Editorial

Insights from the European Respiratory Society 2018 Annual International Congress in the fields of thoracic surgery and lung transplantation

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Introduction

The European Respiratory Society (ERS) Annual International Congress 2018 held in Paris featured exciting research studies on the topics thoracic surgery and lung transplantation (LT) in assembly 8 of the ERS. In this article, we highlight five studies featured at the Congress and discuss their impact.

Tumor marker assessment in cytologically negative pleural effusions from lung cancer by machine learning-based approach

Rapid and concise diagnostics of pleural effusion can be challenging. Cytology of the pleural fluid is usually the least invasive and fastest way to diagnose malignant pleural effusion. Nevertheless, the diagnostic result fluctuates, largely depending on tumor characteristics and its extensiveness, with a diagnostic yield between 62% and 90% (1,2).

Currently, regular biochemistry measures are used in the differential diagnosis of malignant pleural effusion to guide the differential diagnosis in the case of a negative cytology. Tumor marker detection in pleural effusion is not routinely used as its clinical value remains unclear.

Elia *et al.* present a study this ERS to with the aim to identify which combination of tumor markers in serum and pleural fluid would be best suited to improve diagnostic accuracy (3). For this purpose, they designed a study with serum and pleural fluid from 168 patients, of which 124 patients had video assisted thoracoscopic (VATS) biopsy proven malignancy and 44 patients with biopsy proven non-malignant pleural disease. In these patients specimens they measured a panel of tumor makers [carcinoembryonic antigen (CEA), carbohydrate antigen 125 (Ca 125), carbohydrate antigen 19.9 (Ca 19.9), cytokeratin fragment 21-1 (CYFRA 21.1) and neuron-specific enolase (NSE)] in all samples of these patients. Then a machine Learning-based approach was used to derive the model with best diagnostic accuracy [expressed by the highest area under the receiver operating curves (ROC)] and express this using a mathematical formula.

This machine learning based approach indicated that (a formula with) CEA and CYFRA 21-1 in pleural fluid achieved the best diagnostic accuracy in this cohort, with an area under ROC curve of 95%, sensitivity of 97%, specificity of 93% and positive predictive value of 98%. They conclude this algorithm using these two markers is best suited to aid the diagnostic process in patients with cytology negative malignant pleural effusion.

This is not the first study trying to optimize the diagnostic process of malignant pleural effusion using measurement of multiple tumor markers in pleural effusion. For example, Son *et al.* measured a comparable set of markers in pleural effusion and tested which combination of markers had best diagnostic accuracy. In their study the combination of CEA with CA 19-9 reached a sensitivity of 91.5% and a specificity of 98.1% (4). One can question what novelty the current trial brings as at first glance the results regarding sensitivity and specificity seem somewhat comparable. However, the trial of Elia *et al.* encompasses two major novelties: at first this new study used patient-

samples of those with initially negative cytology and VATS proven diagnosis, in contrast to other biomarker studies that generally used cytology-based diagnosis (4). This is an important difference, as the diagnostic challenge and potential added value of using tumor markers lies in those with initially negative cytology that represent a more challenging group.

The second important novelty that also nicely fits in our current era is the use of machine-based learning to device the most precise algorithm using these tumor markers in the diagnosis of malignant pleural effusion.

Nevertheless, their algorithm is not yet ready for general clinical use. Whereas this study could represent a major step forward, important questions do remain. This study was meant to derive a model. This model fits their relatively small dataset perfectly, but for now it remains unclear how it would perform in other cohorts. Independent validation of the algorithm needs to follow.

Knowing that the yield of a first cytology in the case of pleural effusion of unknown origin shows malignancy in around 50%, increasing to 65–70% after a second or third puncture (5), at what point in the diagnostic process the measurement of tumor markers has the most added value?

Prospective tests should follow side by side with the current diagnostic strategy to see how large the added yield of measuring the biomarkers really is, at what point in the diagnostic process, and how many VATS biopsies could be prevented leading to more prompt and less invasive diagnosis. Lastly, it would be interesting to see how easily a mathematically derived formula can be used in general practice.

All in all, this novel trial of Elia *et al.* using rigorous design and computer-based learning gives important new insights in the potential of tumor markers in this field, but questions remain. This development and the novel results will be followed with great interest.

Influences of primary graft dysfunction (PGD) on parenchymal remodeling after lung transplantation detected by mean quantitative computed tomography (QCT)

PGD is a one of the most common early complication after LT. It represents an acute lung injury that typically occurs in the first 72 hours after LT and clinically varies from mild to very severe form. PGD is defined as hypoxemia [defined by the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2 ratio)] combined with the presence of radiographic infiltrates consistent with edema, after exclusion of other causes (cardiac pulmonary edema, bacterial or viral infection, hyperacute rejection of vascular surgical complications). Its severity is determined by the PaO_2/FiO_2 ratio, and PGD is graded at four time points over the first 72 hours after transplantation (6). PGD is associated with both short and long-term adverse outcomes (7).

