American Journal of Surgery Case Reports

Research Article

Relationship of Pleural Effusions with Outcomes in Cancer Patients

*Steven Allen**

Department of Pulmonary and Critical Care, Grand Strand Regional Medical Center, Augusta University, USA

Abstract

Pleural effusions are diagnosed in an estimated 1.5 million individuals annually in the United States. These effusions are caused by a variety of medical conditions including Congestive Heart Failure (CHF), pleural infection, and malignancy. Malignant pleural effusions, characterized by the accumulation of significant amounts of fluid in the pleural space and the presence of malignant cells or tumor tissue, can result in breathlessness, chest discomfort, cachexia, and reduced physical activity, thereby significantly impacting patients' quality of life. Estimates indicate that malignant pleural effusions are diagnosed in 150,000 to 200,000 patients per year in the United States. Dyspnea, chest discomfort, and cough are the most common complaints in symptomatic individuals.

Introduction

Metastatic disease represents the major cause of malignant pleural effusion, with lung cancer in men and breast cancer in women together accounting for 50%-65% of all cases [1-7]. The clinical and economic impact of malignant pleural effusions are both expected to increase in the future, due in part to increases in global cancer rates and increasing post-diagnosis survival of cancer patients resulting from advances in systemic therapy [4,8]. Prognosis in patients with malignant pleural effusion varies significantly and is determined by multiple factors including the type of primary cancer, stage, performance status and pleural fluid proteins [4]. Management of this condition is essentially palliative and median survival is between 3 to 12 months [9-12].

Although knowledge pertaining to the pathophysiology, diagnosis, and management of malignant pleural effusion is being accumulated at a rapid pace, its impact on mortality among cancer patients after their first thoracentesis procedure is not fully understood. Sadly, many effusions accumulate after their initial drainage thus having to undergo additional procedures but succumb to their disease shortly after the second intervention. These patients would have been better receiving palliative care as compared to undergoing additional procedure shortly before their death. Unfortunately, there are no objective criteria that aid the physician to predict such an outcome. We therefore undertook a retrospective analysis to study the association between the first pleural fluid volume and clinical outcomes, especially mortality, in patients with pleural effusions and multiple cancer types.

Citation: Allen S. Relationship of Pleural Effusions with Outcomes in Cancer Patients. Am J Surg Case Rep. 2023;4(8):1089.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Sep 01st, 2023

***Corresponding author:** Steven Allen, Department of Pulmonary and Critical Care, Augusta University, Grand Strand Regional Medical Center, USA

Methods

Subjects enrollment

This retrospective analysis included 108 patients with cancer who underwent their first thoracentesis at our institution between February 2013 and December 2014. Institutional board review was requested and obtained per protocol. All patients were followed through their treatment until death, cure with no detectable disease or loss of follow up. Data recorded included age, gender, and type of cancer.

Pleural fluid collection

All patients had ultrasound-guided thoracentesis upon their initial presentation to the institution. All procedures were done using current standards of practice techniques [13,14]. Bedside ultrasound was used to identify and mark the appropriate location. Sterile technique was used including cleansing the skin with chlorhexidine solution, using a sterile drape, and using sterile personal equipment. Local lidocaine was first administered to the skin and subcutaneous tissue. Then a small nick was made to the skin using a number 11 blade. The catheter and needle system were then inserted while applying negative pressure until fluid was obtained. The catheter was then advanced over the needle into the thoracic cavity. Samples were then collected for analysis. After the effusion was completely drained, the catheter was removed and pressure was held until any bleeding had stopped. Lastly a band aid was applied to the incision [13,14].

Pleural fluid volume, chemical and hematologic characteristics were recorded including total cell count, LDH, protein, glucose, and pH. Patients with transudative effusions were excluded. Patients with cytology proven malignant effusions and those with exudative characteristics were included in the study.

Follow up of all patients was performed in a multi-disciplinary clinic; all patients returned for their follow up based on their oncologic protocol, and were assessed by the Interventional Pulmonology service during the same setting. The duration of survival from the initial thoracentesis to death, or cure was recorded.

Statistical analysis

We analyzed the impact of pleural fluid volume and cellularity (malignant versus benign pleural fluid) on mortality using analysis of

variance (ANOVA). Analysis of the impact of pleural fluid volume on mortality was conducted with the volumes grouped into 5 categories: <500 mL, 500 mL-1000 mL, 1100 mL-1500 mL, 1600 mL-2000 mL, and >2000 mL. The impact of cellularity on mortality was analyzed with the volumes being categorized into 3 groups: <500 mL, 600 mL-1500 mL, and >1600 mL.

Results

Patient demographics and clinical characteristics

The 108 patients included in this analysis ranged in age from 20 to 85 years (Mean 55.3 years; median 57 years). Sixty-six (61.1%) were female. Seventy-three patients (67.6%) were deceased by the end of the follow up period at 40 months, while 19 (17.6%) were alive and 16 (14.8%) were lost to follow up.

Cancer types

Breast cancer was the cancer type diagnosed in 33 patients (30.5%), with Non-Small Cell Lung Cancer (NSCLC) being reported in 18 (16.7%) and other cancer types being reported in 57 (52.8%) (including SCLCA, pancreatic, duodenal, urothelial, gall bladder, ovarian, colon, thyroid, HCC, gastric, appendix, RCC, prostate, sarcoma, spindle cell, neuroendocrine).

Pleural fluid volumes and characteristics

The median pleural fluid volume was 1000 mL. Of the 101 patients with available data on the cellularity of the pleural fluid, 36 (35.6%) had a positive cytology for malignancy and 65 (64.4%) showed non-malignant exudative pleural effusion.

