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Title: Effectiveness of Video-Assisted Thoracoscopic Surgery in Undiagnosed Exudative Pleural Effusions

Short title: Fast Diagnosis in ExudativePleurisy

Authors: Erdoğan Dadaş¹, Eren Erdoğan², Alper Toker², Miray Ersöz³, Tamer Okay³

Institutions: ¹Department of Thoracic Surgery, Adiyaman University School of Medicine, Adiyaman, Turkey

²Department of Thoracic Surgery, İstanbul Universityİstanbul School of Medicine, İstanbul, Turkey

³Department of Thoracic Surgery, Health SciencesUniversitySiyami Ersek Hospital, İstanbul, Turkey

Corresponding Author: Erdoğan Dadaş, Departmentof Thoracic Surgery, Adiyaman University School of Medicine, Adiyaman, Turkey

E-mail: erdogandadas@yahoo.com

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Abstract

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OBJECTIVES: Undiagnosed pleural effusions (mostly require histologic studies for a definite diagnosis. In addition, malignant pleural effusions responsible for a significant part of exudative pleurisy need palliative therapy The purpose of our study is to research the effectiveness of video-assisted thoracoscopic surgery in definitive diagnosis and palliative treatment of unexplained non-parapneumonic exudative pleural effusions.

MATERIALS AND METHODS: The study included 263 patients with non-parapneumonic exudative pleurisy, which could not be diagnosed by an initial clinical, radiological, biochemical, microbiological, and cytological investigation in three centers. All patients underwent video-assisted thoracoscopic surgery for definitive diagnosis between January 2002 and January 2018. Patients' data were retrospectively analyzed in terms of age, gender, symptoms, previously diagnosed cancers, computerized tomography of chest findings, histopathological diagnosis, cytological diagnosis, morbidity, mortality, and success rates of the procedure. Patient groups from the three centers were divided into three groups according to the center of the patient. The groups were compared statistically in terms of cytologic diagnosis rates.

RESULTS: The most common complaint was dysnea (66.5%). Of the 263 cases, 83 were previously diagnosed with cancer. The simple pleural effusion (66.5%) was the most frequent radiological finding. The success rate for definitive diagnosis was detected as 97%. Of all the cases, the rate of specific cytological diagnosis was detected to be 34%. The cytologic diagnosis rate was meaningfully lower in Group 1 than in Groups 2 and 3. The postoperative morbidity rate was detected as 9%.

CONCLUSION: Video-assisted thoracic surgery is not only a rapid and effective diagnostic method, but also a palliative therapeutic method. We think that it should be used immediately after initial diagnostic thoracentesis in undiagnosed exudative PE in the less experienced centers

KEYWORDS: Video-assisted thoracoscopic surgery, exudative pleural effusion, definitive diagnosis, palliative therapy

INTRODUCTION

Pleural effusions (PE) represent extreme accumulation of pleural fluid in the pleural space, in due to infectious and infiltrative pathologies affecting the pleura and lungs or resulting from impaired balance between the pleural fluid production and absorption as a consequence of various systemic diseases [1]. Congestive heart failure, pneumonia, and malignancy are the most common PE causes [2].

PE obtained by diagnostic thoracentesis is divided into transudate and exudate fluid, according to light criteria [1]. There is usually no need for advanced laboratory and interventional diagnostic procedures in transudative PE. In the case of exudative pleurisy, precise etiologic diagnosis

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requires advanced biochemical and microbiological laboratory procedures, cytological studies, and tissue biopsies [3].

The purpose of our study was to investigate the effectiveness of video-assisted thoracic surgery (VATS) in diagnosis and palliative treatment of unexplained non-parapneumonic exudative PEs.

MATERIALS AND METHODS

This retrospective multicenter study conducted in three centers between January 2002 and January 2018 included 263 patients with non-parapneumonic exudative pleurisy that could not be diagnosed by initial clinical, radiological, biochemical, microbiological, and cytological investigations. The biochemical analyzes of pleural fluid included measuring sugar, protein, triglycerides, and lactate dehydrogenase, while the microbiological analyzes consisted of Gram stain, acid fast bacillus smear and culture, and the pleural fluid adenosine deaminase (ADA) level measurements. All patients underwent detailed clinical evaluations with disease history and clinical examinations. Chest computerized tomography (CT) was performed to evaluate the pleural and parenchymal pathologies and assess the feasibility of thoracoscopy. All patients underwent VATS for definitive diagnosis and, if necessary, palliative therapy. The patients who could not undergo thoracoscopy due to advanced adhesions and did not tolerate general anesthesia or lung ventilation were not included in the study. All the patients underwent general anesthesia and double lumen intubation at the lateral decubitus position. First, we placed a 10-millimeter port in the sixth intercostal space at the mid-axillary line and the second port in the fourth intercostal space at the anterior axillary line. After the lung was deflated and all pleural surfaces were observed, pleural fluid was fully aspirated and sent for cytology and culture. Biopsies were taken from the pathological lesions on the pleura. Talc pleurodesis was performed in each case diagnosed as malignant pleurisy by thoracoscopic observation. The trucut biopsies were performed in cases where a lung mass was detected by chest CT. Also, patients with a peripheral pulmonary nodule underwent wedge resection by endostapler. Hemostasis was controlled by electrocautery. The procedure was completed by inserting a chest tube in the telescopic incision. The lung expansion was checked by chest X-ray. The chest drains were removed when the lung expanded and drainage was less than 50 mL per 24 hours.

