Do the Amount of Fluid, Histopathology, Radiology and Pleurodesis Status Affect the Survival in Malignant Pleural Effusions?

Malign Pleural Effusionlarda Sıvı Miktarı, Histopatoloji, Radyoloji ve Plöredez Durumu Sağkalımı Etkiliyor mu?

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Öz

Giriş ve Amacı: Bu çalışmamın birincil amacı, malign pleural efüzyona (MPE) yol açan en yaygın plevral maligniteleri belirlemektir. İkinci amaç, sıvı miktarı ile radyolojik bulgular, etyolojiler, tedavi yöntemleri ve sağkalıma arasındaki ilişkisi değerlendirilmektedir.

Yöntem ve Gerçeçler: Çalışmanın uygulandığı doku tamsıalanmış MPE vakaları dahil ettik.

Bulgular: MPE'nin en yaygın nedenleri akciğer kanserisi (% 73), meme kanserisi (% 8.3) ve mezotelyoma (% 7) idi. Kimyasal plöredez önerilen hastalarda plöredez yaklaşık% 31.1 oranında başarlı olmuştur. Pleural sıvı miktarı ile hücre tipi, sağkalım, pulmoner, ekstrapulmoner malignite ve mezotelyoma arasında ilişki bulunmaktadır, hastalar plöredez başarlı ise daha uzun sağkalma sağlandığı P = 0.005. Pulmoner, ekstrapulmoner ve mezotelyoma nedeniyle MPE'lili hastaların medyan sağkalımı 365±365 gündür. Mezotelyomalı hastaların sağkalımı diğerlerine göre anlamlı olarak daha uzundu (P: 0.000).

Tartışma ve Sonuç: MPE’nin ana nedeni akciğer kanseriydi, ardından meme kanserisi, primer bilimneye maligniteler ve mezotelyoma geldi. Kimyasal plöredez, MPE için geçerli bir palyatif önlemdir. Başarılı plöredezin sağkalımı önemli bir katkıdır.

Anahtar Kelimeler: malign pleural efüzyon, sağkalım, tedavi
INTRODUCTION

Malignant pleural effusion (MPE) is the most frequently detected reason for exudative pleural fluids. Pleural involvement is seen in 30-50% of metastatic malignancies, the amount of pleural fluid varies from non-massive to massive (1,2). MPEs may make malignancies become complicated, despite the fact that lung / breast cancers are the most common reason in this respect (1). It was argued by previous authors that haematogenous spread of malignant cells to visceral pleura with secondary seeding to parietal pleura cause MPE (3). The course of primary disease in the presence of MPE also has a poor prognosis (1). The average survival varies between 3 and 12 months. In addition to the treatment of primary disease, there are treatment alternatives such as tube thoracostomy, pleurodesis and permanent pleural catheter (1).

The present study basically aimed to determine the most prevalent pleural malignancies causing MPE in a large tertiary hospital in Izmir, Turkey. The secondary objective was to evaluate the relationship between the radiological appearance and etiology, treatment methods and survival.

MATERIALS AND METHOD

Study design and population

The files of patients with MPE who were diagnosed with pleural fluid cytology or pleural biopsy between 2013 and 2018 were analyzed retrospectively. The fluid amount and pleural involvement images were evaluated from thoracic computed tomography (CT) and chest radiographs. Primary malignancy was divided into three groups; pulmonary, extrapulmonary malignancies and mesothelioma. Histological subtypes of lung cancers were determined. Treatment methods and the survival of the patients were recorded. Pleurodesis was performed in patients with shortness of breath, massive fluid and no endobronchial lesions. Pleurodesis was performed with t alc in all patients. Pleurodesis was not performed in patients with loculated pleural fluid. No complications developed in patients who underwent pleurodesis.

Imaging

The sizes of pleural effusion were categorized into three classifications on the chest radiograph: mild (less than one-third of hemithorax), moderate (one-third - two-thirds of hemithorax), and massive (more than two-thirds of hemithorax). CT scans were evaluated in terms of pleural thickening (≥10 mm) and nodularity of visceral and parietal layers.

Ethics Approval

Ethical approval was obtained from Local Ethics Committee with the number 49109414-604.02 dated 22.04.2019.

