



ERS International Congress 2021: highlights from the Thoracic Surgery and Lung Transplantation Assembly

Saskia Bos ^{1,2}, Sara Ricciardi ³, Edward J. Caruana ⁴, Nilüfer Aylin Acet Öztürk⁵,
Dimitrios Magouliotis ⁶, Cecilia Pompili ⁷, Marcello Migliore⁸, Robin Vos ⁹, Federica Meloni ¹⁰,
Stefano Elia ¹¹ and Merel Hellemons ^{12,13}

¹Newcastle University Translational and Clinical Research Institute, Newcastle upon Tyne, UK. ²Institute of Transplantation, The Newcastle Upon Tyne Hospital NHS Foundation Trust, Newcastle Upon Tyne, UK. ³Unit of Thoracic Surgery, IRCCS University Hospital of Bologna, Italy and University of Bologna, Bologna, Italy. ⁴Dept of Thoracic Surgery, Glenfield Hospital, Leicester, UK. ⁵Dept of Pulmonology, Uludag University Faculty of Medicine, Bursa, Turkey. ⁶Dept of Thoracic and Cardiovascular Surgery, University of Thessaly, Larissa, Greece. ⁷Thoracic Surgery, University of Verona, Verona, Italy. ⁸Thoracic Surgery, Dept of General Surgery and Medical Specialities and Minimally Invasive Thoracic Surgery and New Technologies, Policlinico University Hospital, University of Catania, Catania, Italy. ⁹Dept of Respiratory Diseases, University Hospitals Leuven and Dept CHROMETA, BREATHE, KU Leuven, Leuven, Belgium. ¹⁰Dept of Respiratory Diseases, University and IRCCS San Matteo Foundation, Pavia, Italy. ¹¹Dept of Thoracic Surgery, University Tor Vergata, Rome, Italy. ¹²Dept of Respiratory Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands. ¹³Erasmus Transplant Institute, Erasmus University Medical Center, Rotterdam, The Netherlands.

Correspondence: Merel Hellemons (m.hellemons@erasmusmc.nl)



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The @EuroRespSoc Thoracic Surgery and Lung Transplantation Assembly highlights sessions on digital health surveillance, pulmonary metastasectomy, mesothelioma care, and lung graft allocation and monitoring, presented at #ERSCongress 2021 <https://bit.ly/3Ce9wHx>

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Abstract

The thoracic surgery and lung transplantation assembly of the European Respiratory Society (ERS) is delighted to present the highlights from the 2021 ERS International Congress. We have selected four sessions that discussed recent advances across a wide range of topics including: digital health surveillance in thoracic surgery, emerging concepts in pulmonary metastasectomy, advances in mesothelioma care, and novel developments in lung graft allocation and monitoring. The sessions are summarised by early career members in close collaboration with the assembly faculty. We aim to give the reader an update on the highlights of the conference in the fields of thoracic surgery and lung transplantation.

Introduction

Assembly 8 includes physicians and surgeons with an extraordinary knowledge of the state of the art in the field of thoracic surgery (Group 8.1) and lung transplantation (Group 8.2). The members of group 8.1 include surgeons who have a special interest in an interdisciplinary approach towards various thoracic pathologies that may require surgical intervention for diagnostic or therapeutic purposes, such as malignancies, pleuro-pulmonary or mediastinal infection, trauma or other benign diseases of the lung, pleura or mediastinum. The group focuses on the possibilities of interactive sessions during the ERS International Congress to foster a culture of interdisciplinary collaboration between surgical and non-surgical members of the ERS.

The members of group 8.2 include pulmonologists/respiratory specialists who have a particular interest in lung transplantation. It is a group strongly engaged in collaborative working to better understand the risk factors, mechanisms and treatment options for lung transplant recipients who develop primary graft dysfunction and/or chronic lung allograft dysfunction affecting their post-transplant survival and causing post-transplant morbidity. This group finalises high-quality symposia during the annual congress, publishes monographs on lung transplantation, has already delivered very successful live and online ERS courses, and organised several Meet the Professor sessions.



