

# Interventional Pulmonology: Past, Present and Future



Stefano Gasparini, Martina Bonifazi and Lina Zuccatosta

**Abstract** Over the last decades, there have been huge progresses in most of fields of medicine, due to a deeper comprehension of pathogenic mechanisms of diseases along with outstanding advance in technology, suitable for diagnostic and therapeutic purposes. This applies also to respiratory medicine, in particular to the area of interventional pulmonology, where the development of sophisticated technological tools has revolutionized diagnostic work-up and therapeutic management of relevant pathologies, such as lung cancer, interstitial lung diseases, obstructive lung diseases (COPD) with advanced emphysema, and severe asthma. Most of these innovative approaches have been tested and adopted for the first time in Italy (sometimes in Europe) in our Pulmonary Diseases Unit, currently recognized as one of the most important centers of interventional pulmonology over the world, and daily visited for training by foreigners coming from several countries. In this review, we summarize the leading lines of research carried out by our team over the last decades, in both diagnostic and therapeutic fields of interventional pulmonology, with the subsequent clinical implications.

## 1 Introduction

Respiratory diseases have become a global health issue, due to the increasing exposure to environmental risk factors and ageing of general population. The lungs, indeed, are the largest internal organ in the body constantly and directly exposed

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S. Gasparini (✉) · M. Bonifazi  
Department of Biomedical Sciences and Public Health, Università Politecnica delle Marche, Via  
Tronto 10/A, 60126 Ancona, Italy  
e-mail: [s.gasparini@univpm.it](mailto:s.gasparini@univpm.it)

M. Bonifazi  
e-mail: [m.bonifazi@univpm.it](mailto:m.bonifazi@univpm.it)

S. Gasparini · M. Bonifazi · L. Zuccatosta  
Respiratory Diseases Unit, Azienda ospedaliero-universitaria Ospedali Riuniti, Via Conca 71,  
60126 Ancona, Italy  
e-mail: [linazuccatosta@tiscali.it](mailto:linazuccatosta@tiscali.it)

to the environment, such as outdoor and indoor air pollution, occupational toxics, tobacco smoke and infectious agents. According to the latest epidemiological estimates, around 235 million people suffer from asthma, more than 200 million people have chronic obstructive pulmonary disease (COPD), of whom 65 million with moderate-to-severe form, more than 100 million people experience sleep disordered breathing, 8.7 million people develop tuberculosis (TB) annually, and more than 50 million people struggle with occupational lung diseases. Lung cancer is currently the leading cause of cancer death around the world, with an overall 5-year survival rate lower than 15% [1].

The huge progresses in the field of respiratory medicine over the last decades, in particular in the area of interventional pulmonology by development of sophisticated technological tools, have revolutionized diagnostic work-up and therapeutic management of most of lung diseases, such as lung cancer, diffuse parenchymal lung diseases, chronic obstructive lung diseases (COPD) with advanced emphysema and severe asthma.

Most of these innovative approaches have been tested and adopted for the first time in Italy (sometimes in Europe) in our Pulmonary Diseases Unit, currently recognized as one of the most important centers of interventional pulmonology over the world, and daily visited for training by foreigners coming from several countries. This successful result has been built, step by step, through a hard job, started almost 40 years ago by our group and witnessed by several papers, published in relevant peer-reviewed journals.

In this review, we summarize the leading lines of research carried out by our team over the last decades, in both diagnostic and therapeutic fields of interventional pulmonology, and research projects, currently ongoing or due to start, that are expected to further extend the landscape of management of major respiratory diseases.

## 2 Diagnostic Work-Up of Thoracic Diseases

The flexible fibreoptic bronchoscope, since its first introduction in the late 1960s, has become the milestone of interventional pulmonology. This is an invaluable tool for diagnosis of many thoracic disorders, with an excellent safety profile, characterized by low morbidity (0.1–2.5%) and negligible mortality (0.05%). The main revolution in this context was represented by the introduction of transbronchial aspiration techniques, that have extended pulmonologists' perspective beyond the airways [2]. In particular, the adoption of flexible transbronchial needles (TBNA) has led to successfully biopsy hilar/mediastinal lesions, as well as submucosal, peribronchial, and peripheral lung nodules/masses (PPN/Ms), avoiding more invasive or risky approaches [3].