Statistical Analysis

Continuous variables were indicated as median (25-75%), categorical variables as numbers. Comparisons were made using the Man Whitney or Chi-square test. Survival analysis was done with the Kaplan Meier and multivariate regression analysis was used for factors affecting survival.

RESULTS

A total of 533 patients (median age 64 years, 336 males) were included in the study. While 504 (95%) of the patients were diagnosed with pleural fluid cytology, 29 (5%) of them were diagnosed with video assisted thoracic surgery (VATS). While primary malignancy was lung cancer in 389 (73%) of the cases, non-pulmonary malignancy was detected in 108 (20%) and malignant mesothelioma in 36 (7%) cases. The distribution of lung cancer by histological types are 289 (54.2%) adenocarcinoma, 18 (3.4%) squamous cell carcinoma, 78 (14.6%) small cell lung carcinoma, 1 (0.2%) large cell lung carcinoma, and 10 (1.9%) were not otherwise specified (NOS). Among the extrapulmonary malignancies, the most common was breast cancer at 44 (8.3%), while the genitourinary system was seen in 28 (5.3%), a gastrointestinal system in 22 (4.1%), lymphoma in 5 (0.9%) and other malignancies were observed in 10 (1.9%) cases. The major underlying diagnoses are given in Table 1.

Table 1. Patient characteristics, diagnostic methods and pleural fluid diagnoses

| Age (Median) | 64 |
|--------------|----|
| Gender ( N,%)|    |
| Male         | 336 (63%) |
| Female       | 197 (37%) |
| Diagnostic method ( N,%)|    |
| Cytology     | 504 (94.6%) |
| Surgery      | 25 (4.7%)  |
| Pulmonary ( N,%)|    |
|                | 389 (73%) |
| Extrapulmonary ( N,%)|   |
|                | 108 (20%) |
| Mesothelioma ( N,%)|    |
|                | 36 (7%)   |
| Pulmonary ( N,%)|    |
| Adenocarcinoma| 289 (54.2%) |
| Squamous Cell Carcinoma | 78 (3.4%) |
| Small cell Carcinoma | 78 (14.6%) |
| Large Cell Carcinoma   | 1 (0.2%) |
| NOS                   | 10 (1.9%) |
| Extrapulmonary carcinoma ( N,%)|  |
| Breast              | 44 (8.3%) |
| Genitourinary system| 28 (5.3%) |
| Gastrointestinal system| 22 (4.1%) |
| Lymphoma            | 5 (0.9%) |
| Other                | 10 (1.9%) |
| Dead ( N,%)| 369 (69.2%) |
| Alive ( N,%)| 164 (30.8%) |
When looking at the radiological view, pleural thickening was observed in 140 (26.3%) cases, nodulation in 71 (13.3%) cases, and loculated fluid in 13 (2.4%) cases. Pleurodesis was applied to 255 (47.8%) cases (Table 2).

No relation was found between the amount of pleural fluid and cell type, survival, pulmonary, extrapulmonary malignancy and mesothelioma (Table 3). There was no difference between the amount of pleural fluid and survival (Figure 1).

Pleural nodularity was significantly higher in patients with mesothelioma. Patients were found to live longer if pleurodesis was successful (HR: 1.79 CI: 1.19-2.69, p = 0.005) (Table 4). However, there was no relation between primary malignancy or the amount of pleural fluid and the success of pleurodesis.

Median survival of patients with malignant pleural effusion due to pulmonary, extrapulmonary and mesothelioma was respectively, 77 ± 12.8, 150 ± 48.4 and 365 ± 0 days. The survival of the patients with mesothelioma was significantly longer than those with pulmonary and extrapulmonary (Figure 2).

**DISCUSSION**

The most common reasons for MPEs were reported to be lung cancer (73%), breast cancer (8.3%) and mesothelioma (7%) in the present patient population. Pleurodesis was successful in ca. 31.1% of patients, who were offered chemical pleurodesis, and who were followed-up for at least 3 months.