Both groups are strongly interconnected with the other Scientific Assemblies, focusing on surgical options for the treatment of lung diseases. The overall number of members is over 500, and the number of contributions to the annual ERS congress shows a steady rise. The highlights of the 2021 ERS congress in the field of thoracic surgery and lung transplantation are presented in this article.

Group 8.1

Digital health surveillance in the thoracic surgery pathway

In her presentation, Cecilia Pompili (Leeds, UK, and Verona, Italy) shared her experience in collecting patient-reported outcomes (PROs) after lung cancer surgery and highlighted the importance of these data to monitor symptoms and evaluate the patient experience during the surgical treatment [1, 2].

Over the last decade it has become increasingly clear that morbidity and mortality alone are inadequate measures of patient outcome. Several studies have underlined how patient-reported outcome measures (PROMs) may be considered valuable predictors and more objective parameters of short-term outcomes, especially in cancer patient cohorts [3, 4].

The integration of PROs into electronic health records, especially when combined with patient and staff feedback, can be useful in improving clinical care, helping to manage and detect patients' problems, and facilitating the interaction between patient and healthcare providers. The post-operative use of remote ePRO software systems can enable faster and better management of post-operative recovery: patients can report symptoms from home and obtain fast guidance on self-management of mild symptoms and advice on communicating to the hospital in the event of severe symptoms. Ambulatory monitoring and web-accessible exercise were classified by patients as an additional benefit to regular care and feasible to apply before and after lung surgery [5].

Efforts should focus on the implementation of routine ePRO monitoring as part of the surgical pathway to modernise the surgical approach to outcome assessment and improve patient care [6]. Despite the potential benefits of integrating telehealth into routine clinical care, there are clear barriers to overcome. One of these is the perceived difficulties in remote clinical examination for surgical patients compared to other specialities. Also, one of the main barriers to applying ePROs is the clinicians' knowledge and expertise to meaningfully interpret and incorporate PROs data into their clinical practice [7–9]. Another important concern about implementation of telehealth involves the equitable access to care for all patients, particularly for elderly patients [10]. To implement the use of telehealth in thoracic surgical pathways it is important to understand the barriers and facilitators of our specific patient population: internet access, support and training of both patients and healthcare providers are mandatory for the success of the application of telehealth [11].

Babu Naidu (Birmingham, UK) focused his talk on the preoperative phase: surveillance can be linked to intervention in order to educate the patient to help in smoking cessation, nutritional assessment and pulmonary rehabilitation. A prospective observational study collected PROs in a cohort of lung cancer patients who underwent a minimally invasive resection between 2014 and 2017. Higher preoperative physical function PRO scores were related with shorter length of stay (LOS). Collection of PROs prior to surgery can identify patients at greater risk for increased LOS and allow for timely interventions [12].

The use of an integrated system may help to intervene. It can be tailored to each patient and personalised according to the needs of each one, incorporating outcomes, health information and motivation theories with baseline data. This can be useful to help patients prepare for post-operative symptoms management and to enhance physical activity. A fitness test can be used to monitor the patient's progress and add motivational feedback to the routine practice; a nutritional test can be applied to assess the nutritional status and, in case of high risk, the necessary adaptation to improve their status can be applied [13].

Telehealth surveillance can reduce the stress related to travel, costs and use of time: patients are more connected to health physicians, and this platform can be used as a screening tool to evaluate when a patient needs an in-person outpatient appointment or when a videocall is enough. Thanks to telehealth, patients are more connected and do not feel abandoned; moreover, both short- and long-term outcomes are accessible to surgeons, nurses and junior surgeons who can be included in clinical practice.

A recognised problem in the application of technological devices in clinical practice is the accessibility of elderly patients and those with socioeconomic problems to the programme. These difficulties should be overcome as the potential utility of digital health in reducing hospital readmission, LOS and improving patient outcomes is well established. Also, legal and privacy issues need to be streamlined.