Patients' data were retrospectively analyzed in terms of age, gender, symptoms, previously diagnosed cancers, chest CT findings, histopathological diagnosis, cytological diagnosis, morbidity, mortality, and procedure success rates. Patient groups from the three centers were divided into three groups according to the center of the patient. The groups were compared statistically in terms of cytologic diagnosis rates. The Ethics Committee of Adiyaman University Medical School approved the study protocol (5/22/2018, 2018/4-6).

Statistical Analysis

We conducted the study according to the principles of the Declaration of Helsinki. We used the Statistical Package for the Social Sciences 16.0 (SPSS Inc.; Chicago, IL, USA) software for statistical analysis. A chi-squared test was utilized to compare the differences between the groups. A P-value <0.05 was considered to be statistically significant.

RESULTS

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The majority of cases were male patients (161 males and 102 females). The most common complaint was dyspnea (66.5%). One hundred and eighty cases had no malignant disease, whereas 83 cases had previously diagnosed cancer. Single PE (66.5%) was the most frequently observed radiological finding. Clinical and radiological characteristics of 263 patients are presented in Table 1. The histopathological data could be obtained from 249 of 263 patients. The definitive diagnosis was achieved in 242 (97.2%) of 249 patients, while the specific diagnosis was not obtained in only 7 (2.8%) patients. The success rate for definitive diagnosis was detected at 97%. The success rate of palliative therapy was found to be 95%. The histopathological characteristics are presented in Table 2. Cytopathological data were obtained from 195 patients. The specific cytological diagnosis could be set in only 67 of 195 patients. The cytologic diagnosis rate was significantly lower in Group 1 than in Groups 2 and 3 ($P=0.000$). The cytological characteristics are presented in Table 3. The postoperative morbidity rate was detected as 9% ($n=24$; Table 4). Also, the mortality rate was 2.7% ($n=7$).

DISCUSSION

Many recent studies have investigated some novel cancer biomarkers including ADA, tumor necrosis factor, interleukin-6, ceroreactive protein, carcinoembryonic antigen [4], vascular endothelial growth factor [5], reactive oxygen metabolites [6], and ceruloplasmine [7] in pleural fluid for discriminating between malignant pleurisy (MP) and benign pleurisy (BP), but there is still a lack of diagnostic MP markers with sufficient sensitivity and specificity, which drove us to find and test novel biomarkers [8,9]. Of these biomarkers, only ADA shows high sensitivity and specificity for tuberculosis (TBC) pleurisy. If a patient has a lymphocytic pleurisy and an ADA level greater than 45 U/mL, it is highly probable that PE is dependent on the TBC pleuritis. In such patients, it is not necessary to confirm the diagnosis of TBC pleuritis by pleural biopsy [10].

Cytologic studies of the pleural fluid may reveal if pleurisy is malignant or benign. A positive cytology rate is approximately 60% in patients with MP [11]. Factors such as the type of tumor, pleural tumor burden, and expertise of the cytologist determine the success rate of cytologic diagnostic studies [12]. Traditionally, when the pleural fluid cytologic diagnostic studies fail, the next step is the closed pleural biopsy. It is a cheaper and easily accessible method. However, in the literature, diagnostic rates of covered pleural biopsy are approximately 44% [13]. In a recent comparative study, while the success rate of closed pleural biopsies was only 21.7%, success rates of medical thoracoscopic pleural biopsies were found to be 78.3% [14]. Recently, a large number of studies on medical thoracoscopy have been published. However, diagnostic effectiveness of medical thoracoscopy seems to be behind the VATS [15,16].

As a more current practice, the pleural biopsy can be performed under the guidance of a chest CT or ultrasound (USG). According to a prospective study performed by Metintas et al. [17], diagnostic sensitivity of the chest CT guided-needle pleural biopsy in patients with PE is approximately 82%. It was detected that the chest USG-guided needle pleural biopsy had a 66% diagnostic sensitivity in the same study. But the imaging-guided pleural biopsies require experienced interventional radiologists, and it is not possible in all hospitals. In general, approximately 50% of all patients with PE cannot be diagnosed after the initial diagnostic thoracentesis [8].

