Confocal laser endomicroscopy to guide sampling of a pure ground-glass opacity

To the Editor:

We read with great interest the article "Needle-based confocal laser endomicroscopy [CLE] for real-time diagnosing and staging of lung cancer" by Wijmans *et al.* [1], recently published in the *European Respiratory Journal*, demonstrating the feasibility and safety of realtime lung cancer detection by endosonography-guided CLE. The authors elegantly describe three CLE characteristics for lung cancer: dark, enlarged pleomorphic cells; dark clumps; and directional streaming. The accuracy of CLE for detecting malignancy was 90% in tumours and 89% in metastatic lymph nodes.

This realtime visualisation of tumours is of great interest to the pulmonology community. If realtime cancer diagnosis using CLE is obviously not "ready for prime time", CLE could help localise the tumour before sampling, particularly for peripheral lesions. In this work, however, of the 27 lesions explored, most were lymph nodes (n=22) that are sampled through realtime endobronchial ultrasound (EBUS) control, limiting the clinical impact of CLE, and six were solid tumours that are also well visualised using radial EBUS (rEBUS). The most challenging lesions to visualise using rEBUS are ground-glass opacities (GGOs), with a diagnostic yield of only 14% for rEBUS alone [2]. Electromagnetic navigation (EMN), a technology that combines virtual navigation imaging with sensing of the position of a bronchoscopic catheter, matching virtual and real bronchial trees, is usually preferred in this setting.

We herein report the case of a 57-year-old, nonsmoking woman referred to our department for the differential diagnosis of a 15-mm, progressive, pure GGO of the left lower lobe with bronchus sign (figure 1a). Computed tomography (CT)-guided transthoracic biopsy had been considered a risk by radiologists due to proximity to vasculature (figure 1a). EMN was thus performed under general anaesthesia and we hypothesised that probe-based (p)CLE could help for realtime positioning of the guiding catheter. After reaching the nodule using EMN (figure 1b and c), the CLE probe was used through the sheath, and showed studding alveolar walls with an increased frequency of small alveolar entrance rings, septal fibres, and a rigid and dense acinar elastic network (figure 1e) similar to what was previously described by Salaün *et al.* [3] in interstitial lung disease GGOs. Eight forceps biopsies were performed after positioning the guiding sheath in the most abnormal areas using realtime CLE imaging, revealing an atypical single-cell proliferation, which was thyroid transcription factor 1 positive, corresponding to a lepidic-predominant adenocarcinoma (figure 1e and f). No infiltrating component was observed.

Along with the study by Wijmans *et al.* [1], the feasibility of solid-nodule CLE imaging has been demonstrated in other 48 patients after rEBUS localisation [4]. To our knowledge, however, ours is the first report of realtime CLE visualisation of a lepidic adenocarcinoma. We believe this could be of importance because GGOs, unlike solid nodules [5], cannot be seen using fluoroscopy and rEBUS [2], and no technique is available for realtime visualisation of GGOs. In the large NAVIGATE prospective, multicentre trial, sensitivity of EMN was 69% for peripheral pulmonary lesions [6]. This imperfect sensitivity may be due, among other factors, to the non-realtime aspect of this approach, airway anatomy being slightly different under general anaesthesia and ventilation compared to the forced inspiration of CT acquisition. Sensitivity of EMN could be increased using systematic realtime control: rEBUS control for solid nodules and thus, maybe CLE for pure GGOs. GGOs will become an increasing challenge for

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Confocal laser endomicroscopy imaging of lepidic adenocarcinomas is feasible. This technique should be further evaluated as a realtime guiding tool during virtual electromagnetic navigation bronchoscopy for ground-glass opacities https://bit.ly/3uzTcMU