Regarding the diagnostic work-up of PPN/Ms, these may be approached both percutaneously and transbronchially. Percutaneous needle aspiration (PCNA), performed under fluoroscopic or CT guidance, plays a relevant role in the management of PPN/Ms, showing a sensitivity that ranges from 70 to 97%. However, concerns

have risen about the safety profile of this technique, due to the relatively frequent occurrence of hemorrhage and pneumothorax. The endobronchial approach using standard flexible bronchoscopy with transbronchial needles, although characterized by a more heterogeneous diagnostic yield, is a safer procedure and it offers the advantages to provide, during a single examination, a pathological diagnosis of nodules, information on mediastinal staging and airways involvement, as well as to identify potential synchronous lesions.

Due to the lack of studies directly comparing these two procedures, an evidence-based recommendation on the best choice between them has yet to be established, but a relevant contribution in this context was published by our group, reporting one of the largest experience (more than 1.000 consecutive patients) on combination of these techniques in the PPN/Ms management [4]. In particular, a single diagnostic team (a pulmonologist, radiologist, and cytopathologist), performed both the procedures under fluoroscopic guidance in a sequential algorithm, in which flexible bronchoscopy with TBNA was carried out first, due to the safer profile and the possibility to obtain a simultaneous mediastinal staging, and PCNA after, in case of inconclusive results at immediate cytologic assessment performed by the cytopathologist, present in the bronchoscopy suite. We concluded that transbronchial and percutaneous approaches must be considered complementary, rather than alternative, as their integrated use not only increased the diagnostic yield but also provided important information for the staging of lung cancer. Another relevant key message of this paper was focused on the utmost importance of the multidisciplinary approach in order to optimize the diagnostic management of PPN/Ms with a reduction in hospitalization time and consequent cost saving. Since the diffusion of this report in 1995, other papers have been published on this content by our team over the following two decades, including further experiences, qualitative and systematic reviews [5–8].

In most recent years, new technologies have been proposed for the bronchoscopic approach to PPN/Ms, including ultra-thin bronchoscopes, able to penetrate more distally into the bronchial tree, and innovative guidance systems such as virtual bronchoscopy, endobronchial ultrasound (EBUS) and electromagnetic navigation, currently used in our center. The main advantage of new guidance techniques is related to the possibility of approaching even small lesions that are not visible by fluoroscopy. In particular, the use of electromagnetic navigation bronchoscopy (ENB) has gained popularity as a complementary guidance tool during bronchoscopic biopsy of peripheral nodules. These systems utilize preoperative CT data and an electromagnetically tracked guide for procedure planning and guidance, but is not a real-time procedure. To overcome this limitation, our main perspective over the next years, will be to adopt the cone-beam CT (CBCT), that enables 3-dimensional (3D) fluoroscopic image guidance, with high sensitivity, low complication rates and acceptable amount of radiation dose (comparable with CBCT-guided percutaneous needle interventions and considerably lower than conventional CT guidance).

As above mentioned, TBNA is an invaluable sampling technique also for diagnostic work-up of mediastinal adenopathies/masses, since allows to diagnose and stage malignancies during the same procedure, avoiding some unnecessary surgical

approaches. This advantage was proven and quantified in a large prospective international multi-institutional clinical study, involving selected community hospitals and academic medical centers worldwide, including the ours. In this study, TBNA, in a complementary approach with CT scanning, precluded additional thoracic surgery in almost one third of patients, known to have significant cardiopulmonary and vascular comorbidity, confirming the essential role of transbronchial procedure in this context [9]. This concept was further underlined in subsequent reports and comprehensive reviews [7, 10–12].