The implementation of telehealth surveillance in thoracic surgical pathways is of paramount importance to enhance quality of care for our patients and optimise the routine collection of PROs in clinical practice. This is mandatory to ameliorate the clinical path of both preoperative and post-operative patients.

Take-home messages

- PROs are the best predictors of short-term outcomes after lung cancer surgery.
- In the preoperative phase, surveillance can be linked to telehealth interventions such as prehabilitation to improve patient outcomes.
- Despite the potential benefits of integrating ePROs and telehealth into routine clinical care, there are clear barriers that need to be overcome.

Lung metastasectomy: let's pour some water on the fire

The session on pulmonary metastasectomy was delivered by two speakers: Marcello Migliore (Catania, Italy) who emphasised the importance of patient selection, and Carole Ridge (London, UK) who spoke about her experience in lung tumour ablation and the evidence underpinning this practice.

M. Migliore discussed the results of the topical PulMiCC (Pulmonary Metastasectomy *versus* Continued Active Monitoring in Colorectal Cancer) study in some detail, which included a prospective cohort and a nested randomised controlled trial with 93 patients of whom 65 patients were included in the final analysis [14]. In the observational cohort, 263 patients (67%) underwent surgical metastasectomy, with survival curves demonstrating a survival advantage in the metastasectomy group that persisted up to 5 years. It is noted, however, that patients in this non-randomised group were highly selected, being younger, with better lung function, better performance status, more likely to have solitary pulmonary lesions, less likely to also have liver lesions and less likely to present with an elevated carcinoembryonic antigen compared to a control group of 128 patients with pulmonary lesions who did not undergo metastasectomy [15]. In the randomised group, 46 patients (49%) were allocated to pulmonary resection. In the resultant well-matched groups, there was no difference in survival between those who underwent surgery and those managed conservatively [14]. M. Migliore concludes that accurate preoperative staging and thoughtful patient selection is essential to maximise benefit from those offered local treatment for pulmonary metastasis. The results of PulMiCC have been a topic of much discussion and controversy since their recent publication; however, it is worth noting that poor recruitment limits the power and interpretability of the clinical results [16, 17].

M. Migliore then moved on to discuss the heterogeneity seen in this patient population, with patient, disease and treatment factors interacting to determine outcome; and to propose a recently updated concept of a dedicated staging system for pulmonary metastasis (pmTNM) [18, 19]. This considers the complex interaction between lesion number, nodal involvement and extra-thoracic disease, and aims to present stage-grouping to help inform decision making for local treatment according to a traffic-light system. This proposes that patients with designated Stage 1 or 2 (Green) disease (up to three lesions in both lungs, or more than three lesions restricted to a single lung, but with no lymph node involvement or extra-thoracic disease) should be considered for metastasectomy, while patients at pmTNM Stage 4 (Red) (more than three lesions with a bilateral distribution, any intrathoracic lymph node involvement contralateral to unilateral pulmonary lesions, and involvement of more than one extra-thoracic site) should be excluded from local therapies. Stage 3 (Orange) represents an intermediate group where a cautious indication may exist [18, 19]. Although preliminary successful validation has been reported at the meeting on a retrospective cohort of 264 patients, this approach is being validated in a larger group of patients [20].

This early work is presented as a way to standardise the terminology in pulmonary metastasectomy, to help support treatment planning and prognostication, and to facilitate research collaboration and synthesis, although multiple limitations are acknowledged such as the histology of the main tumour that should be taken into consideration in the decision making.

C. Ridge discussed the role of percutaneous lung tumour ablation for metastasis, which is currently primarily applied in her practice to patients who are non-surgical candidates, as supported by a recent consensus document on pulmonary metastasectomy [21]. There are additional indications for patients with deep-sited lesions, who would otherwise require large anatomical resections to achieve local control, or for small lesions that may not be easily palpable.

