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## Quality assurance in endobronchial ultrasound

In their study of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), Kemp and colleagues report variation in the learning curves for five operators, studied by using the cumulative sum (cusum) technique,<sup>1</sup> with which we have some experience.<sup>2</sup> The authors speculate on whether variations in lymph node size, prevalence of underlying diagnoses or rate of accrual of cases may explain these differences. We believe there may be other important influences. Successful EBUS-TBNA is a multi-disciplinary process: help is invaluable from colleagues in radiology for identification of suitable target nodes, in bronchoscopy nursing for adequate specimen preparation and in cellular pathology for confident diagnosis based on cytopathological specimens alone. In our experience, each of these aspects is subject to variation between centres. In addition, it is likely that access to prior positron emission tomography (PET) scanning, or different immunocytochemical stains, may have varied. In our view the results should be regarded as being those of the centres in question, and not those of the operators alone.

Kemp and others appear to have misinterpreted the cusum plots shown in their figure 1. The authors use the graphical representation of the cusum favoured by Kestin.<sup>3</sup> In this representation, if the plot crosses two boundaries in succession from below, without crossing a boundary from above in between, unsatisfactory performance is confirmed for the procedure interval between the two upward crossings.<sup>4</sup> Competence is confirmed by analogous downward crossing of two boundaries. Thus operator 4 demonstrates unacceptable performance between procedures 50 and 70 (these procedure numbers are approximate because the graphs reproduced are too small to permit their exact estimation), and to say that he has 'attained competence almost immediately' is not the whole story. Simi-

larly the cusum of operator 2 demonstrates unacceptable performance during the following procedure intervals: 32–43, 43–80 and 80–96. It never demonstrates satisfactory performance. Indeed, the only procedure intervals for which competence is confirmed in figure 1 or figure 2 are procedures 75–95 for operator 1 and 7–47 for operator 4. Therefore, only operator/centre 1 demonstrates competence by the end of the first 100 procedures. Indeed this is the only operator/centre with evidence of any learning—the others perform no better after 100 procedures than before. An alternative interpretation of the results, therefore, is that for some, and possibly most, operators or centres, no learning curve is expected in EBUS-TBNA at all, provided that standards substantially lower than those in the published literature are accepted.

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## Authors' response

We agree with Drs Slade and Slade that success in endobronchial ultrasound-guided transbronchial needle aspiration relies on many factors other than the skill of the actual bronchoscopist and, as such, the term 'operator' may have been misleading. Nevertheless, the operator is going to have the greatest bearing on the results obtained. The article<sup>1</sup> was intended to highlight the need for more accurate methods of assessment of competency in any given task or procedure, using endobronchial ultrasound-guided transbronchial needle aspiration only as an example.

I am sure Drs Slade and Slade recognise that, as in medicine, there are valid alternative interpretations for data. In the referenced paper by Bolsin and Colson,<sup>2</sup> the discussion of Kestin's Cusum plots states that 'acceptable performance will be denoted on this format by a Cusum line which is roughly horizontal or down-sloping'—that is, a line crossing multiple decision intervals from above is not required to say that performance is acceptable. While a horizontal line does not indicate learning per se, this may not necessarily be an appropriate objective in more experienced practitioners/centres where the focus is on monitoring ongoing competence.

The interpretation of statistical methods is always open to differences, but there is little doubt that Cusum analysis allows the effective monitoring of practices and procedures and, when a change in outcomes is observed (whatever predetermined criteria are used), we as clinicians should reflect on our practice in order to determine which aspects of that practice require attention.

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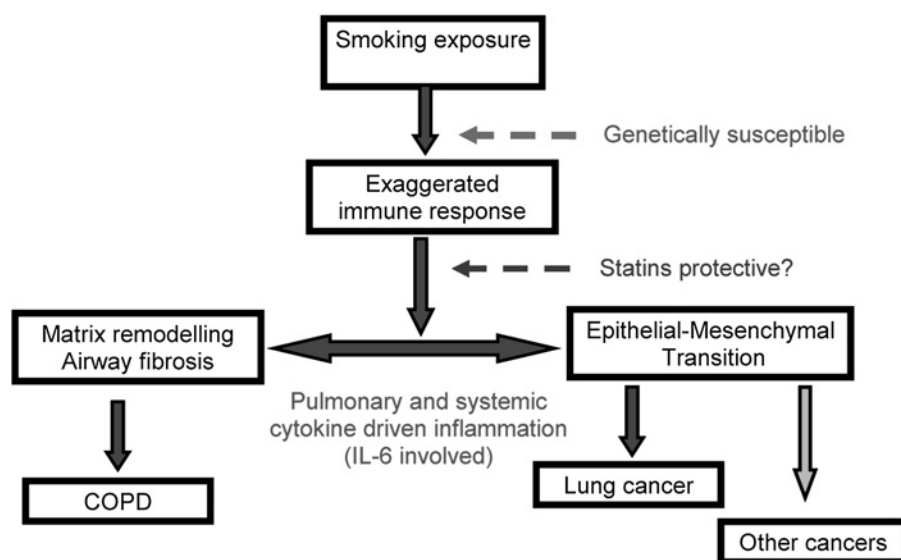
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## Effect of statins on cancer in chronic obstructive pulmonary disease

We read with interest the article by van Gestel *et al*<sup>1</sup> reporting a protective effect of statins on cancer mortality in chronic obstructive pulmonary disease (COPD) patients and suggest here a plausible explanation.

