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Course of minimal pleural effusions in non-small cell lung cancer

Minimal pleural effusions in non-small cell lung cancer patients

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Abstract

Aim: Patients with lung cancer may develop effusions at diagnosis or follow-up that can take three different forms: malignant pleural effusions (MPEs), paramalignant pleural effusions (PMPEs) and non-malignant effusions of known causes. Differentiating between MPE and PPE is crucial for the determination of appropriate patient management. This study examines the course of pleural effusions, and minimal pleural effusions in particular, that were detected at diagnosis and did not interfere with curative treatment during routine examinations following scheduled treatment.

Material and Methods: This retrospective study included Non-Small Cell Lung Cancer (NSCLC) patients with minimal pleural effusions who were scheduled for curative treatment (concurrent chemoradiotherapy [CRT] and surgery) between January 1, 2014 and December 31, 2020. The changes in pleural effusions at follow-up were assessed.

Results: At 3 months follow-up, there were six (6.3%) patients without follow-up and 14 (14.6%) patients who did not come for their follow-up appointments. Of the 76 patients with follow-up results, seven had increased pleural effusion quantities and 23 had decreased pleural effusion quantities, while the amount was similar in 46 patients. At 12 months follow-up, there were eight (8.3%) patients without follow-up, 13 (13.5%) patients who did not attend their follow-up appointments, and two (2.1%) patients who died. Of the 73 patients with follow-up data, 11 had increased pleural effusion quantities and 23 had decreased pleural effusion quantities, while the amount was similar in 39 patients.

Discussion: Patients without distant metastasis at diagnosis may be considered for curative treatment, which provides better survival, based on a careful assessment of the clinical and radiological variables of the minimal pleural effusions in such patients at diagnosis.

Keywords
Pleural Effusion, Lung Cancer, Paramalignant

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Introduction

Patients with lung cancer develop pleural effusions in varying amounts at diagnosis or at follow-up due to several etiologies. Such effusions can take three forms [1]:

1. Malignant pleural effusions (MPEs): Identified during cytological examinations or from malignant cells in a parietal pleural biopsy.
2. Paramalignant pleural effusions (PMPEs): Pleural effusions resulting from malignancy. Malignant cells cannot be detected in the pleural fluid or tissue without direct pleural infiltration by tumor, and in such cases, the effusion accumulates due to secondary causes, such as bronchial obstruction, lymphatic obstruction or pulmonary embolism [2].
3. Non-malignant pleural effusions of known causes: Effusion develops as a result of congestive heart failure, chronic kidney failure or hypoalbuminemia.

PMPEs are detected in approximately 5% of patients with lung cancer, and are equally present in all pathohistological types of lung cancer, with an incidence of 5-10% in non-small cell lung cancer (NSCLC) and 6.5% in small cell lung cancer [3,4].

Differentiating between MPE and PPE is crucial for the determination of appropriate patient management, and should therefore be considered important

With the change from T4 to M1a in the seventh edition of the TNM classification, the accurate assessment of pleural effusion has become more important for tumor staging [5], although little is known about the epidemiological or prognostic implications of minimal pleural effusions in patients with lung cancer.

The present study examines the course of pleural effusions, especially minimal pleural effusions, which were detected at diagnosis and did to not interfere with curative treatment during routine examinations following scheduled treatment.

Material and Methods

This retrospective study included Non-Small Cell Lung Cancer (NSCLC) patients with minimal pleural effusions who were scheduled for curative treatment (concurrent chemoradiotherapy (CRT) and surgery) between January 1, 2014 and December 31, 2020. The patients' demographic data, disease stage, pathological cell type, lesion characteristics (atelectasis, mediastinal and lymphovascular invasion), pleural effusion sampling status, location and biochemical characteristics of pleural effusion, Standard Uptake Value (SUV) of the pleural effusion on Positron Emission Tomography/Computed Tomography (PET/CT) and type of treatment administered (concurrent chemoradiotherapy and type of surgery) were obtained from the patient files.

Minimal pleural effusion was defined as <10 mm thick effusion in the pleural space.

All patients with pleural effusions underwent thoracic ultrasound-guided thoracocentesis for diagnostic purposes if the effusion level was sufficient before initiating any treatment, and biochemical and cytological examinations were planned. Effusions were diagnosed as transudative or exudative based on Light's criteria [2]. Samples of the pleural effusion materials were processed three times for cytological studies. The study included patients with small effusions that could not be detected by the thoracic US and that were not considered malignant clinically or radiologically, and patients with samples of effusion in whom malignant cells could not be identified.