There is emerging recognition of the need for QCT imaging to move beyond mere subjective interpretation (8). Recent studies have found QCT metrics demonstrate stronger correlations with pulmonary function tests than semi-quantitative scores by radiologists.

The group of Salito *et al.* examined the use of functional mask derived CT parameters to determine whether development of PGD is associated with short and/or long term postoperative evidences of pulmonary function alterations (9). They selected 18 consecutive patients that underwent bilateral LT. PGD scores were recorded at 24, 48 and 72 hours after LT according to the criteria (6), and CT scans were performed at 3 and 12 months after LT. The group of patients was divided in patients without PGD (defined as PGD 0 at all-time points) and patients with PDG (defined as PGD 2 and/or 3). The CT scans were analyzed for a range of patterns, being; specific gas volume (SVg) changes normalized on expiratory SVgEXP of the whole lung (ΔSVg/SVgEXP) and functional masks of density variation (ΔHU), namely maps of low ventilation (LV), consolidation (C), air trapping (AT) and healthy parenchyma (H).

After LT there was evidence of a marked decrease in ΔSVg/SVgEXP, indicative of a high degree of ventilation defects. The patients that had PGD had higher percentages of LV, whereas percentages of AT and C were negligible.

No prior studies have looked into the effects of PGD on imaging patterns. It is known that PGD is an significant independent risk factor for bronchiolitis obliterans syndrome (BOS) development and progression after LT, with increased severity of PGD being associated with higher risk of development and progression of BOS and consequently mortality (10). However, the mechanisms through which this occurs remain poorly defined. The results in this study indicated that PGD was associated with consecutive higher degree of ventilation defects, but not air trapping, although air trapping is generally considered a hallmark feature of bronchiolitis obliterans (8). The current study therefore demonstrates feasibility of giving insight into the effects on pulmonary patterns after PGD, using CT functional mask, but so far has not yet brought us closer to understanding the long-term effects of PGD

on pulmonary function nor on the link between PGD with BOS at this point. We hope further studies using such novel techniques will help us better understand the effect of PGD on pulmonary graft function.

Relationship between emphysematous lung volume and pulmonary function changes for lobectomized patients

Emphysema can be quantified noninvasively from CT measurements of lung attenuation. It has been shown that despite only mild to moderate airway obstruction, the presence of these emphysematous areas is associated with impaired exercise ventilatory efficiency and poor exercise tolerance (11).

In the study of Yokoba *et al.* it was examined whether there was a correlation between the post-surgery pulmonary function changes and symptoms and the resected amount of low attenuation volume (LAV) in patients undergoing a lobectomy for lung cancer (12).

They examined 57 lung cancer patients that underwent resection of one or more lobes. Of those patients 27 were diagnosed with chronic obstructive pulmonary disease (COPD) with mild to moderate airflow obstruction, others did not have airflow obstruction. In total 35 upper lobes and 23 lower lobes were resected. The amount of LAV was quantified from three-dimensional volume rendering lung images by HRCT. The mean amount of LAV was 20–28% in the upper lobes and 11–12% in the lower lobes, in agreement with general findings that upper lobe emphysema is most prevalent.

Lung function (VC, FEV1, %FEV1, %DLco, %DLco/VA) and symptoms (Modified medical research council (mMRC) dyspnea score and COPD assessment test (CAT) score) were measured at 3 and 12 months post-surgery, and the changes in these measures between 3 and 12 months where correlated to the LAV. The authors previously reported an improvement of the VC after right lung lobectomy and improvement on %DLco on lower lobe lobectomy between 3 and 12 months post-surgery. Their rationale on these findings is that a part of the lung parenchyma and function are lost, but this can improve again depending on the quality of the lung area resected and the time elapsed from the surgery. In their current analysis their previous findings were however not clearly found to be related to the LAV of the resected lobe.

Theoretically, resecting a relatively emphysematous lobe of lung could give space to the relatively less emphysematous parts of the lung and this help improving ventilation, analogous to what has been shown in surgical lung volume reduction surgery (13). However, this would only be the case in patients with evidence of air trapping and hyperinflation in selected lobes.

Possibly, the small numbers of this study and especially the small number of patients with moderate airflow obstruction precluded concise conclusions and it remains unclear what the significance of the found associations is at this point.

