

RESEARCH IN THORACOSCOPY (PLEUROSCOPY)

TORAKOSKOPİ ARAŞTIRMASI (PLÖROSKOPİ)

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Abstract

Thoracoscopy (pleuroscopy) is the gold standard in the diagnosis and treatment of pleural diseases. With the development of novel devices, thoracoscopy has become very popular among pulmonologists, since it solves diagnostic and therapeutic problems in pleural disease. Its diagnostic yield is 95% in patients with malignant pleural disease. Its main therapeutic application is pleurodesis with talc poudrage, achieving a success rate of 90% for malignant pleural effusion and 95% for pneumothorax. In recent years, beside its diagnostic and therapeutic utility, thoracoscopy has become an important tool in the research of pleural pathophysiology and molecular biology, with the development of new devices in combination with novel molecular techniques and concepts. Collaboration between clinicians and researchers is crucial in further studying pleural diseases and thoracoscopy is certainly a means towards better understanding and treating these disorders. Therefore, young pulmonologists should be trained in thoracoscopy in the same way as they are in bronchoscopy.

Key words: Thoracoscopy, pleuroscopy, flex-rigid, semi-rigid, narrow band imaging, NBI, autofluorescence, infrared, pneumothorax, pleural effusion, empyema, lung cancer, mesothelioma, pleurodesis, talc

Özet

Torakoskopi (plöroskopi) plevral hastalıkların tanı ve tedavisinde gerçekten altın standarttır. Yeni cihazların geliştirilmesi ile torakoskopi göğüs hastalıkları uzmanları arasında oldukça popüler hale gelmiştir, çünkü plevral hastalıkta tanısal ve terapötik problemleri çözmektedir. Malign plevral hastalığı olan hastalarda tanısal verimi %95'tir. Başlıca terapötik uygulaması talk pudrası ile plörodezdır ve başarı oranı malign plevral efüzyonda %90'a, pnömotoraksta %95'e ulaşır. Son yıllarda torakoskopi, tanısal ve terapötik kullanımının yanı sıra, yeni cihazların geliştirilmesi ve yeni moleküler teknikler ve fikirlerle kombine edilmesi ile birlikte plevral patofizyoloji ve moleküler biyoloji araştırmalarında önemli bir araç haline gelmiştir. Plevral hastalıkların daha ileri araştırılmasında klinisyenler ve araştırmacılar arasındaki iş birliği çok önemlidir ve torakoskopi bu bozuklukları kesinlikle daha iyi anlamının ve tedavi etmenin bir yoludur. Bu nedenle, genç göğüs hastalıkları uzmanları bronkoskopiye olduğu şekilde torakoskopi eğitimi de almalıdır.

Anahtar kelimeler: Torakoskopi, plöroskopi, fleks-rigid, semi-rigid, dar bant görüntüleme, DBG, otofloresans, infrared, pnömotoraks, plevral efüzyon, ampiyem, akciğer kanseri, mezotelyoma, plörodez, talk

Introduction

When a century ago, the Swedish physician Hanz-Christian Jacobaeus first introduced a cystoscope into the pleural cavity of a patient with pleural tuberculosis, he could not imagine that thoracoscopy would become the gold standard for the diagnosis of pleural effusions (1). Indeed, the diagnostic yield of thoracoscopy is 95% in patients with malignant pleu-

ral disease, even in cases of difficult localisation such as costodiaphragmatic angles, mediastinum or pericardium (Figure 1) (2,3). Also, its success rate for pleurodesis is 90% for malignant pleural effusion and 95% for pneumothorax (3,4). In the recent years, with the development of novel devices, thoracoscopy has become an important tool not only in the diagnosis but also in the clinical and basic research of pleural diseases (5).