The patients were followed up clinically and radiologically for disease progression and pleural effusion increase every three months for one year, and were questioned about symptoms (cough, dyspnea, pleuritic chest pain) that may develop secondary to increased pleural effusion. Especially at 3 months, when the first radiological follow-up after curative treatment was performed, and at 12 months, the change in the amount of pleural effusion (similar, increase, decrease) and the status of disease progression were recorded.

Patients with increased pleural effusions at follow-up were assessed for disease progression, malignancy in cytology (if fluid could be collected during the thoracic US), and for systemic diseases that might have caused such a fluid increase.

In patients with decreased pleural effusions at follow-up it was assessed whether the decrease was due to the treatment of the primary disease. If possible, the effusion was sampled and examined for malignancy in cytology. Follow-up was continued in patients with effusions that were too small to be sampled.

Patients with malignant pleural effusions, small cell lung carcinoma and malignant mesothelioma, and those with pleural effusions secondary to oligometastatic disease, chronic renal failure, heart failure, cachexia and hypoalbuminemia were excluded from the study.

This study was approved by the Ethics Committee of Ankara Chest Diseases and Thoracic Surgery, Health Sciences University (Date: 2021-09-16, No: 5)

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.). The normality of the distribution of continuous variables was ascertained from a Kolmogorov-Smirnov test, and Levene's test was used to evaluate the homogeneity of variances. Unless otherwise specified, continuous data were described as mean±SD (minimum value-maximum value) for normal distributions, and as mean±SD and median (minimum value-maximum value) for skewed distributions. Categorical data were described as the number of cases (%). Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test. A p-value of <0.05 was considered significant in all statistical analyses.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A review was made of 615 patient files with early and locally advanced NSCLC between 2014 and 2020. After the exclusion criteria were applied, 96 patients with pleural effusions <10 mm at diagnosis were included in the study (Figure 1).

The study sample comprised 90 (93.8%) females and six (6.3%) males, with a mean age of 66.99±7.81 years within a range of 49–82 years. Of the total number, 50 (52.1%) patients had comorbidities (Table 1).

Considering the diagnoses of the patients, 57 (59.4%) had squamous cell carcinoma (SCC), 27 (28.1%) had adenocarcinoma, 10 (10.4%) had NOS (not otherwise specified) and two (2.1%) had adenosquamous cell carcinoma.

According to the stages, the patients had primarily locally

advanced stages of the diseases (Table 2).

There was lymphovascular invasion in 4 (10.8%), mediastinal invasion in 12 (32.4%), atelectasis in 10 (27.0%), lymphovascular invasion + mediastinal invasion in 6 (16.2%) patients and mediastinal invasion + atelectasis in five (13.5%) patients.

Considering the location of the pleural fluid, it was ipsilateral to the mass in 84 (87.5%), contralateral in four (4.2%) and bilateral in eight (8.3%) patients.

Effusion sampling was performed through thoracic US in 38 (39.6%) patients. Among these patients, no pleural effusion could be collected in 11 (28.9%) due to the very small amount, while effusions were sampled in 27 (71%). The pleural effusion was transudative in one (2.6%) patient and exudative in 26 (68.4%) patients.

While there was no SUV uptake of pleural effusions on PET/CT in 72 (75.0%) patients, there was uptake in 24 (25.0%). The SUVmax ranged from 1.25 to 9.93 in patients with pleural effusion uptake on PET/CT, with a mean SUVmax of 2.92±1.85 and a median SUVmax of 2.34. An increase in effusion was identified only in one of the patients with SUV uptake on PET/CT at 3 months follow-up, but the disease was considered stable. At 12 months follow-up, an increase in effusion was identified in four patients, but the disease was considered stable.

Of all patients, 61 (63.45%) patients received chemoradiotherapy as the first-line therapy. Surgery was the first-line therapy in 35 (36.5%) patients, with lobectomy in 28 (80.0%) and pneumonectomy in seven (17.1%) patients.