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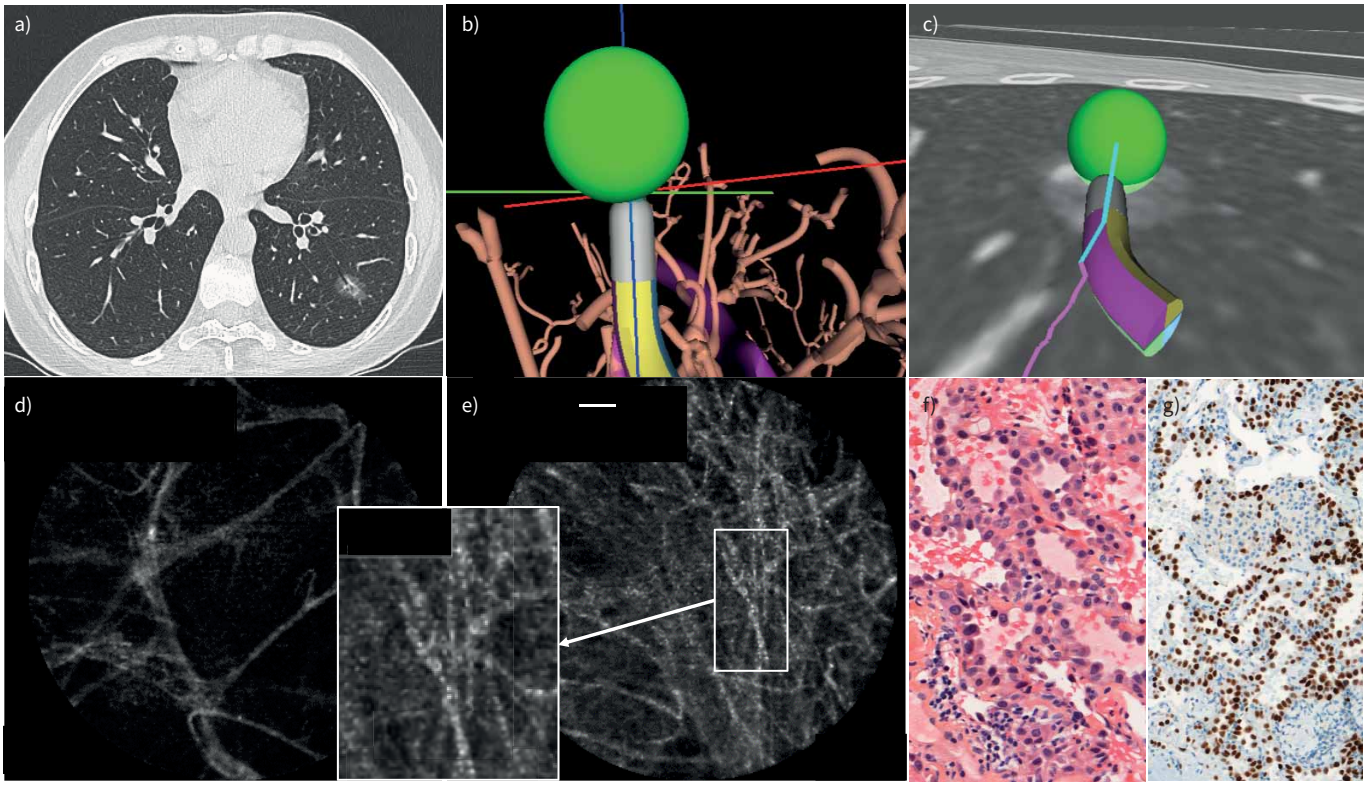

FIGURE 1 a) Pulmonary transverse window image of chest computed tomography scan showing a pure ground-glass opacity of the left lower lobe with bronchus sign. b and c) Position of the catheter in the ground glass opacity during electromagnetic navigation procedure. d and e) probe-based confocal laser endoscopy (pCLE) image comparing a normal *versus* a lepidic pattern in pCLE with studding alveolar walls and dense acinar elastic network. Scale bar=50 µm. f) Haematoxylin and eosin stain shows an atypical single-cell proliferation lining alveolar walls (magnification 40×). g) Immunohistochemical staining with anti-thyroid transcription factor (TTF)1 antibodies (brown) highlights a $TTF1^{+}$ cell proliferation (magnification 20×).

pulmonologists with the generalisation of low-dose CT screening programmes after the positive results of the NELSON trial [7]. NCCN (National Comprehensive Cancer Network) guidelines recommend solely CT follow-up (6–12 months) for ⩾6-mm pure GGOs, which tend to be associated with good prognosis [8]. In cases of growth and/or apparition of a solid component, direct surgical resection or biopsy can be discussed during a multidisciplinary meeting [9]. This first observation suggests an approach combining virtual EMN and a realtime pCLE "feedback" to identify the optimal areas for sampling, which could increase the yield of bronchoscopy for GGOs. Furthermore, if surgery obviously remains gold of standard in this setting, new potential bronchoscopic approaches (radiofrequency, microwave, cryo- or vapour ablations) for the treatment of peripheral early-stage non-small cell lung cancer are emerging [10]. A very accurate localisation control will be needed and CLE could be of help in cases of lepidic adenocarcinomas.

In conclusion, CLE imaging of lepidic adenocarcinomas is feasible. This technique should be further evaluated as a realtime guiding tool during virtual EMN bronchoscopy for GGOs.

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