immunotherapies or best supportive care treatment options. The numbers of patients in each category therefore further reduces the power of the survival analysis. However, given that patients with sarcomatoid mesothelioma have low mesothelin levels and a poor prognosis, one would not a priori anticipate a close correlation unless patients are stratified according to histology—that is, elevated mesothelin levels could indicate greater tumour bulk (worse prognosis) or greater epithelial differentiation (better prognosis). We are currently evaluating the prognostic value on patients enrolled in a standardised treatment regime. In both studies pleural effusion levels of mesothelin were not related to survival.<sup>1,2</sup> While serum mesothelin levels may indeed have prognostic value with Grigoriu and colleagues showing in their analysis of 76 patients that high serum mesothelin levels (>3.5 nM) had prognostic significance, it is unclear at this stage whether an individual's mesothelin level will have a strong clinically relevant predictive value that adds to that of the currently used prognostic indicators.<sup>3</sup>

As emphasised by Lee<sup>4</sup> in his editorial published with our paper and by Grigoriu and Scherpereel, we support the need for an international multicentre investigation into the value of soluble mesothelin in the management of patients with mesothelioma.

**J Creaney, B Musk, N De Klerk, B W Robinson**

University of Western Australia and Sir Charles Gairdner Hospital, Nedlands, Australia

**Correspondence to:** Dr J Creaney, School of Medicine and Pharmacology, University of Western Australia, Sir Charles Gairdner Hospital, Verdun Ave, Nedlands, Western Australia 6009, Australia; creaneyj@cyllene.uwa.edu.au

**Competing interests:** None.

## REFERENCES

1. **Creaney J**, Yeoman D, *et al*. Soluble mesothelin in effusions: a useful tool for the diagnosis of malignant mesothelioma. *Thorax* 2007;**62**:569–76.

2. **Grigoriu BD**, Scherpereel A, *et al*. Utility of osteopontin and serum mesothelin in malignant pleural mesothelioma diagnosis and prognosis assessment. *Clin Cancer Res* 2007;**13**:2928–35.
3. **Burgers JA**, Damhuis RA. Prognostic factors in malignant mesothelioma. *Lung Cancer* 2004;**45**(Suppl 1):S49–54.
4. **Lee YC**. Hunting for a pleural fluid test for mesothelioma: is soluble mesothelin the answer? *Thorax* 2007;**62**:561–2.

## Diagnostic value of soluble mesothelin in malignant mesothelioma

We read with great interest the article by Creaney *et al*<sup>1</sup> together with the associated editorial by Lee<sup>2</sup> published in the July issue of *Thorax*. After the seminal paper by Robinson *et al* in 2003,<sup>3</sup> there has been a lot of interest in the diagnostic value of soluble mesothelin in malignant pleural mesothelioma (MPM). Dr Lee emphasised the similarity between his results and those obtained by us.<sup>4</sup> We completely agree with his statement that this new marker seemed therefore to be robust but could not be used as the sole diagnostic tool.<sup>2</sup>

We would like to comment on the finding of Creaney and coworkers that soluble mesothelin has no prognostic value. The same group of authors have previously suggested that an increasing serum level of this marker may reflect the tumour burden,<sup>3</sup> thus suggesting that soluble mesothelin may have a prognostic value. The series reported by Creaney *et al* included only 52 cases of mesothelioma, and this figure may be insufficient to arrive at a firm statistical conclusion. In our first study which included 60 patients with MPM, we were also unable to find any relationship between patient outcome and soluble mesothelin assessed either in serum or in pleural effusion.<sup>4</sup> However, when the same analysis was performed on a much larger series including almost 60% more patients with MPM,<sup>5</sup> soluble mesothelin appeared as an independent prognostic factor along with the histological subtype, while tumour stage fell short as a significant parameter probably owing to the still low number of cases. Although both the Australian and French series may be subjected to bias, these data stress the urgent need for an international multicentre investigation on the value of soluble mesothelin in the management of malignant mesothelioma before we can firmly recommend the use of this marker in clinical practice.