Figure 1. Pericardial and diaphragmatic metastatic disease from breast adenocarcinoma

Development of New Devices

The classic procedure uses single-port rigid devices under local anaesthesia in the endoscopy suite, under cardiovascular and respiratory monitoring. The diameters of trocars, optics, and forceps are 7-11 mm, 6-10 mm, and 4-6 mm, respectively. Minithoracoscopy has allowed the use of a smaller, 4 mm trocar with a 3.3 mm telescope and 3 mm forceps in patients with undiagnosed pleural effusion (6). Its diagnostic yield is 93% (equal to the classic rigid), with an excellent cosmetic result (6). Visualisation using minithoracoscopic instrumentation allows thorough inspection of the pleural space. The main limitations of this technique are difficulties related to adhesions, and increase of the duration of the intervention (6).

In the 80s, some authors used a flexible bronchoscope to perform thoracoscopy (5). The results were disappointing in terms of diagnostic accuracy, due to the fully flexible corps of the bronchoscope (7). Yet, this experience helped the development of the flex-rigid (or semi-rigid) thoracoscope, which is a device with a rigid corps and a flexible tip. Its resemblance to a flexible bronchoscope, and its similar handling, helped to spread the technique (1).

This new thoracoscope (Olympus, Tokyo, Japan) has a handle and a shaft measuring 7 mm in its outer diameter and 27 cm in length. The shaft is made up of two sections: a 22 cm proximal rigid portion and a 5 cm flexible distal end. The flexible tip is movable by a lever on the handle, which allows two-way angulation. It has a 2.8 mm working channel that accommodates



Figure 2. Treatment by single-port rigid thoracoscopy of pleural empyema

biopsy forceps, and other accessories, used for flexible bronchoscopy and gastrointestinal endoscopy, that are available in most endoscopy units. This combination ensures flexibility for better inspection of the pleural cavity and, at the same time, improves biopsy sampling with the rigid part. The diagnostic accuracy of flex-rigid thoroscopes in cases of undiagnosed pleural effusion is the same as for rigid devices (on average 93%) (8,9). Although a recent study showed equal results in diagnostic accuracy with a rigid device, further large comparative studies are needed to confirm the results (1).

Devices already used in gastroenterology, such as narrow band imaging (NBI), or in bronchoscopy, such as autofluorescence, were developed in recent years (5). NBI has the ability to enhance blood vessels using two narrow bands of light, which have absorption spectrum peaks of haemoglobin within the visible wavelength of light. Using NBI, neo-angiogenesis is recognisable in malignant pleural disease by the development of heterogeneous vessel caliber by CD34 staining of microvascular proliferation (10). NBI seems to be useful for recognising vascularisation differences of the tissues between malignant and benign pleural diseases (10). Since molecular staging of malignancies is, today, becoming a 'must' in the expansion of the use of targeted therapy, this important observation opens a new area of research (1,11). However, limitations exist in cases of thickened pleura. Indeed, it is difficult to determine spots of biopsy and, therefore,

improve the diagnosis of malignancy in comparison to non-specific pleuritis (1).

Another device recently used to increase the diagnostic yield of thoracoscopy is fluorescence (12). Autofluorescence excitation in the system used in patients with undiagnosed exudative pleural effusion (12) (R. Wolf GmbH, Knittlingen, Germany) is achieved by means of a 300 W xenon lamp in the violet-blue range (390-460 nm). The combination of white light thoracoscopy and autofluorescence thoracoscopy may improve diagnostic yield in these patients. Sensitivity is 100% but specificity is low (75%). The calculated positive predictive value is 92% (12). Also, this technique is limited in differentiating malignancy when the macroscopic appearance of the pleura looks like diffuse fibrotic pleuritis (12).

Fluorescence thoracoscopy has also been used after inhalation of fluorescein, to detect bullae and substantial areas of parenchymal abnormalities in patients with primary spontaneous pneumothorax (PSP) (13). Areas of abnormal parenchymal and pleural lesions could also be identified with this technique in normal individuals during thoracoscopy for other causes (14). These findings suggest that PSP is probably a more diffused (and inflammatory) disease of the pleura than a localised one (15).