C. Ridge observed that microwave ablation may offer benefits over the more conventional radiofrequency ablation in that it does not require grounding pads, allows quicker ablation and better spread, and is associated with less heat-sink. The practice is generally reserved for patients with isolated pulmonary

disease, lesions <3 cm in size and lesions >1 cm from the tracheobronchial tree, the oesophagus or the great vessels [22]. A pre-treatment cyto-histological diagnosis should be achieved whenever possible. Patients with nodal involvement are excluded.

It is noted that patients should normally experience a shorter hospital admission (median 2 days) and a faster recovery when compared to surgical metastasectomy. This is increasingly appealing in the midst of the ongoing coronavirus disease 2019 (COVID-19) pandemic. Nonetheless, local data demonstrate a mortality rate of 1 in 200 and a morbidity rate of 6 in 10 (5 in 10 pneumothorax, 4 in 10 pleural drain, 1 in 20 pulmonary haemorrhage) [23].

C. Ridge went on to present the outcomes after ablation for pulmonary metastasis, where comparison to surgical metastasectomy is thwarted due to an inconsistent reporting of outcomes in the literature. Ablative therapies are associated with local control rates in the region of 80% at 1 year and 70% at 3 years [24]. C. Ridge proposed that these numbers may be similar to the outcomes after surgery.

Take-home messages

- Surgical pulmonary metastasectomy might be a feasible treatment option in well-selected patients and after accurate preoperative staging.
- A pulmonary metastasectomy staging system could standardise the terminology in pulmonary metastasectomy, help support treatment planning and prognostication, and finally facilitate research collaboration and synthesis.
- Percutaneous lung tumour ablation for metastasis can be used in patients who are not eligible for surgery, and also for deep-sited lesions that would otherwise require large anatomical resections, with similar outcomes compared to surgery.

Diagnostic and therapeutic advances in mesothelioma care

In her presentation, Françoise Galateau-Salle (Lyon, France) described the value of the implementation of artificial intelligence in mesothelioma diagnosis. Malignant pleural mesothelioma (MPM) is a highly complex and genetically heterogeneous tumour, posing important challenges to diagnosis and treatment decisions. In this context, deep-learning and artificial intelligence approaches based on whole slides images (WSI) may assist in tumour 1) diagnosis, 2) subtyping, 3) grading, 4) discovery of prognostic biomarkers, 5) genetic analysis and 6) target prediction.

During the last decade, F. Galateau-Salle and her team have built a database of over 50 000 WSI. Using these data, they have developed a new deep-learning approach called MesoNet to accurately predict the overall survival (OS) of mesothelioma patients from WSI [25]. Furthermore, in another study, the team demonstrated that a deep-learning approach can provide enhanced diagnostic assistance to identify complex morphologies in histopathological samples [26]. Finally, F. Galateau-Salle stated that deep learning might assist pathologists in the separation of benign *versus* malignant mesothelioma tissues [27]. The future steps include the use of deep-learning methods to predict cancer signature hallmarks and to improve the identification of tumour RNA-seq expression and treatment targets, by assisting pathologists and not by replacing them [28].

Jens Sørensen (Copenhagen, Denmark) and Isabelle Opitz (Zurich, Switzerland) presented new treatment advances in MPM. During the period of 2004–2019, no new treatment agents were approved. In fact, regarding antiangiogenic treatments, bevacizumab has not received European Medicines Agency (EMA) approval, while nintedanib has not received either Food and Drug Administration (FDA) or EMA approval [29, 30]. Regarding targeted treatments, there are no genomic agents with confirmed efficacy. Now a new era is starting: with regard to immunotherapy, there are recent encouraging outcomes with programmed death-ligand 1 (PD-L1) inhibitors alone or in combination with other agents as second-line treatment [31]. Tremelimumab combined with durvalumab, an anti-PD-L1 monoclonal antibody, showed promising outcomes as either first-line or second-line treatment for MPM [32]. In addition, nivolumab combined with ipilimumab was found superior to first-line chemotherapy for unresectable MPM cases, in terms of median OS, and has now received FDA and EMA approval as first-line treatment for unresectable MPM patients [33]. Since there is no clear evidence regarding potential biomarkers, several studies are ongoing to investigate the role and prognostic value of the immune micro-environment. Furthermore, ongoing trials might further uncover the potential role of immunotherapy in the treatment of resectable MPM, while encouraging outcomes have emerged from other immunological approaches with cell-based techniques [34].