**B D Grigoriu, A Scherpereel<sup>2</sup>**

<sup>1</sup> Department of Pulmonary Diseases, University of Medicine and Pharmacy, Iasi, Romania; <sup>2</sup> Clinique des Maladies Respiratoires, CHRU of Lille, France

**Correspondence to:** Dr B D Grigoriu, Department of Pulmonary Diseases, University of Medicine and Pharmacy, Iasi 700115, Romania; b\_grigoriu@hotmail.com

**Competing interests:** None.

## REFERENCES

1. **Creaney J**, Yeoman D, Naumoff LK, *et al*. Soluble mesothelin in effusions: a useful tool for the diagnosis of malignant mesothelioma. *Thorax* 2007;**62**:569–76.
2. **Lee YCG**. Hunting for a pleural fluid test for mesothelioma: is soluble mesothelin the answer? *Thorax* 2007;**62**:561–2.
3. **Robinson BW**, Creaney J, Lake R, *et al*. Mesothelin-family proteins and diagnosis of mesothelioma. *Lancet* 2003;**362**:1612–6.
4. **Scherpereel A**, Grigoriu B, Conti M, *et al*. Soluble mesothelin-related peptides in the diagnosis of malignant pleural mesothelioma. *Am J Respir Crit Care Med* 2006;**173**:1155–60.
5. **Grigoriu BD**, Scherpereel A, Devos P, *et al*. Utility of osteopontin and serum mesothelin in malignant pleural mesothelioma diagnosis and prognosis assessment. *Clin Cancer Res* 2007;**13**:2928–35.

## Asthma exacerbations

In their excellent article on asthma exacerbations,<sup>1</sup> Aldington Beasley, ask “...why there is such a huge discrepancy between the management of severe asthma recommended by evidence based guidelines, and that observed in clinical practice”.

Although the guidelines are in fact quite simple and straightforward, I think that non-specialist junior physicians in the emergency department are confused by the apparent complexity of, for example, fig 3 from their article reproduced from the British Thoracic Society guidelines, especially when faced with an extremely unwell patient with asthma.

For a number of years, I have taught a very simple “6 P rule” for the assessment of asthma:

- ▶ **PEFR**—baseline and response to first nebuliser.
- ▶ **Pulse**, >120 (it is not due to salbutamol).
- ▶ **pO<sub>2</sub>** (measure and then titrate oxygen against O<sub>2</sub> saturation).
- ▶ **Panic** (ie, ability to speak/respiratory rate).
- ▶ **Paradox** (patients cannot sustain this for long).
- ▶ **Pneumothorax** (make sure the trachea is central until you can obtain a chest x ray; and do not allow *anyone* to put in a subclavian line).

This is the basic information needed to assess severity, and decide on management, and it is more easily taught and remembered than a complex figure.

## A Woodcock

**Correspondence to:** Professor A Woodcock, University of South Manchester, Southmoor Rd, Manchester M23 9LT, UK; ashley.woodcock@manchester.ac.uk

**Competing interests:** None.

## REFERENCE

1. **Aldington S**, Beasley R. Asthma exacerbations - 5: Assessment and management of severe asthma in adults in hospital. *Thorax* 2007;**62**:447–58.

## Authors' reply

We appreciated Professor Woodcock's comments and practical suggestion of the 6P rule as a quick and simple method for assessing asthma severity. We consider that the crucial issue in considering assessment tools is whether their use results in an appropriate therapeutic response. This can be achieved if assessment tools are directly linked to guidelines for management, which is the approach recommended in the British Thoracic Society algorithm (see fig 3). In this way, management is dictated by the results of the assessments made. Thus while the 6P rule is certainly quick and easy to remember, an appropriate decision will still need to be made, and the British Thoracic Society algorithm represents an ideal system to achieve this outcome.

## R Beasley

**Correspondence to:** Professor R Beasley, Medical Research Institute of New Zealand, PO Box 10055, Wellington, New Zealand; richard.beasley@mri.nz

**Competing interests:** None.

## Innate immune activation in neutrophilic asthma

We would appreciate the opportunity to comment on the very interesting recently published paper by Simpson and colleagues,<sup>1</sup> putatively describing innate immune activation in a “neutrophilic variant” of asthma, in inhaled corticosteroid (ICS) treated patients. We feel that the paper is especially important and effective in highlighting the heterogeneity of airway cellular infiltrates in asthma, especially after exposure to corticosteroid.