Koegelenberg and et al found that the most common underlying diagnoses are lung cancer (n=174, 63.5%), breast cancer (n=32, 11.7%), malignant mesothelioma (n=27, 9.9%) and unknown primary (n=22, 11.7%) (4). Lung cancer is the most frequent reason for MPEs, and accounts for nearly half of all cases (5).

Cytology is an initial test that has a mean sensitivity of 60%; however, this depends on underlying primary tumours, preparation of samples, and experience of cytologist (6). Pleural fluid cytology’s diagnostic yield regarding mesothelioma was reported lower, and many guidelines suggest the use of pleural biopsy as a preferred diagnostic method over fluid cytology.

Table 2. Radiological features and pleurodesis method of malignant pleural fluid

| Feature               | N   | %    |
|-----------------------|-----|------|
| Pleural thickening    |     |      |
| Present               | 140 | 26.3 |
| Abcent                | 393 | 73.7 |
| Nodulation            |     |      |
| Present               | 71  | 13.3 |
| Abcent                | 462 | 86.7 |
| Ankiste fluid         |     |      |
| Present               | 13  | 2.4  |
| Abcent                | 520 | 97.6 |
| Localization of fluid |     |      |
| Right                 | 302 | 56.7 |
| Left                  | 168 | 31.5 |
| Bilateral             | 60  | 11.3 |
| Amount of fluid       |     |      |
| Mild                  | 126 | 23.6 |
| Middle                | 180 | 33.8 |
| Massive               | 219 | 41.1 |
| Pleurodesis           |     |      |
| Present               | 255 | 47.8 |
| Abcent                | 278 | 52.2 |
| Pleurodesis method    |     |      |
| Closed underwater drainage | 247 | 46.3 |
| Pleural catheter      | 12  | 2.3  |
| Other                 | 3   | 0.6  |
Table 3. The relationship between radiology, etiology and pleurodesis method according to the amount of pleural fluid

| Amount of pleural fluid | Mild | Moderate | Massive | P  |
|-------------------------|------|----------|---------|----|
| Diagnostic Method       |      |          |         |    |
| Cytology                | 118  | 172      | 206     | 0.547 |
| Surgical                | 7    | 6        | 12      |    |
| Pleuralthickening       |      |          |         |    |
| Abcent                  | 95   | 135      | 155     | 0.532 |
| Present                 | 31   | 45       | 64      |    |
| Nodulation              |      |          |         |    |
| Abcent                  | 107  | 160      | 187     | 0.502 |
| Present                 | 19   | 20       | 32      |    |
| Ankiste fluid           |      |          |         |    |
| Abcent                  | 122  | 174      | 216     | 0.384 |
| Present                 | 4    | 6        | 3       |    |
| Localization of pleural fluid |   |          |         |    |
| Right                   | 76   | 109      | 114     | 0.076 |
| Left                    | 36   | 46       | 83      |    |
| Bilateral               | 13   | 25       | 21      |    |
| Etiology                |      |          |         |    |
| Pulmonary               | 95   | 125      | 161     | 0.218 |
| Extrapulmonary          | 20   | 46       | 42      |    |
| Mesothelioma            | 11   | 9        | 16      |    |
| Pleurodesis method      |      |          |         |    |
| Closed underwater drain-| 33   | 79       | 132     | 0.698 |
| age                     | 1    | 4        | 7       |    |
| Pleural catheter        | 1    | 0        | 2       |    |
| Other                   |      |          |         |    |
| Pleurodesis             |      |          |         |    |
| Unsuccessful            | 5    | 16       | 23      | 0.531 |
| Successful              | 22   | 48       | 95      |    |
| Exitus                  | 85   | 132      | 148     | 0.391 |
| Alive                   | 41   | 48       | 71      |    |

Table 4. Multivariate regression analysis for overall survival

|                         | P     | HR   | % 95 CI |
|-------------------------|-------|------|---------|
|                         | Min   | Max  |
| Nodulation              | 0.720 | 0.92 | 0.59   |
| Ankiste pleural fluid   | 0.306 | 0.67 | 0.31   |
| Localization of pleural fluid | 0.392 | 1.10 | 0.87   |
| Etiology of pleural fluid | 0.094 | 0.79 | 0.60   |
| Amount of pleural fluid | 0.763 | 0.96 | 0.79   |
| Pleurodesis success rate | 0.005 | 1.79 | 1.19   |
|                        |       |      |         |

although fluid cytology is adequate in several experienced laboratories (7-10). Also, cytology may not be sufficient in some cases due to the need for tissue for targeted therapy (11). In our study, most patients were diagnosed with cytology. The majority of patients diagnosed with VATS were patients with mesothelioma.