Consistent with the literature, the study shows that COPD is associated with an elevated risk of lung cancer. Recently, we reported that COPD is pre-existing in 70% of lung cancer cases compared with 15% in unselected matched smokers.<sup>2</sup> We agree with van Gestel *et al*<sup>1</sup> that this link is likely to be secondary to a pro-inflammatory disposition resulting from both smoking and genetic susceptibility. In this regard serum interleukin (IL)-6, which is elevated by genetic and



**Figure 1** Relationship linking chronic obstructive pulmonary disease (COPD), lung cancer, extrapulmonary cancer and inflammation.

smoking effects, has been shown to be inversely correlated with the forced expiratory volume in 1 s in prospective studies.<sup>3</sup> In a murine model, overexpression of IL-6 resulted in the development of COPD (emphysema and airway fibrosis).<sup>3</sup> It has been proposed that elevated IL-6 is also associated with epithelial cancers through its growth-promoting effects<sup>4</sup> and the promotion of epithelial–mesenchymal transition (EMT), a well recognised feature of chronic inflammation and a precursor to malignant transformation in the lung.<sup>3</sup> Other cytokines involved in pulmonary inflammation are tumour necrosis factor alpha, IL-1 $\beta$  and IL-8,<sup>3,4</sup> which, together with growth factors like transforming growth factor beta 1 are implicated in EMT.<sup>3</sup> All of these pathways are mediated via guanosine triphosphatase (GTPase) signalling molecules (Rho Rac and Ras).<sup>3</sup> There is also growing interest in the role of systemic inflammation, which not only characterises COPD,<sup>3</sup> but may also be relevant in extrapulmonary epithelial cancers (eg, prostate, breast and colon).<sup>4</sup> These findings might partly explain the increased susceptibility of COPD patients to both lung cancer and extrapulmonary cancers (figure 1).<sup>1</sup>

In a recently published review of statins in COPD,<sup>3</sup> we suggest that the anti-inflammatory effects of statins, through inhibition of GTPases, may explain the protective effect of statin use on lung cancer incidence as reported in three large observational studies (OR 0.45–0.70)<sup>3</sup> and also by van Gestel *et al*<sup>1</sup> (OR 0.46–0.74). Studies show that statins can directly inhibit EMT through GTPase inhibition and inhibit the effects of IL-6, an effect that has been shown to block tumour progression.<sup>4,5</sup> We suggest that the anti-inflammatory actions of statins (eg, anti-IL-6 activity) could underlie the protective effects for both lung cancer<sup>1,3</sup> and extrapulmonary malignancies (figure 1).<sup>1</sup> These observations add considerable weight to existing data that

suggest that statins may be very beneficial to patients with COPD.

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#### Authors' reply

We thank Drs Young and Hopkins for their interest in our study<sup>1</sup> and their interesting explanation for the results observed. It is indeed likely that the relationship between chronic obstructive pulmonary disease (COPD) and cancer (both pulmonary and extrapulmonary) is attributed to cytokine-

induced inflammation mediated by guanosine triphosphatase (GTPase) signalling molecules. This is advocated by the results of Man *et al* who showed that the increased inflammatory state in patients with COPD is associated with future cancer mortality including extrapulmonary cancers.<sup>2</sup>

Statins are associated with reduced cardiovascular morbidity and mortality in patients with cardiovascular disease. Besides the reduction in low-density lipoprotein cholesterol levels, statins also reduce inflammation through reduced expression of inflammatory cytokines which is known as one of the pleiotropic effects of statins.<sup>3,4</sup> A recent double-blind placebo controlled trial in patients who had undergone vascular surgery showed that patients who were treated preoperatively with fluvastatins had significantly decreased levels of interleukin 6 at the time of surgery compared with the placebo group (–33% and –4%, respectively;  $p < 0.001$ ).<sup>4</sup> The same was observed for high-sensitivity C reactive protein, another marker of inflammation, which was decreased by 21% in the fluvastatin group and increased by 3% in the placebo group ( $p < 0.001$ ). Furthermore, patients with elevated inflammatory levels are more likely to benefit from statin therapy than those without elevated levels.<sup>5</sup> This might explain the increased beneficial effects of statins in patients with COPD and cancer observed in our study. Although the results of our study are in line with those of previous studies which suggest that statins might have an important role in patients with COPD (with or without cancer), further studies are needed before statin treatment can be recommended for patients with COPD.

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