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Editorial

Shining light on pleural biopsy in Mesothelioma – is it time to get 'smart'?

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Malignant Pleural Mesothelioma (MPM) is primarily caused by asbestos inhalation (85% of cases) and predominantly diagnosed in men (M:F, 4:1). Approximately 2500-3000 new cases are reported each year in the United Kingdom with similar numbers in the United States[1,2]. As a result of ongoing exposure in parts of Asia and South America, combined with a prolonged latency period of up to 40 years, the worldwide incidence of MPM is still on the rise.

A major barrier to progress in treatment is the delay of diagnosis and the inability to detect "early disease", not least due to MPM symptoms being largely non-specific and late in disease progress. Prognosis is highly variable but average survival rates are poor, with median survival of 6.5 months, 1 year survival 38% and 3 year survival 7% [3]. Some improvement is anticipated in coming years, with the emergence of immunotherapy and the potential for more targeted treatment. Prognosis depends on many factors, including the stage at diagnosis and therefore early detection has been shown to improve survival in MPM.

Medical thoracoscopy permits macroscopic examination of the pleural surface using white light and obtaining sizeable pleural biopsies, with sensitivities reaching 94%[4]. Where thoracoscopy is not possible, alternative biopsy approaches, under CT and ultrasound guidance, can be offered. However, not infrequently, these yield inconclusive histopathological results such as fibrosis and non-specific pleuritis. Often due to unacceptable surgical biopsy risk, this leaves patients with the anxiety of an uncertain diagnosis and subject to a minimum of 1 year radiology follow up[5]. Combined data from three series, comprising 280 patients, demonstrate that pleural malignancy is eventually diagnosed in up to 15% of these patients [5–7].

In this edition of CHEST, *Wijmans et al* report their study on the use of real-time confocal laser endomicroscopy (CLE) to perform targeted pleural biopsies, a form of 'smart' biopsy. This novel endoscopic method permits real-time microscopy at time of biopsy. The technology has been present since the late 1950's but its clinical application was first described in the literature in 2004[8] as a tool to perform real-time histological analysis of colonic mucosa during colonoscopy for diagnosing colorectal cancer *in vivo*. Since then, its utility in various organ systems has been widely investigated. In the scope of interventional pulmonology, this had previously been limited to lung cancer; where there is still insufficient evidence to advocate routine use, mainly due to uncertain diagnostic yields and inaccurate CLE image characteristics of malignant lesions. *Wijmans et al* also recently described its use in transbronchial lung cryobiopsies in interstitial lung disease. A small case series was published earlier this year reporting the first use of probe-based CLE during medical thoracoscopy[9].

Wijmans et al should be congratulated on the first prospective study of this technique in pleural biopsy. This was a feasibility study, from two centres in Amsterdam, of 15 patients with suspected MPM on PET-CT imaging. Twenty procedures were evaluated comprising a combination of transthoracic (US or CT guided) (n=12), endoscopic

ultrasound (EUS) (n=1), and surgical excision biopsies (n=3) using needle-based CLE (nCLE) as well as thoracoscopic biopsies (n=4) where the pleural surface was scanned using probe-based CLE prior to obtaining the biopsy (pCLE). A further *ex-vivo* examination of the biopsy specimens was conducted using CLE by holding the probe in contact with the tissue surface and a video recording taken, prior to being sent for histological analysis.

The literature on CLE, mostly from gastrointestinal (GI) endoscopy, suggests that adverse events are primarily related to the allergic properties of contrast agents. In a study of >2000 GI CLE procedures using intravenous fluorescein, no serious events were reported and mild adverse events occurred in 1.4%[10]. The primary outcome of this study by *Wijmans et al* would echo this favourable safety profile with no study related adverse events reported.

In terms of performance of CLE in diagnosing MPM, taking into account the small numbers, in 16 biopsies obtained from 3 thoracoscopy patients, CLE outperforms white light with a modest increase in sensitivity from 74% to 79%. However, use of the two techniques in combination led to correct detection of malignancy 13 out of 14 biopsy locations (sensitivity 93%).

From a practical perspective, admittedly unexpected to the investigators, there was a significant time difference between fluorescein reaching the pleura (5-7 mins) compared to intrathoracic tumours and lymph nodes (1 minute). In addition to the standard equipment set up, typically about 10 minutes, time consumption may prove to be a limitation for its use in pleural biopsy.

However, there appears to be significant potential in the concept of utilising CLE in the diagnosis of MPM, particularly with regard to the distinct CLE images the investigators identified between benign and malignant pleural disease. Their notion that identifying a 'non-cellular bundle' pattern on CLE eventually proving highly specific for pleural fibrosis and potentially negating the need for biopsy is thought-provoking and warrants further study. Significant consideration will be needed as to how this potential biopsy pathway is delivered, with input from the proceduralist and pathology probably required.

Only moderate IOA was observed between the 3 blinded raters of the CLE recordings despite specific training. Similar to every advanced endoscopy technique, CLE in the setting of pleural disease would require a robust training pathway, in both histopathology and technical aspects. With the basic equipment set costing around $175,000 and probes in the range of $7,000-$10,000 each[11], certainly in publicly funded national health care systems, such as ours in the UK, further studies are needed to determine practicality and cost-effectiveness, before CLE has a realistic chance of being integrated into practice.

Nonetheless, Wijmans et al have designed and delivered an excellent study demonstrating exciting technology to be safe and feasible. Early disease detection will be vital to progress in MPM, and CLE has huge potential in this regard. If fully validated as a 'smart' biopsy device, the future may include its utility as a MPM screening tool in asbestos-exposed individuals, with the prospect of facilitating risk stratification to inform who and when to biopsy.

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