However, against very high specificity (96–100%), the sensitivity of TBNA varies greatly in the published literature, being influenced by selected clinical and procedural aspects. In order to better define the role of such factors, our group has carried out a systematic review, the only available in the literature so far, providing an extensive description and synthesis of the main results from all published studies evaluating TBNA yield predictors for the diagnosis of mediastinal lymphadenopathies/masses [13]. In summary, major predictors in unselected population, as well as in suspected/known lung cancer clinical setting, included an increasing lymph node size, the presence of abnormal endoscopic findings, underlying malignant conditions, station 4R and 7 as site of samples, and the use of histological needle by an “experienced” bronchoscopist, although the type and duration of educational interventions evaluated varied widely among studies. With reference to the number of needle passes, although data were limited, we concluded that it is necessary to perform at least three needle passes up to a maximum of five to obtain the best accuracy. Other predictors in patients with suspected/known lung cancer included selected features of primary tumor, as the presence of small cell lung cancer (SCLC) subtype rather than non small cell lung cancer NSCLC and right-side location. There was also evidence on the role of rapid on-site cytological evaluation (ROSE) [13].

The immediate cytological assessment plays, indeed, an important role during sampling procedures, as it allows to assess quality of specimens collected in the diagnostic suite, providing relevant information to the operator, who could stop the exam if samples are adequate for diagnosis, as well as modify the technique or target site, if not. Furthermore, the operator could require to collect additional material for ancillary studies to further characterize the lesions, such as immunocytochemical stain, electron microscopy and microbiological evaluation. The evaluation of cytological sample adequacy has become even more important in the last years, with the advent of targeting lung cancer therapy, that requires specimens with enough material for performing immunocytochemistry and biomolecular assessment. Despite these advantages, ROSE is not routinely performed in all interventional pulmonology centers, because of the lack of cytopathologists available to join the procedures. To overcome this problem, our group conducted a study to evaluate whether a trained pulmonologist could be able to on-site assess the adequacy of TBNA specimens for the diagnosis of hilar/mediastinal adenopathies after an extensive educational intervention, including a training period alongside a board-certified cytopathologist and theoretical in-depth studies. One pulmonologist of our Pulmonary Diseases Unit underwent a three months training, taking part in the weekly diagnostic cytopathological session (3 h per session, for a total of 18 sessions) under the guidance and the

supervision of a board-certified pathologist. This pulmonologist and the cytopathologist, deemed as gold standard, performed ROSE of 361 TBNA on 84 patients with by hilar/mediastinal lymphadenopathies and classified specimens into five diagnostic categories in a blinded fashion. There was an overall substantial agreement between observers ( $\kappa_{aw} = 0.73$ , 95% CI 0.61–0.86;  $p < 0.001$ ), that became excellent in cases of malignant disease. The diagnostic accuracy of ROSE performed by pulmonologist was not statistically different from that provided by cytopatologist. Our study provided the first evidence worldwide that a trained pulmonologist may be able to on-site evaluate the adequacy of cytological specimens, allowing to obviate most of the difficulties related to the involvement of the cytopathologists in daily diagnostic activities, and to reduce the costs, further optimizing the cost-effectiveness profile of TBNA [14].

However, TBNA is a blind technique without guidance system, and this has represented the rationale to develop a tool that uses reflected sound waves to visualize structures surrounding the airways. The endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA), by means of echoendoscope, offers the operator a real-time visualization of lymph nodes and surrounding structures, enabling to direct the tip of the needle to the target area. Overall, in the hands of experienced operators, EBUS provides an excellent diagnostic accuracy, leading to avoid more invasive procedures, and serious complications are extremely rare. As a result, EBUS practice has rapidly increased, especially after the advent of linear technology, and a large amount of experiences worldwide have been published over the last years, including our contributes [15–17]. Although a superiority of the imaging-guided over the conventional procedure could be reasonably supposed by pooled estimates from literature, evidence-based data on a direct comparison between the two procedures in randomized fashion had been lacking and the choice between them had been based more on empirical evaluations of operators rather than on established diagnostic algorithms. In this context, our group performed the first randomized controlled trial to test the superiority of EBUS-TBNA over c-TBNA for the diagnosis of hilar/mediastinal lesions of unknown origin. We aimed also to evaluate the cost-effectiveness profile of a staged strategy, including c-TBNA as initial test, immediately followed by EBUS-TBNA, in case of inconclusive results at rapid on-site evaluation in the same bronchoscopy session. Two hundred and fifty-three patients were randomized to either EBUS-TBNA ( $n = 127$ ) or c-TBNA ( $n = 126$ ). Thirty-one patients of c-TBNA group subsequently underwent EBUS-TBNA. The sensitivity EBUS-TBNA was higher, but not significantly superior to that of c-TBNA (respectively 92%, [95%, CI 87–97%] and 82% [95%, CI 75–90%],  $p > 0.05$ ). The sensitivity of the staged strategy was 94% (95%, CI 89–98%). No major adverse events occurred. We showed that EBUS-TBNA was the single best diagnostic tool, although not significantly superior to c-TBNA. Due to the favorable cost-effectiveness profile of their sequential combination, we proposed to introduce this staged strategy into clinical practice [18].