Of those who underwent surgery, 25 (26.0%) received

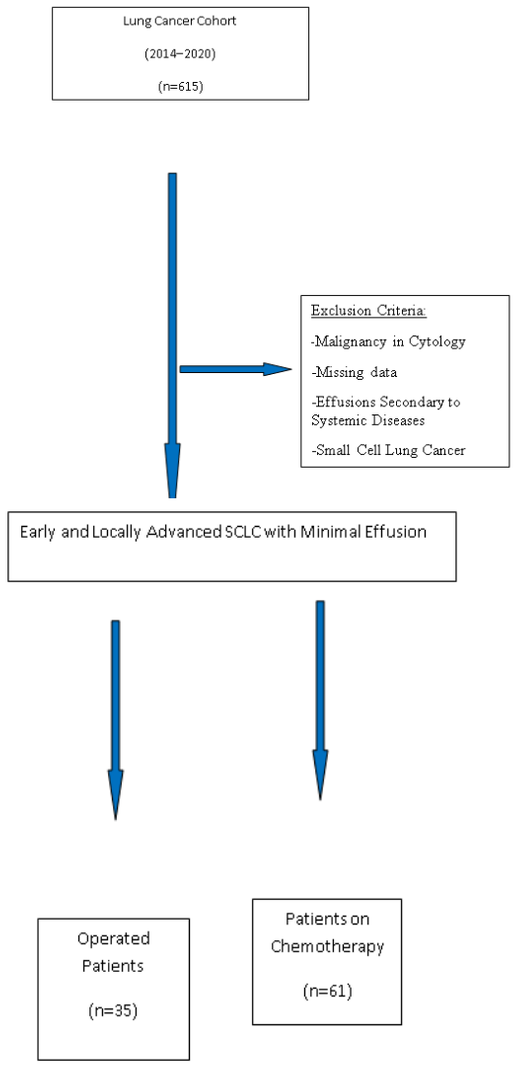

Figure 1. Patient Enrollment Flowchart

Table 1. Demographic Data of Patients

Variables	All Cases (n=96)
Age, year, ±SD (Min-Max)	66,99±7,81 (49-82)
Gender	
Woman	6 (6,3%)
Male	90 (93,8%)
Histopathology	
Squamous	57 (59,4%)
Adenocarcinoma	27 (28,1%)
NOS	10 (10,4%)
Adenosquamous	2 (2,1%)
Comorbidite	
No	46 (47,9%)
Yes	50 (52,1%)
Lesion Feature	
Lymphovascular Invasion	4 (10,8%)
Mediastinal Invasion	12 (32,4%)
Atelectasis	10 (27,0%)
Lymphovascular + Mediastinal Invasion	6 (16,2%)
Mediastinal Invasion + Atelectasis	5 (13,5%)
Effusion Site	
Same Side	84 (87,5%)
Opponent	4 (4,2%)
Bilateral	8 (8,3%)
Effusion Sampling Status	
Yes	38 (39,6%)
No	58 (60,4%)
Effusion Feature (n=38)	
Failed to Retrieve	11 (28,9%)
Transude	1 (2,6%)
Exudate	26 (68,4%)
SUV involvement	
No	72 (75,0%)
Yes	24 (25,0%)
SUV MAX, ±SD Median (Min-Max) (n:24)	2,92±1,85, 2,34(1,25-9,93)
Treatment	
Surgical	35(36,4%)
CRT	61(63,45%)
CRT; Chemoradiotherapy	

Table 2. Distribution of Patients by Stages

Stage	n=96	%
I A	2	6.25%
I A 2	1	1,00%
I A 3	2	2,10%
I B	2	2%
II A	6	6,30%
II B	14	14,60%
III A	32	33,30%
III B	29	30,20%
III C	3	5.2%

Table 3. Comparison of Effusion Amount Between Groups in the 3rd Control Month

	Patients Receiving CRT (n=44)	Surgical Patients (n=32)	p
Increase in Effusion	5 (11,4%)	2 (6,2%)	
Decrease in Effusion	11 (25 %)	12 (37,5%)	0,434
Similar	28 (%)	18 (56,3%)	

adjuvant chemotherapy and six (6.3%) received adjuvant chemoradiotherapy.

At 3 months follow-up, there were six (6.3%) patients without follow-up and 14 (14.6%) patients who did not come for their follow-up appointments. Of the 76 patients with follow-up data, seven had an increased amount of pleural effusion and 23 had a decreased amount of pleural effusion, while the amount was similar in 46 patients.

At 3 months follow-up, the rate of patients with decreased effusions was higher in patients who had surgery than in those who received CT, while the rates of patients with increased and similar effusions were lower, although there was no statistically significant difference between the groups (p>0.05) (Table 3).

At 3 months follow-up, the disease was stable in 55 (72.4%) and progressed in 21 (27.6%) patients.