We endorse the proposal that neutrophils are involved pathogenically, even in stable asthma. This is likely to be the case even when neutrophils are not grossly elevated in number, and indeed they may be at least as relevant as eosinophils across the board, as suggested in early bronchoscopic studies.<sup>2</sup> In these published data, neutrophil cellular activation, and also macrophage activation, were more marked than their absolute number suggested, even in patients with relatively mild, stable asthma.

Cumulative studies suggest that the role of eosinophils has perhaps been over emphasised in the airways of patients with mild, non-ICS treated asthma. Because eosinophils are so absent generally in normal control data, they give a very strong average signal in asthma. They also decrease markedly in numbers generally with ICS treatment,<sup>3</sup> although symptoms and bronchial hyperresponsiveness may persist. We found it interesting that in the data presented by Simpson and colleagues,<sup>1</sup> the actual numbers of sputum eosinophils in absolute terms in “neutrophilic” asthma were just as elevated

as they were in their “eosinophilic” group. The former sputum samples were generally much more cellular and so the eosinophil percentage was found to be markedly lower. It is difficult to know if this is the more relevant end point to focus on.

Many asthmatic airways are acellular even under baseline conditions, and become even more so with ICS treatment,<sup>3</sup> as Simpson and colleagues<sup>1</sup> point out. This fact tends to get overlooked when using mean data for statistical purposes. The response to ICS therapy is also variable, and some individuals with asthma given ICS show an increase in airway neutrophils<sup>4</sup>; it may be this variant that Simpson and colleagues are describing.<sup>1</sup> Their “paucigranulocytic” group may reflect the more general trend to become less cellular with ICS.<sup>3</sup> Interestingly, we have previously found that long acting  $\beta_2$  agonists had an antineutrophilic and especially an anti-interleukin 8 effect on airway inflammation,<sup>4</sup> which may explain some of its added value in combination with ICS.

Simpson and colleagues<sup>1</sup> did not find an elevation in soluble CD14 in sputum in neutrophilic asthma, as an index of innate immune activation, as we have previously in bronchoalveolar lavage in post-lung transplant bronchiolitis obliterans syndrome, where bacterial infection is likely to be part of the pathogenesis.<sup>5</sup> We wonder whether the increase in toll-like receptor mRNA that they describe could not just reflect the corresponding increase in absolute number of neutrophils and macrophages which carry these receptors? Although Simpson and colleagues<sup>1</sup> raise some highly pertinent issues, many of the questions that arise from their cross sectional study will inevitably need further longitudinal interventional studies.

E H Walters,<sup>1</sup> R Wood-Baker,<sup>1</sup> D E C Reid,<sup>1</sup> C Ward<sup>1,2</sup>

<sup>1</sup>Respiratory Research Group, Menzies Research Institute, University of Tasmania, Tasmania, Australia; <sup>2</sup>Institute of Cellular Medicine, University of Newcastle-upon-Tyne, UK

**Correspondence to:** Professor E H Walters, Department of Clinical Sciences, Menzies Research Institute, University of Tasmania Medical School, Collins St, Hobart, Tasmania 7001, Australia; haydn.walters@utas.edu.au

**Competing interests:** None.

## REFERENCES

1. **Simpson JC**, Grissell TV, Doures J, *et al*. Innate immune activation in neutrophilic asthma and bronchiectasis. *Thorax* 2007;**62**:211–18.
2. **Kelly C**, Ward C, Stenton CS, *et al*. Number and activity of inflammatory cells in bronchoalveolar lavage fluid in asthma and their relation to airway responsiveness. *Thorax* 1988;**43**:684–92.
3. **Ward C**, Reid DW, Orsida BE, *et al*. Inter-relationships between airway inflammation, reticular basement membrane thickening and bronchial hyper-reactivity to methacholine in asthma, a systematic bronchoalveolar and airway biopsy analysis. *Clin Exp Allergy* 2005;**35**:1565–71.
4. **Reid DW**, Ward C, Wang N, *et al*. Possible anti-inflammatory effect of salmeterol against interleukin-8 and neutrophil activation in asthma in vivo. *Eur Respir J* 2003;**21**:994–9.