This recent theory is also supported by the findings of infrared thoracoscopy (16). Non-vascularised areas of lung parenchyma, such as blebs, bullae, and emphysematous lesions are detectable by infra-red thoracoscopy by being white, while normal lung parenchyma is coloured in blue. This is due to the decreased blood flow of emphysematous lesions detectable by decreased indocyanine green intensity, compared with normally perfused lung tissue (16,17). Both fluorescence and infrared thoracoscopy are a step forward in the understanding of PSP by identifying those lesions that would otherwise be undetectable (1,18).

Research in the Understanding and Treatment of Pleural Diseases

Actually, the gold standard of pleurodesis in patients with malignant pleural effusion is considered to be thoracoscopic talc poudrage, using calibrated, asbestos-free talc (Steritalc*, Novatec, La Ciotat France) (3). Its efficacy is over 90% (3), resulting in a long-lasting pleurodesis at a very low cost (19,20). Talc has a local inflammatory effect in the pleura (21,22). Its mechanism of action is still under investigation, yet it also seems to cause pleural coagulation-

fibrinolysis imbalance (favouring the formation of fibrin adhesions), the recruitment and subsequent proliferation of fibroblasts, and collagen production in the pleural space (23,24). The pleural mesothelial lining is the primary target, playing a pivotal role in the whole pleurodesis process, including the release of several mediators such as interleukin-8, transforming growth factor-beta, and basic fibroblast growth factor (24). Also, recent studies have focused on the potential local antitumour effect of talc inducing the apoptosis of cancer cells, by altering angiostasis balance via endostatin (23,25,26).

In pneumothorax, studies showed a significant benefit in achieving pleurodesis with low recurrence rates when compared with blebs resection alone (27,28). Thoracoscopic talc pleurodesis in patients with PSP also has significantly lower recurrences and a lower duration of hospitalisation, resulting in lower costs over chest tube drainage (29). Simple thoracoscopic pleurodesis costs three times less than VATS or thoracotomy with bullectomy and pleural abrasion in patients with PSP (30). The rationale for sparing lung parenchyma is that the presence of blebs and/or bullae has never been proved to be a real risk factor for PSP occurrence (4,31,32). The need for a phase III randomised study comparing surgical procedures with simple thoracoscopy talc pleurodesis is warranted to definitively select the best management of patients with PSP (31,32).

Another area of clinical research is pleural infection. Recently published guidelines look more 'eminence' than 'evidence'-based guidelines, since few Bs and only two As are present (33,34). Still, too many patients undergo surgical drainage after either thoracoscopy or thoracotomy with pleural decortication (35). The management of patients with pleural empyema in experienced centres improves patients' outcome, and reduces mortality rates and costs (34,36). A question among others is whether those patients should undergo early thoracoscopy or classic treatment. Early thoracoscopy is effective and less invasive than thoracotomy, and was shown to provide significant benefit compared with classic treatment in two small, non-blinded, randomised studies (37-40). Also, early minimal intervention with pleuroscopy (Figure 2) has shown excellent results in recent reports. Yet, a large, controlled, phase III trial to further define its place in the treatment of pleural infection is required, since the few studies reporting results with a small number of patients are not sufficient to draw conclusions (41-43).



