More than meets the eye

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Shareable abstract (@ERSpublications)
Autofluorescence bronchoscopy can detect proximal preneoplastic lesions. Intensive surveillance with this modality, however, may not alter health outcomes. https://bit.ly/3s98vN1

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Lung cancer biology has changed, with a histological shift from the previously dominant central squamous cell carcinoma to peripheral lung adenocarcinomas. Changes in cigarette characteristics and smoking practice are commonly attributed; however, other carcinogens such as air pollution and diesel fumes may also play an as yet unidentified role in lung cancers in never-smokers [1]. This shift and advances in cross sectional imaging have resulted in increasing adoption of low dose computed tomography (CT)-based lung cancer screening, when earlier attempts with chest radiography and sputum cytology failed [2].

Nonetheless, due to global case numbers (>2 million), there is an ongoing clinical need to address this challenging subset of central cancers and effectively prevent and/or manage potentially pre-neoplastic changes and cellular atypia, ranging from hyperplasia, metaplasia, grades of dysplasia and carcinoma *in situ*, to avoid invasive cancer.

Bronchoscopic inspection and longitudinal surveillance is the basis of the clinical approach to pre-invasive airway lesions [3–5], and has also enabled research which posits a stepwise evolution of ever more disordered pre-invasive lesions, ranging from mild and moderate dysplasia (low-grade lesions) to severe dysplasia and carcinoma *in situ* underpinned by accumulating molecular aberrations [6]. Moreover, the observation that bronchial airway gene expression alterations may predict risk of lung cancer development is consistent with field cancerisation [7], emphasises the link between morphology and biology and has led to efforts to translate a candidate airway epithelial biomarker [8, 9].

While higher grade lesions more often progress to invasiveness, this is not invariable [10–13], with progression rates using different endpoints reported between 43% and 87% [14], making generalisation to surveillance algorithms difficult.

White light bronchoscopy has been boosted by technological advances, adding on autofluorescence bronchoscopy (AFB) and/or narrow band imaging [15–19], with both in combination potentially more sensitive than each technique, but of course resulting in a more costly strategy [20]. Other technologies, such as optical coherence tomography, confocal endomicroscopy and laser Raman spectroscopy, are in active development [21].

In this issue of the *European Respiratory Journal*, Guisier *et al.* [22] describe a large, prospective, French multicentre randomised study comparing surveillance strategies for patients with heavy smoking (60% active smokers) including the 20% with histologically confirmed low grade preinvasive lesions at initial bronchoscopy. Participants were randomised to routine follow-up (clinical review and 6-monthly chest radiograph), or an added intensive AFB bronchoscopic surveillance at 6- or 12-month intervals; all underwent bronchoscopy and CT scan at 36 months with long-term follow-up. They report that mild or moderate dysplasia at baseline bronchoscopy was a significant lung cancer risk factor both at 3 years (OR 6.9, 95% CI 2.5–18.9) and at maximum follow-up (OR 5.9, 95% CI 2.9–12.0). While intensive

bronchoscopy surveillance did not improve patient outcomes, smoking cessation was significantly associated with clearance of bronchial dysplasia at follow-up (OR 0.12, 95% CI 0.01–0.66; p=0.005) and with a reduced risk of lung cancer at 5 years (OR 0.15, 95% CI 0.003–0.99; p=0.04), reminding us that smoking cessation continues to be front and centre to counter this cancer.

We congratulate the authors on their significant achievements in a challenging disease to research; a cohesive collaboration maintaining focus for a high quality randomised controlled trial across multiple centres to achieve adequate follow-up and minimising dropouts, central pathology review and convincing statistical handling. No study is perfect however, with some uncertainty resulting from: potential biases from recruitment of the group with occupational exposure compared to those with previous curatively treated smoking-related cancers and those with just a heavy smoking history as their lung cancer risks would almost certainly differ; the fact that the central panel review did not include every biopsy undertaken with some histopathological discordance; and the possibility that these tiny lesions may be completed removed at biopsy (a concept advanced by the legendary pathologist, Adi Gazdar, pre-eminent pioneer of lung preneoplasia research).

The authors conclude that while intensive bronchoscopy surveillance does not improve patient outcome, the identification of bronchial dysplasia during initial bronchoscopy may be useful for risk stratification strategies in lung cancer screening programmes, as a substantial proportion of lung cancers that developed during the surveillance programme were peripheral lung adenocarcinomas. This concept has been tested in trials, in various combinations with sputum cytology and low dose CT screening [23–26] but not yet proven ready for prime time.