Another huge revolution in the field of interventional pulmonology has been the introduction of transbronchial lung criobiopsy (TBLC) in the diagnostic work up of Interstitial Lung Diseases (ILDs). For instance, advances in comprehension of ILDs pathogenesis has coupled with exciting evolutions in technologies related to

tissue sampling, no longer exclusive domain of thoracic surgeons. The term “ILDs” includes a wide spectrum of heterogeneous entities with different prognosis, as well as treatment options. Due to the recent progresses in therapeutic landscape of ILDs management, the distinction between idiopathic pulmonary fibrosis (IPF), the most prevalent and severe form, and other diseases, has become even more important. Nowadays, two oral anti-fibrotic drugs, pirfenidone and nintedanib, are available in the market for the treatment of IPF, although the long-term prognosis of these patients remain poor. An accurate diagnosis of IPF is a challenging process that requires an integrated multidisciplinary approach involving pulmonologists, radiologists, and, when lung tissue is needed, also pathologists. In this context, the role of conventional transbronchial lung biopsy is limited to the exclusion of specific disorders (i.e. sarcoidosis, carcinomatous lymphangitis, organizing pneumonia), since the small sample size, the rate of crush artifacts and the high likelihood to sample mostly centrilobular areas do not allow to properly identify more complex and spatially heterogeneous morphological patterns. This is the reason why the current guidelines recommend surgical lung biopsy (SLB), when a pathological assessment is needed to establish a diagnosis. However, SLB is characterized by appreciable costs and risks, with a mortality rate of 2–4% within 90 days. Moreover, many subjects are not eligible because of a combination of advanced stage, age, comorbidities, respiratory failure, and pulmonary hypertension. More recently, TBLC has been proposed as a valuable alternative tool for the pathologic assessment of ILDs. Actually, the use of cryoprobes for bronchoscopic procedures was firstly described as early as 1977 for therapeutic purposes in case of airways occlusions. The ingenious novelty consists in using a flexible cryoprobe through a flexible bronchoscope to obtain parenchymal lung tissue. Our center was one of the first center in the world to adopt TBLC, and, later, the growing amount of data on successful experiences has led to its routine adoption in selected interventional pulmonology centers worldwide. In this context, our group, in collaboration with an another Italian center, reported the first retrospective comparison on DY and safety between SLB and TBLC in a large population, and provided the first systematic review and meta-analysis of studies published on this topic [19, 20]. Overall, 150 patients underwent SLB and 297 underwent TBLC. The median time of hospitalization was 6.1 days (SLB) and 2.6 days (TBLC;  $p < 0.0001$ ). Mortality due to adverse events was 2.7% (SLB) and 0.3% (TBLC) of the patients. Pneumothorax was the most common complication after TBLC (20.2%) and No severe bleeding was observed. TBLC was diagnostic for 246 patients (82.8%), SLB for 148 patients (98.7%,  $p = 0.013$ ). The meta-analysis of 15 investigations including 781 patients revealed an overall DY of 0.81 (0.75–0.87); the overall pooled probability of developing a pneumothorax, as retrieved from 15 studies including 994 patients, was 0.06 (95% CI 0.02–0.11). Based on these data, we concluded that TBLC is an effective and safe procedure, with lower complication and mortality rates compared to SLB. We also proposed an algorithm according to which TBLC should be considered the first diagnostic approach for obtaining tissue in ILDs, reserving the surgical approach for cases in which TBLC is not feasible. The ‘final’ risk of mortality, considering TBLC and SLB together in a “staged” approach, proves to be 0.3–1.4%, is significantly lower than the overall mortality with SLB alone.