Finally, Till Markowiak (Regensburg, Germany) presented the current concepts regarding hyperthermic intrathoracic chemotherapy (HITOC) [35, 36]. To begin with, HITOC plays a crucial role as an additive

procedure to cytoreductive surgery for the treatment of MPM. Despite the differences in protocols among different centres, along with the small study populations in the available literature, HITOC has been associated with improved outcomes compared to non-HITOC treatment in terms of recurrence-free survival (RFS) and OS, an outcome that is further confirmed by a recent meta-analysis [37, 38]. It has also been demonstrated that higher doses of HITOC were associated with better outcomes in terms of RFS and OS [39]. Nonetheless, special concern should be provided regarding the safety of the personnel and the special measures that should be taken, along with the patient's safety, by providing well-measured doses of the agents. A special challenge is to provide the appropriate dosage of cisplatin to reduce the risk of local recurrence while limiting the risk of renal insufficiency. To face all these challenges, further well-designed studies are necessary.

Take-home messages

- Artificial intelligence with deep learning is able to predict survival in MPM and may aid in diagnosis.
- Nivolumab plus ipilimumab has now been approved as a first-line treatment option for unresectable MPM cases.
- HITOC as an additive procedure to cytoreductive surgery can be associated with improved outcomes in selected patients.

Group 8.2

Lung graft allocation and monitoring in the 21st century

In his presentation focused on organ allocation, Jens Gottlieb (Hannover, Germany) emphasised that there is no uniform European donor lung allocation system, with currently three different systems being used. These systems all have their specific advantages and disadvantages.

The first and most widely used allocation system is the lung allocation score (LAS), which covers 61% of lung transplant activity worldwide after its introduction in the USA in 2005. Within Europe the LAS is used in Germany, the Netherlands and Italy, and within the eight Eurotransplant countries for transborder organ exchange solely. The LAS is based on the predicted survival benefit (the difference between projected waitlist survival and post-transplantation survival), based on objective and transparent data from 17 items obtained in spirometry, blood gas analysis, 6-min walk test, laboratory and right heart catheterisation [40]. Analysis from the impact of the introduction of the LAS showed that waitlist mortality decreased (by eight deaths per 100 lung transplants) and patients with restrictive lung diseases are relatively favoured for transplantation, resulting in shorter waitlist times [41].

The second type of allocation system uses allocation based on centre decision and is mostly used in countries where the transplant centre covers a large area or in countries with a limited number of transplant centres. This system is logistically advantageous as the centre has substantial autonomy but, on the other hand, is subjective, lacks transparency and does not support broader organ sharing. The last type of allocation system is a national urgency system. This kind of allocation scheme is often used on top of a centre decision system. It increases justice and supports wider organ sharing, but it only works if the number of urgent patients is limited [40].

Eurotransplant and ScandiTransplant are two examples within Europe of supranational systems with transborder exchange. In Eurotransplant, 26% of all donor lungs are exchanged across borders. To determine the priority the LAS is used, but also the "country balance" and national waiting time are taken into account to form a balanced exchange system [40]. There are future plans to come up with even better models, for which data are currently being collected.

Since there are insufficient suitable donors to match the demand, options to expand the donor pool and donor use rates are being explored, and this was highlighted by Chandima Divithotawela (Brisbane, Australia) [42]. The use of marginal donor lungs is limited because of the fear of post-transplant lung allograft failure. *Ex vivo* lung perfusion (EVL) may provide the possibility to reassess and potentially treat certain marginal donor lungs to increase donor organ utilisation rates. Currently, three EVLP protocols are used (Toronto, Lund, Organ Care System), the basic principles of which are the same: the lungs are preserved in an organ chamber and are gradually rewarmed, perfused and ventilated after which, at a temperature of 37°C, lung evaluation and treatment can be performed [43]. During evaluation, basic respiratory parameters and gross examination of structural abnormalities, as well as bronchoscopic and radiographic evaluations, are possible. Additionally, EVLP can be used as a preservation tool, extending the preservation time beyond the usual 7–12 h [44]. Finally, EVLP can be used as a therapeutic tool to perform bronchoscopic interventions, repair lung parenchyma tears, treat pulmonary oedema, etc. Several studies demonstrated comparable short- and long-term survival in EVLP-treated marginal donor lungs