Perhaps more fruitful will be innovative research exploiting “omics” to molecularly characterise pre-malignant lung lesions in the proximal airways, with emerging new knowledge [8, 27] and anticipated from the multicentre multiomic Lung PreCancer Atlas effort [28, 29]. A better understanding of preneoplasia evolution will not only help us design better screening strategies, but also help address the void in secondary prevention [30] for central cancers as well as peripheral cancers.

Lung cancer is evolving and in the late 20th century, pulmonary adenocarcinoma became predominant, overtaking squamous cell carcinoma. This is presumed to be a consequence of changes in tobacco agriculture, curing and manufacturing processes, including the use of ventilated filters, leading to higher levels of free-base nicotine, more addictive products, deeper inhalation of cooler and less harsh smoke, and increased tobacco-specific nitrosamine concentrations [31]. In this regard, it is notable that evidence is mounting that electronic cigarettes can also exert marked adverse biological effects on the airways [32], and that vape liquids contain known carcinogens [33–35].

To conclude, this helpful study adds considerably to our relatively limited knowledge of lung preneoplasia, strongly reinforces smoking cessation benefits, speaks against low value medical interventions that do not improve health outcomes and spurs research efforts [36] in order to harness modern “omics” and advanced bronchoscopy to enable more effective screening, detection and secondary prevention strategies for this terrible disease. Much more is needed than meets the eye.