Imaging techniques have significant roles in the diagnosis of patients who have suspected MPEs. Recently, thoracic ultrasound (TUS) is used routinely by respiratory physicians to guide pleural interventions for minimizing complications (12). National and international guidelines strongly recommend the technique (13). Evidence indicates that TUS might procure important data on the diagnostic pathway of pleural effusion. In TUS, pleural/diaphragmatic thickening and nodularity are highly specific in terms of malignancy and might assist to expedite timely investigation in patients who have high risks (14). In our study, we only used ultrasound for location marking during thoracentesis.
In our present day, contrast-enhanced thoracic computed tomography is the gold standard imaging modality in this respect, and might also procure useful data on the pleural cavity as a whole and the primary tumor site and stage. In our study, the most common radiological feature in computed tomography was pleural thickening and nodulation. The group in which the amount of pleural fluid was monitored massively was lung carcinoma and was mostly in the adenocarcinoma group. In the extrapulmonary group, massive effusion was seen more in breast cancer, while the amount of fluid was less in mesothelioma. Another study found that the amount of fluid in mesothelioma was higher. Also in the same study, the size was nearly equally spread from small to large in lung cancer (4). No relationship was found between the amount of pleural fluid and cell type, survival, pulmonary, extrapulmonary malignancy and mesothelioma, in our study.

The treatment options for MPE are therapeutic thoracentesis, Indwelling pleural catheters (IPC) and pleurodesis. Therapeutic thoracentesis can be repeated (as an outpatient), particularly for patients who have slow recurrence rates, in those with very short anticipated survival or poor performance (1). It was reported in a recently published retrospective cohort study that guidelines using definitive procedures (IPC or pleurodesis) compared with repeated thoracentesis were correlated with fewer subsequent procedures and complications, but pleurodesis resulted in more inpatient days (15). Chemical pleurodesis, which is achieved by the installation of a sclerosant via an intercostal drain (ICD) is still favored as the first-line intervention in patients who have anticipated survival of >3 months (16). Chemical pleurodesis (achieved via intercostal drain or pleuroscopy) and IPC show equal effects on patient-based results, despite the fact that patients treated with IPC spend less time in hospital and less requirement for repeated pleural drainage intervention (17). The most common method used in our study was tube thoracostomy. Pleurodesis was found to be successful in 31.1% of the patients. In a study, it was seen that the rate of patients offered pleurodesis (41.8%) and 3-month radiological treatment had a success rate of 88.0%, which is higher than our success rate, and success rates generally ranged between 30% and 50% and 75% and 90%, respectively (18).

The median survival is between 3 and 12 months; however, it might also vary at significant levels according to cell types, performance status, staging, and whether a chemosensitive malignancy is detected (19). In our study, if pleurodesis was successful, it was found that patients lived longer. The survival of patients with mesothelioma was significantly longer than those of the lungs and extrapulmonary ones. It was observed that the extrapulmonary ones lived significantly longer than those with lung cancer.

One of the strengths of our study is that the number of patients is sufficient. However, the number of mesothelioma patients being less than lung cancer patients may be a limitation. One of the limitations of our study is that pleural fluid biochemical parameters that affect the success of pleurodesis are not included in the study. Another limitation is that apart from the type of tumor affecting prognosis, the patient’s performance is also not recorded due to the retrospective study. A limitation of the study was the retrospective design and likely selection bias because patients who had advanced malignancy might have been referred directly for palliative care, without further investigation.

In conclusion, the main reason for MPEs was lung cancer, followed by breast cancer and mesothelioma in the present study. It was seen that the amount of pleural fluid did not have any clues regarding etiology. In this population, chemical pleurodesis was a viable palliative measure for MPE. It was also observed that successful pleurodesis had a significant contribution to survival.

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