compared to standard transplantation [45, 46]. Research is currently performed on additional potential extensions of this technique, for example on silencing blood group antigens to allow blood group incompatible lung transplantation or silencing major histocompatibility complex expression to reduce allograft immunogenicity [47, 48].

In her presentation on outcomes of telehealth care for lung transplant recipients, Cecilia Chaparro (Toronto, Canada) presented promising results from the first experiences, showing non-inferiority in terms of mortality between telehealth in stable lung transplant recipients >2 years post-transplant and in-person follow-up, reduced costs and increased patient satisfaction [49, 50]. The further implementation of telehealth was accelerated during the COVID-19 pandemic with excellent patient and caregiver satisfaction. An example of this is the customisable, web-based platform “MyCare” with personalised care plans, biometric data monitoring, clinical alerts and more [51]. Moreover, web-based telerehabilitation showed that exercise participation and progression were evident despite lack of equipment and fewer hours of training [52]. According to a pilot study by SCHENKEL *et al.* [53], supplementing routine care with remote monitoring by Bluetooth devices after discharge might reduce readmission. C. Chaparro underlined that evolving technology holds promise for the future of aftercare for lung transplant recipients and will enable new platforms to communicate and interact with patients, although in-person assessments are still needed for complex issues [51].

Lastly, Johnny Verschakelen (Leuven, Belgium) discussed computed tomography (CT) features of small airways disease (SAD) and how CT can help to detect and differentiate small airway pathology after lung transplantation. This is relevant in the field of lung transplantation to differentiate between (chronic) allograft rejection, respiratory infections, drug toxicity and aspiration. Acute SAD often presents as tree-in-bud and bronchiolectasis, sometimes in combination with ground-glass opacification or consolidation. An indirect sign of SAD is mosaic attenuation and is best assessed on expiratory CT scan. Predicting bronchiolitis obliterans syndrome (BOS) with CT screening is an appealing concept, but the actual application is limited owing to lack of sensitivity and specificity [54]. New developments, including objective quantitative measurements and machine learning technologies, hold more promise [53–55]. Quantitative CT metrics including lung volume and air trapping volumes correlated better with forced expiratory volume in 1 s and were better predictors than semi-quantitative scores [55]. The ratio of the airway lumen area to the cross-sectional area of the adjacent blood vessel was significantly increased in subjects who developed progressive BOS [56]. Machine learning algorithms could identify eventual BOS developers while no pulmonary function tests or clinical parameters could, and a maximal accuracy of 85% was obtained by combining baseline functional respiratory imaging features such as right middle lobe volume, right upper lobe airway resistance and central airway surface [57].

Take-home messages

- Three models of lung allocation are used in Europe: centre allocation, centre allocation plus national urgency, and the LAS.
- EVLP can be used as an evaluation, preservation and therapeutic tool to expand the donor pool.
- Telehealth is an excellent way to provide care to lung transplant patients.
- Quantitative CT and machine learning technologies are improving and may be an important tool for prediction, quantification and follow-up for lung transplant patients.

Conclusions

Owing to the ongoing COVID-19 pandemic, this congress was the second fully virtual congress of the ERS and again a great success. Topics were very diverse and included important sessions on innovation and state of the art in thoracic surgery and lung transplantation. In this article, we have summarised the highlights of the most important sessions of this congress, representing a wide range of topics. We look forward to the next ERS International Congress, to be held in Barcelona, Spain, from 4 to 6 September 2022.

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