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References

1 Lam S. Lung cancer screening in never-smokers. *J Thorac Oncol* 2019; 14: 336–337.
2 Marshall HM, Bowman RV, Yang IA, *et al.* Screening for lung cancer with low-dose computed tomography: a review of current status. *J Thorac Dis* 2013; 5: Suppl. 5, S524–S539.
3 Salaun M, Bota S, Thiberville L. Long-term follow-up of severe dysplasia and carcinoma in situ of the bronchus. *J Thorac Oncol* 2009; 4: 1187–1188.
4 van Boerdonk RA, Smesseim I, Heideman DA, *et al.* Close surveillance with long-term follow-up of subjects with preinvasive endobronchial lesions. *Am J Respir Crit Care Med* 2015; 192: 1483–1489.
5 Jeremy George P, Banerjee AK, Read CA, *et al.* Surveillance for the detection of early lung cancer in patients with bronchial dysplasia. *Thorax* 2007; 62: 43–50.
6 Wistuba II, Behrens C, Milchgrub S, *et al.* Sequential molecular abnormalities are involved in the multistage development of squamous cell lung carcinoma. *Oncogene* 1999; 18: 643–650.
7 Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* 1953; 6: 963–968.
8 Beane J, Mazzilli SA, Tassinari AM, *et al.* Detecting the presence and progression of premalignant lung lesions via airway gene expression. *Clin Cancer Res* 2017; 23: 5091–5100.
9 Silvestri GA, Vachani A, Whitney D, *et al.* A bronchial genomic classifier for the diagnostic evaluation of lung cancer. *N Engl J Med* 2015; 373: 243–251.
10 Breuer RH, Pasic A, Smit EF, *et al.* The natural course of preneoplastic lesions in bronchial epithelium. *Clin Cancer Res* 2005; 11: 537–543.
11 Daniels JM, Sutedja TG. Detection and minimally invasive treatment of early squamous lung cancer. *Ther Adv Med Oncol* 2013; 5: 235–248.
12 Ishizumi T, McWilliams A, MacAulay C, *et al.* Natural history of bronchial preinvasive lesions. *Cancer Metastasis Rev* 2010; 29: 5–14.
13 Merrick DT, Gao D, Miller YE, *et al.* Persistence of bronchial dysplasia is associated with development of invasive squamous cell carcinoma. *Cancer Prev Res (Phila)* 2016; 9: 96–104.
14 Kalinke L, Thakrar R, Janes SM. The promises and challenges of early non-small cell lung cancer detection: patient perceptions, low-dose CT screening, bronchoscopy and biomarkers. *Mol Oncol* 2021; 15: 2544–2564.
15 Palcic B, Lam S, Hung J, *et al.* Detection and localization of early lung cancer by imaging techniques. *Chest* 1991; 99: 742–743.
16 Shibuya K, Hoshino H, Chiyo M, *et al.* High magnification bronchovideoscopy combined with narrow band imaging could detect capillary loops of angiogenic squamous dysplasia in heavy smokers at high risk for lung cancer. *Thorax* 2003; 58: 989–995.
17 Bota S, Auliac JB, Paris C, *et al.* Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence endoscopy. *Am J Respir Crit Care Med* 2001; 164: 1688–1693.
18 Fuso L, Pagliari G, Boniello V, *et al.* Autofluorescence bronchoscopy to identify pre-cancerous bronchial lesions. *Monaldi Arch Chest Dis* 2005; 63: 124–128.
19 Haussinger K, Becker H, Stanzel F, *et al.* Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: a European randomised controlled multicentre trial. *Thorax* 2005; 60: 496–503.
20 Gizinger OA, Zarucheinova OV, Zima MA, *et al.* The evaluation of detection rate of *Mycoplasma hominis* and *Ureaplasma* spp. using cultural technique and polymerase chain reaction. *Klin Lab Diagn* 2017; 62: 60–64.
21 Ohtani K, Lee AM, Lam S. Frontiers in bronchoscopic imaging. *Respirology* 2012; 17: 261–269.
22 Guisier F, Deslee G, Birembaut P, *et al.* Endoscopic follow-up of low-grade precancerous bronchial lesions in high-risk patients: long-term results of the SELEPREBB randomised multicentre trial. *Eur Respir J* 2022; 60: 2101946.
23 Tremblay A, Taghizadeh N, McWilliams AM, *et al.* Low prevalence of high-grade lesions detected with autofluorescence bronchoscopy in the setting of lung cancer screening in the pan-Canadian lung cancer screening study. *Chest* 2016; 150: 1015–1022.
24 Spiro SG, Shah PL, Rintoul RC, *et al.* Sequential screening for lung cancer in a high-risk group: randomised controlled trial: LungSEARCH: a randomised controlled trial of Surveillance using sputum and imaging for the EARly detection of lung Cancer in a High-risk group. *Eur Respir J* 2019; 54: 1900581.
25 McWilliams AM, Mayo JR, Ahn MI, *et al.* Lung cancer screening using multi-slice thin-section computed tomography and autofluorescence bronchoscopy. *J Thorac Oncol* 2006; 1: 61–68.
26 McWilliams A, Mayo J, MacDonald S, *et al.* Lung cancer screening: a different paradigm. *Am J Respir Crit Care Med* 2003; 168: 1167–1173.
27 Teixeira VH, Pipinikas CP, Pennycuick A, *et al.* Deciphering the genomic, epigenomic, and transcriptomic landscapes of pre-invasive lung cancer lesions. *Nat Med* 2019; 25: 517–525.
28 Srivastava S, Ghosh S, Kagan J, *et al.* The precancer atlas (PCA). *Trends Cancer* 2018; 4: 513–514.
29 Spira A, Yurgelun MB, Alexandrov L, *et al.* Precancer atlas to drive precision prevention trials. *Cancer Res* 2017; 77: 1510–1541.

30 Keith RL, Blatchford PJ, Merrick DT, *et al.* A randomized phase II trial of pioglitazone for lung cancer chemoprevention in high-risk current and former smokers. *Cancer Prev Res (Phila)* 2019; 12: 721–730.
31 Office of the Surgeon General. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, Centers for Disease Control and Prevention, 2010.
32 O'Farrell HE, Brown R, Brown Z, *et al.* E-cigarettes induce toxicity comparable to tobacco cigarettes in airway epithelium from patients with COPD. *Toxicol In Vitro* 2021; 75: 105204.
33 Byrne S, Brindal E, Williams G, *et al.* E-cigarettes, Smoking and Health. A Literature Review Update. CSIRO (Australia), 2018.
34 National Academies of Sciences, Engineering, and Medicine. Public Health Consequences of E-Cigarettes. Washington, The National Academies Press, 2018.
35 Larcombe A, Allard S, Pringle P, *et al.* Chemical analysis of fresh and aged Australian e-cigarette liquids. *Med J Aust* 2022; 216: 27–32.
36 Gomez-Lopez S, Whiteman ZE, Janes SM. Mapping lung squamous cell carcinoma pathogenesis through *in vitro* and *in vivo* models. *Commun Biol* 2021; 4: 937.