Because of the limiting reasons mentioned above, in many centers including ours, a non-diagnostic thoracentesis is followed by thoracoscopy [18]. Our study showed that the most common

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symptom and chest CT finding were dyspnea and single PE. The clinical and radiological features were similar to the world literature [5,18,19]. We also detected that in our large study group, VATS had high diagnostic success with favorable morbidity and mortality rates. In our study, which included patients from three different centers, the rate of cytologic specific diagnosis was similar to the one in the world literature in Groups 2 and 3 [11,20]. However, the rate of cytologic specific diagnosis in Group 1 was very low, which should be taken under consideration. There is no doubt that the reason for this is the absence of an experienced cytopathologist in this center. Furthermore, it should also be kept in mind that the presence of experienced interventional radiologist outside advanced centers is almost impossible. Therefore, since there are no experienced radiologists and cytologist in our center, it is almost impossible to diagnose pleural pathologies with pleural biopsy by imaging or cytology of pleural fluid. Moreover, single PE is the most frequently observed radiological feature for PE, and therefore, the probability of a diagnostic closed pleural biopsy is very low. On the other hand, we believe that rapid and highly successful diagnostic methods should be used early on in cases of unexplained exudative PE due to the need for definitive diagnosis, initiation of specific or palliative treatment, and prognosis determination.

In conclusion, VATS is not only a rapid and effective diagnostic method, but also a palliative therapeutic method. We think that VATS should be used right after the diagnostic work conducted with initial thoracentesis in undiagnosed exudative PE in the less experienced centers so that diagnosis can be obtained faster, and diagnostic delay can be avoided in malignant PE.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Adiyaman University Medical School (5/22/2018, 2018/4-6).

Informed Consent: Due to their respective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.D; Design - ED; Supervision - A.T, T.O; Resources - E.D; Materials E.D, E.E; Data Collection and/or Processing – E.D, E.E, N.E.; Analysis and/or Interpretation - E.D, E.E; Literature Search - E.D, E.E., N.E; Writing Manuscript - E.D; Critical Review - A.T; Other - T.O

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

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Table 1. Clinical and radiological characteristics

Variables	Number (%)
Mean age (year)	59.54±14.92
Gender	

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Male	161 (61.2)
Female	102 (38.8)
Symptoms	
Dyspnea	175 (66.5)
Chest pain	41 (15.6)
Cough	34 (12.9)
Weight loss	4 (1.4)
Hemoptysis	7 (2.7)
Fever	2 (0.8)
Previously diagnosed cancers	
Lungcancer	36 (13.7)
Extrathoracic cancers	47 (17.9)
Total	83 (31.6)
Chest CT findings	
Single pleural effusion	175 (66.5)
Pleurisy+Pleural nodular/Diffuse thickening	50 (19.0)
Pleurisy+Lung mass	38 (14.5)

Table 2. Histopathological characteristics

Histopathologic diagnoses	Number(%)
Malign disease	
Lung cancer	52 (20.9)
Malignant pleural mesothelioma	39 (15.7)
Breast cancer	17 (6.8)
Gastric cancer	5 (2)
Non-Hodgkin lymphoma	4 (1.6)
Soft tissue sarcoma	3 (1.2)
Undifferentiated round cell tumor	3 (1.2)
Others	11 (4.2)
Total	134 (55)
Benign diseases	
Chronic nonspecific inflammation	67 (26.9)
Tuberculosis	19 (7.6)
Reactive mesothelial hyperplasia	16 (6.4)

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Others	6 (2.4)
Total	108 (45)

Table 3. Cytopathological characteristics and comparison of three study groups

	Group 1(%)	Group 2(%)	Group 3(%)	p*
Specific diagnosis established	1(2.2)	41(41.8)	25(48.1)	0.000
No specific diagnosis established	44(97.8)	57(58.2)	27(51.9)	
Totalnumber	45	98	52	

*Pearson chi-squaredtest, Group 1: Adiyaman University Medical School Thoracic Surgery Department, Group 2: Istanbul University Istanbul Medical School Thoracic Surgery Department , Group 3: Health Sciences University Siyami Ersek Hospital Thoracic Surgery Department

Table 4. Postoperative morbidities

Morbidities	Number (%)
Prolonged airleak	7 (2.7)
Prolonged drainage	6 (2.3)
Pneumonia	3 (1.1)
Atrial fibrillation	3 (1.1)
Expansion defect	2 (0.8)
Hemorrhage	2 (0.8)
Wound infection	1 (0.4)
Total	24 (9.1)

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