Clinical implications of host-bacteria-virus interactions in lung transplantation

The development of chronic lung allograft dysfunction (CLAD) is one of the most frequent limitations of extended survival after LT. BOS is the major cause of CLAD after LT. The exact pathogenesis of BOS remains unclear and it prognosis is poor with limited therapeutic options in established disease. It is characterized by a persistent FEV1 decline from baseline post-transplant value of <80% predicted for at least 3 weeks (14). Bacterial, viral and fungal infections have been associated with the development of BOS (15-17). Furthermore, antibiotic treatment of BOS may result in decreased airway inflammation and stabilization or improvement of BOS (18).

Wurlod *et al.* examined changes in bacterial and viral load after LT (19). A total of 135 bronchoalveolar lavages (BAL) from 36 patients after LT were analyzed. After isolation of DNA and RNA, they examined bacterial load using 16SrRNA gene sequencing and anellovirus load by quantitative PCR. They then derived a bioinformatics tool based on Similarity Network Fusion for the aggregation of complementary information linked to lung microbiota composition and host gene expression profile. In their study, they found four clusters between which transplant recipients were commonly observed to switch. Two closely related clusters linked to highly active host humoral and cellular immunity, respectively, displayed low bacterial load, BAL neutrophils and infection rate. In contrast, an inflammatory cluster that markedly differed based on these criteria was associated with higher anellovirus carriage, stronger expression of host matrix degradation genes and a consistently lower ratio of current FEV1 to best post-transplant FEV1. They conclude that integration of data on bacteria, viruses and host cells may represent the status of organ function and has potential for prediction of outcomes.

Non-culture based techniques have been developed to characterize the entire human microbiome in various

diseases (20). Data on dysregulation of the lung microbiota have shown different results varying from increased to decreased diversity of the microbiome and other BAL results of infection and inflammatory status (21-23). This study by Wurlod *et al.* contributes to previous data that the microbiome after LT can alter over time, with distinct clusters to be identified possibly in relation to clinical outcome. Up to date, it is not known whether the alterations in host-bacteria-virus interactions after LTs contribute to airway inflammation and thus BOS itself or are the result of altered and disordered immune tolerance.

Uniportal video thoracoscopic surgery on awake patients

While traditional thoracotomy remains the standard approach for many thoracic surgeons throughout the world, in the era of modern thoracic surgery, minimally invasive procedures such as robotic thoracic surgery and VATS are gaining ground year by year with some of them becoming the gold standard. Awake thoracoscopic procedures are not a new idea in the area of thoracic surgery, since they were the method of choice before the introduction of mechanical ventilation in the 60's (24).

In the study of Athanassiadi *et al.* 46 patients underwent awake thoracoscopic procedures for various thoracic diseases (25). Concerning the anesthetic technique, propofol, fentanyl and pethidine were used, without the presence of an anesthetist. Regarding the surgical technique, the uniportal approach was sufficient in all cases, without having the need for an extra port in any of the cases. The variety of operations performed comprised simple procedures as well as more complex ones like pulmonary nodule resection and pleural decortication.

The authors presented excellent results for all of the patients. Average time of surgery was h 41.0 min, average length of chest tube drainage post-surgery varied from 2–15 days depending on the indication. No complications were noted.

Based on these results the authors concluded that the awake VATS procedure with uniportal access is a technically feasible and cost-effective minimally invasive alternative for various chest diseases.

In the last decade, an increasing number of papers regarding awake thoracoscopic procedures has been published. In regards to the technique itself, Bedetti *et al.* and Pompeo *et al.* both reported that with different anesthetic management, either regional anesthesia or combination of local anesthesia and propofol, a surgeon can perform various procedures with low morbidity, low cost and excellent diagnostic yield (24,26).

Similar results were reported from McDonald *et al.* in a study comparing the efficacy and cost of awake thoracoscopy versus VATS in cases of undiagnosed pleural effusions (27). Awake thoracoscopy, performed by an experienced team, seems to have no significant statistical difference concerning the diagnostic yield. Also, the complication rate is non-inferior and no additional pleural procedures were needed. Finally, the mean cost for the awake patients was lower due to the shorter mean duration of hospitalization and the higher procedures' costs for the regular VATS patients.

On the other side, it should be noted that not all indications are suitable for awake uniportal VATS, but still require multiportal VATS or thoracotomy. Also, the absence of anesthetist warrants alternative safety measures and additional training for the team.

In summary, the excellent efficacy and low cost of the awake thoracoscopic procedures for selected cases was confirmed by Athanassiadi *et al.*, not requiring an anesthetist in the operating theater without it having an effect on morbidity or complication rate even in relatively complex procedures. Thus, awake VATS could be a safe and feasible alternative in meticulously selected patients with a similar diagnostic yield as conventional VATS and with shorter length of stay and lower average per-procedure cost.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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