We are currently the regional tertiary referral center for diagnosis and management of ILDs, and we have a strict network of collaboration with the other national and international centers. In our center, more than 200 patients per year are currently diagnosed and managed and a patients' association has been recently founded. Moreover a dedicated care pathway ("percorso diagnostic terapeutico-PDTA") for ILD management has been developed to optimize timing and resources. Several clinical research activities in ILDs are currently ongoing, and some of them are focused on tissue phenotyping/characterization, as the advent of TBLC, with its favourable risk/benefit profile, has hugely improved our chances of sample collection, suitable for clinical as well as for research purpose.

### 3 Therapeutic Management of Respiratory Diseases

Over the last fifty years, interventional pulmonology's role has become increasingly established also in the field of therapeutic management of selected respiratory diseases, such as pleural disorders and chronic obstructive lung diseases.

The term "Pleural Diseases" includes a wide spectrum of heterogeneous entities, as a pleural involvement may occur in several neoplastic and non-neoplastic conditions with different etiologies, prognosis, as well as treatment options. Pleural effusion is commonly faced by clinicians in daily practice, and, due to the increasing burden of pleural diseases worldwide, a personalized cost-effective management of these conditions is essential to optimize the healthcare sources. To date, more than 50 causes of pleural effusions have been identified and include local diseases, systemic conditions, organ dysfunction and drug reactions. Therefore, a multidisciplinary approach from different specialties is highly recommended to ensure the best management, which lies, first of all, in a tailored treatment or, at least, control of the underlying cause. Pleurodesis, intended to produce a pleural symphysis via thoracoscopic (poudrage) or chest tube (slurry) insufflation of a sclerosing agent, is still considered as the first-line therapy, except for patients with 'trapped lung', which significantly decreases the probability of a successful procedure. A recent network meta-analysis of studies on interventions for the management of malignant pleural effusion led to conclude that talc poudrage is the more effective technique, as it resulted in a significantly lower rate of failures than the other methods. Our group took part in one of the most important and large study in this context, that was a multicentre, open-label, prospective cohort study of 558 patients with malignant pleural effusion who underwent thoracoscopy and talc poudrage with 4 g of calibrated French large-particle talc in 13 European hospitals, and one in South Africa. The primary endpoint was the safety profile of talc pleurodesis, that was overall favourable, as no acute respiratory distress syndrome occurred [21]. Such report had a huge impact on malignant pleural effusion management, and talc pleurodesis has definitely become the gold standard in this context. A substantial proportion of neoplastic pleural involvement is caused by pleural mesothelioma (PM), that is



a rare, devastating tumor, strongly related to asbestos exposure. The variable incidence of PM worldwide mostly reflects asbestos utilization and exposure. Due to the extremely long latency period between first exposure and disease occurrence, epidemiological projections of PM incidence in Western Europe indicate a peak around 2020, and a trend towards reduction only afterwards. The prognosis of PM is extremely poor, with 5-years survival around 10%. Available data from clinical trials on its management are limited and controversial. Therefore, treatment approaches, that include chemotherapy (pemetrexed or raltitrexed and platinum-based agents as the only approved drugs), radiotherapy and surgery, either in combination or as single treatment, are highly heterogeneous worldwide. The different treatment strategies adopted by clinicians represented the rationale for a study recently published by our group in collaboration with the department of Epidemiology of University of Milano, aiming to assess treatment and prognosis of PM in a large real world cohort of patients from Lombardy, the largest Italian Region (about 10 million inhabitants) through a record linkage between healthcare administrative databases [22]. Out of 1326 patients with PM identified in the study period 2006–2011, 754 (56.9%) received any treatment for PM: 205 (15.5%) underwent surgery, and 696 (52.5%) used chemotherapy. Surgery was spread across several hospitals, and most patients diagnosed in non-specialized centres (70%) underwent surgery in the same centres. Age at diagnosis was a strong inverse determinant of surgery. Determinants of receiving chemotherapy were younger age, a more recent first diagnosis, and first diagnosis in a specialized centre. OS was 45.4% at 1 year, 24.8% at 2 and 9.6% at 5 years (median 11 months). OS decreased with age, and was higher for who underwent surgery, but not for those treated with chemotherapy. We confirmed that management of PM varied widely in clinical practice and significant predictors of treatment were younger age and recent diagnosis, though a high proportion of patients were not treated. Patients were treated in various hospitals indicating the importance of concentrating serious rare neoplasms in Comprehensive Cancer Centers.