Figure 3. Epithelioid mesothelioma invading the pleural cavity

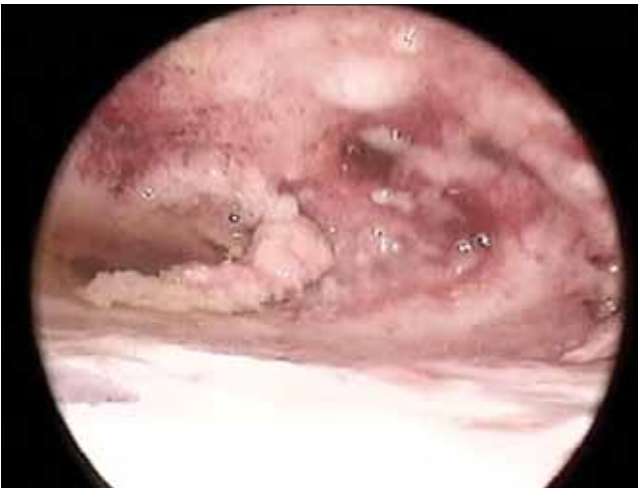


Figure 4. Sarcomatoid mesothelioma invading the pleural cavity

Malignant pleural mesothelioma (MPM) is a neoplasm with increasing incidence and poor prognosis, with a median survival of 12 months (44,45). The diagnosis of MPM by cytology and closed biopsy is extremely difficult (46,47). Thoracoscopy, with a yield of >90% in mesothelioma, is the best method for diagnosing this tumour (Figures 3, 4), when suspected on clinical or radiological data (47,48). The staging of patients with mesothelioma, before inclusion in therapeutic trials, is based on imaging. However, imaging may underestimate or miss tumour localisations in visceral, diaphragmatic or mediastinal pleura, as well as pericardial and lymph node invasion (49-51). Thoracoscopy, therefore, is necessary in all patients with suspected mesothelioma, for accurate histological diagnosis and staging, which therapeutic management and prognosis rely on (51-56). All patients, before being included in therapeutic trials, should undergo thoracoscopy,



Figure 5. Pleural metastasis and metastatic lymphangitis from lung adenocarcinoma

since response rates and survival very much depend on replace by “these” parameters.

As current treatment of MPM is globally disappointing, research aims at identifying novel potential prognostic markers for use in target therapy (23,57). In recent years, many studies on VEGF/VEGFR, the PI3K/AKT/mTOR pathway, mesothelin, and immunotherapy/gene therapy have brought new advances (57,58). Further in-depth analysis still needs to be done to identify the step-by-step process leading from early increased mesothelial cell proliferation to invasive mesothelioma, from which we expect the development of definitively effective therapy (57). Therefore, it is essential that all MPM patients are recruited to clinical and translational studies to speed up research and to improve the management of this rare and aggressive cancer (57).

Pleural metastatic effusion in patients with non-small cell lung cancer (NSCLC) has been reclassified by the IASLC as M1a disease, since the outcome of these patients is as poor as in distant metastatic disease (59,60). Also, patients with small cell lung cancer (SCLC) and pleural metastasis have an intermediate prognosis between limited and diffuse disease (61). This ‘aggressive behaviour’ of pleural involvement might be given by the study of tumour biology (23). Thoracoscopy has an important role to play in the investigation of pleural disease in lung cancer patients (Figure 5), by obtaining large biopsies to identify the molecular profile of each patient candidate for new targeted therapies (62). Also, in patients with NSCLC and resected tumour, intraoperative positive pleural lavage is a poor prognostic indi-



Figure 6. Peripheral lung adenocarcinoma directly invading parietal pleura

cator (63,64). Pleural lavage is a useful tool for the study of pleural physiology and is easily performed during thoracoscopy (65). Therefore, a step forward in the assessment of patients with NSCLC and peripheral lesions (Figure 6) might be the systematic investigation of pleural cytology for potential micrometastatic disease. This would lead to better prediction of survival and hence, to better management of these patients (18).

Conclusion

The impact of thoracoscopy, the oldest interventional technique in respiratory medicine, in the diagnosis and treatment of pleural diseases has increased over recent years. It has become a research tool by the addition of new ideas, devices, and concepts for the study of the pathophysiology and molecular biology of pleural disease. Clinical trials should, however, define the place of thoracoscopy in the management of specific diseases. Further improvement of technologies will add important tools for better diagnosis, more profound basic research, and personalised treatment of pleural diseases. As pleural diseases are frequent in routine clinical practice, training in thoracoscopy should be considered as essential as bronchoscopy for respiratory physicians.

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