At 12 months follow-up, eight (8.3%) patients were without follow-up, 13 (13.5%) patients did not attend their follow-up visits and two (2.1%) patients died. Of the 73 patients with follow-up data, 11 had increased pleural effusion amounts and 23 had decreased pleural effusion amounts, while the amount was similar in 39 patients.

The rate of patients with decreased effusion was higher in patients who had surgery than in those who received CT, while the rates of patients with increased and similar effusion were lower, although there was no statistically significant difference between the groups (p>0.05) At 12 months follow-up, the disease was stable in 55 (72.4%) and progressed in 21 (27.6%) patients.

The disease progressed in five of the seven patients with increased effusions at 3 months follow-up and in six of the seven patients with increased effusions at 12 months follow-up.

No malignant effusion was identified in the evaluations of patients with increased pleural effusions at follow-up.

Discussion

Pleural effusion is a common clinical presentation in patients with non-small cell lung cancer. Most effusions are malignant and indicate pleural metastases and unresectable disease, although some are potentially benign reactive fluid collection that do not interfere with curative surgery.

Our study addresses the importance/prognostic value of accurate characterization of minimal pleural effusions based on clinical and radiological variables in patients with non-small cell lung cancer who are candidates for curative therapy.

Thoracentesis is the initial diagnostic approach to characterize pleural effusions, although it is not recommended if the pleural effusion is minimal (<10 mm thick) on lateral decubitus radiographs or computed tomography (CT) scans [2,4,6]. While the cytological examination of pleural fluid is currently the least invasive and fastest approach to the diagnosis of malignancy, it is not always diagnostic, with a sensitivity in the 40–87% range [8]. In the present study, 38 (39.6%) patients underwent thoracentesis, while 58 patients did not due to a fluid amount of <10 mm, which is in line with the findings of previous studies [2,7]. Fluid could be sampled only in 27 (71%) of the patients who received thoracentesis.

Although we suggest that PET/CT, biochemical parameters and interventional methods are accurate diagnostic tools for distinguishing benign from malignant pleural effusion [9-12], our study focused more on the varying amounts of effusions during follow-up, rather than evaluating the course of minimal pleural effusions in cases where malignant pleural effusion was ruled out.

Our study re-assessed the presence of MPEs in patients with the progressed disease and increased pleural effusion at 3 months and 12 months of follow-up. Although most patients with malignant pleural effusions tend to have moderate-to-high effusion amounts, ranging from 500 to 2000 mL, none of our patients had effusions exceeding 1/3 of the hemithorax at follow-up. The malignant potential of pleural effusions was assessed by the thoracic US, sampling if the effusion amount was sufficient, questioning the presence of effusion-secondary symptoms and PET/CT. Clinical, radiological and cytological assessment revealed no malignant pleural effusion in any patient.

The radiological finding of a nodular pleural thickening of >1 cm and mediastinal involvement suggest malignant pleural thickening in malignant pleural effusions, although no such findings were observed in our patients at diagnosis.

Mediastinal or hilar bulky lymphadenopathy, atelectasis and lymphovascular invasion are known to be potential causes of pleural effusions in patients with lung cancer. In the present study sample, lymphovascular invasion was noted in four (10.8%) patients, mediastinal invasion in 12 (32.4%) patients, atelectasis in 10 (27.0%) patients, lymphovascular invasion+mediastinal invasion in six (16.2%) patients and mediastinal invasion+atelectasis in five (13.5%) patients. The increase in effusion in those with disease progression at 3 and 12 months was attributed to the development of lymphovascular invasion, mediastinal invasion and atelectasis.

Guidelines suggest [2,13] that clinical and radiological findings, as well as biochemical parameters, can aid in the diagnosis of MPEs and PPEs. In the present study PPEs were diagnosed primarily based on clinical and radiological findings, as the effusions of the patients could not be sampled due to the very small amounts.

Since malignant effusions prevent curative resection, it is important to differentiate between the benign and malignant forms in patients with potentially resectable non-small cell lung cancer [6].

The importance of this assessment is highlighted by our study that pleural effusions detected radiologically at diagnosis, although too small in amount for sampling, can be considered paramalignant after careful clinical and radiological assessment, especially in patients appropriate for curative treatment, thus providing the potential of having resectable disease and curative treatment.

The main limitation of this study is its retrospective design and sample size.

Although there is no similar study, our findings can be supported by similar studies with a larger number of patients.

Conclusion

We found that patients without distant metastasis at diagnosis may be considered for curative treatment, which provides better survival, based a careful assessment of the clinical and radiological variables of minimal pleural effusions in the patient at diagnosis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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