Due to our clinical and research experience on pleural diseases, we were invited by a peer-review journal to summarize the latest insights regarding this field in a comprehensive qualitative review, recently published [23].

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease, characterized by persistent airflow limitation associated with chronic inflammation of the airways and lungs, in response to noxious particles and gases. COPD is a protean disease that includes different phenotypes, and therapeutic strategy should be personalized and tailored to specific patient features. In particular, patients with advanced emphysema gain and perceive limited benefits from existing pharmacological treatment options, due to the lack of efficacy in reducing hyperinflation, that is the key physiopathological mechanism in this context. Lung hyperinflation is defined as an abnormal increase of the amount of gas in the lungs and airways at the end of the tidal (spontaneous) expiration, highly influencing respiratory dynamics. Therefore, lung hyperinflation plays a central role in the perception of dyspnea and poor exercise tolerance and it contributes to a worse disease prognosis irrespective of the lung function. Such a relevant physiopathogenic mechanism offered the rationale for the development of a targeted treatment option, the lung volume reduction



(LVR). This procedure is intended to reduce hyperinflation by excluding the most damaged area of lung parenchyma, in order to optimize respiratory mechanics of the remaining tissue, reducing the work of breathing. The first attempts of surgical lung volume reduction (LVRS) were performed in the 1950s, but it was only in 2003, with the publication of the results of the National Emphysema Treatment Trial that this procedure demonstrated to significantly improve clinical and functional status in selected emphysematous patients. However, the questionable cost-effectiveness profile, as well as the considerable morbidity and mortality associated with LVRS, prompted reflection on alternative, less invasive, approaches to achieve LVR, such as endoscopic techniques (BLVR). In the past 20 years, the ambitious purpose of achieving the same clinical benefits with reduced risks and costs has permeated the world of interventional pulmonology and several different techniques have been successfully developed and labeled in the market. According to the underlying mechanism of action and reversibility, they can be divided into 2 main groups: blocking reversible devices, and nonblocking irreversible devices. The first group, represented by unidirectional valves, relies on occlusion and atelectasis of the most hyperinflated lobe. Nonblocking devices are designed to exclude the targeted lobe by inducing an irreversible parenchymal reaction, and include coils and sclerosis agents, such as sealants and thermal vapor ablation. Our center was one of the first worldwide, in which any of these devices was tested.

Unidirectional valves are the most widely investigated devices in the context of BLVR therapy, with the largest series of patients treated so far. We took part of the first international randomized trials [24–26], including the Endobronchial Valve for Emphysema Palliation Trial (VENT), conducted in the US (321 patients in 31 centers) [24] and in Europe (171 patients in 23 sites) [25, 26], that showed a statistically significant, improvement in lung functions, exercise tolerance and quality of life compared to controls subjects on best medical therapy. The growing evidence on efficacy and safety of this treatment over years has allowed to include it in the current guidelines as a valuable option for patients with advanced emphysema and selected morphological features, identified as predictors of successful outcomes. In our center, so far, more than 100 patients have been treated with valves and followed-up over time to assess long-term benefits of this procedure. Moreover, a research study on other aspects that might impact the success of treatment, such as the presence of a predominant small airways involvement, is currently ongoing.

Nonblocking devices, such as coils, sealants and thermal vapor ablation were also tested and adopted in our center for the first time in Italy, and since then, several patients have been studied and treated over years, allowing to become one of the groups with the large experience in Europe, as witnessed also by reviews published on this topic [27, 28].

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