Pleural fluid volume was seen to be inversely related to duration of survival (Figure 1). Analysis of variance demonstrated statistically significant differences between the pleural fluid volume categories with regard to mortality, with lower volumes being associated with significantly higher median survival durations (P=0.0134). The average months of survival for the 5 groups (<500, 500-1000, 1100-1500, 1600-2000, >2000) were 9, 2, 2, 1.75, and 0.75 respectively.

In contrast, pleural fluid cellularity did not have an impact on mortality. There were no statistically significant differences apparent through ANOVA analysis in median survival durations between patients with malignant pleural fluid in comparison to those with cytology-negative pleural effusions (Figure 2).

Discussion

We showed in our retrospective analysis that in patients with cancer and pleural effusions, the pleural fluid volume drained at the initial thoracentesis exerts a significant impact on mortality.

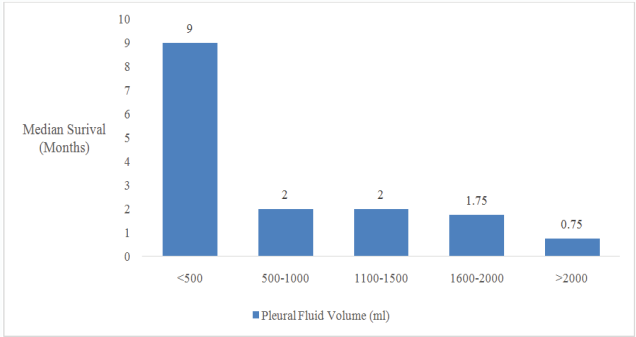

Figure 1: Impact of pleural fluid volume on mortality.

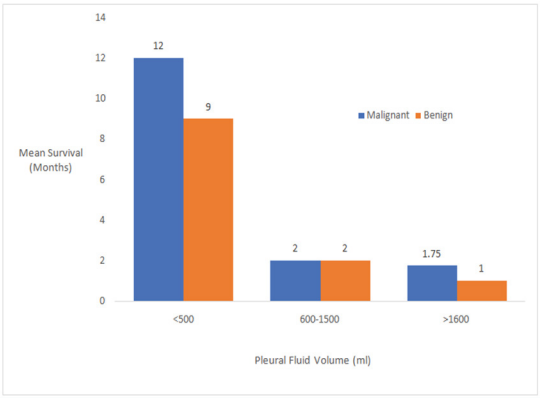

Figure 2: Impact of pleural fluid cellularity on mortality.

In addition, there is no difference between cytologically-positive and negative effusions in the prediction of mortality. Or finding is in parallel with previous data showing significant morbidity and mortality. Benign etiologies can carry 30-day and 1-year mortalities of 29% and 55% respectively *vs.* malignant and paramalignant effusions carrying 28%-37%, 30-day and 75%-77% 1-year mortality [10]. Even when singling out CHF as the cause, the 30-day and 1-year mortality is 22% and 53% respectively [10].

Not surprisingly, our study adds to the current literature as it shows that initial thoracentesis pleural fluid volume exerts a significant impact on mortality with a statistically significant inverse relationship between pleural fluid volume and median duration of survival. This may potentially reflect the increased tumor burden in patients with higher initial pleural fluid volumes resulting in worst overall outcome. The latter is an important finding as it suggests significant potential change in the management of these patients. Historically, cancer patients presenting with recurrent pleural effusions are candidates for tunneled pleural catheters placement of chemical pleurodesis in an attempt to palliate their symptoms. Though this procedure may result in palliation, they are associated with potential complications that include infections at the surgical site, loculations in the chest cavity, catheter malfunction and obstruction, increase hospitalization [15]. Our data suggests that in cancer patients with pleural effusions, the decision of performing further palliative pleural procedures may not be the absolute path to follow; the physician is encouraged to assess the benefit of any further intervention based on the volume of the pleural fluid at the initial thoracentesis. For instance, and based on our data, in patients with initial pleural fluid volume greater than 1500 cc, the mortality is almost 95% within the following month after drainage. As such, any complication from an additional procedure in these patients will be deleterious, and not palliative. On the other hand, if the initial thoracentesis yielded a lower volume, further palliative procedures will be beneficial for palliation as the life expectancy is significantly higher.

When analyzing cytologically positive *versus* cytologically negative effusions, we showed that mortality increased with increasing effusion size, irrelevant of cytology. De Biasi et al. [10] categorized these two etiologic entities into malignant and paramalignant effusions, with the latter defined as an effusion that is cytologically negative but most likely secondary to cancer. In our study, all three effusion size groups (<500, 600-1500, >1600 ml) were analyzed separately to compare malignant *versus* non-malignant effusions and the mortality rates were the same in all groups. Part of the reason is likely what is

being described as a paramalignant effusion, where even though the effusion is cytologically negative, the underlying etiology is still likely due to cancer. The latter finding is also important in the management of cancer patients with exudative cytologically-negative pleural effusions; the decision for further investigation of the exudative effusion with further invasive procedures and pleural biopsies should be probably limited to patients with low initial thoracentesis volumes. As we have shown, patients with cytopathology negative initial pleural fluid with high volumes have high mortality, and therefore no further interventions are suggested.

This study does have some limitations. First, it is a retrospective analysis of a relatively small dataset, thus prospective studies with larger numbers of patients will be needed to better understand the relationship between pleural fluid characteristics and mortality. Second, all patients were collected from one institution which may limit generalization of the results. The third factor that may affect generalizability is that the majority of thoracentesis performed in our study was performed by dedicated proceduralists thus results may differ in institutions where non-procedural specialties perform thoracentesis. Notwithstanding these limitations, our study provides novel preliminary information for a different perspective on pleural effusions that has not been studied previously. Our results can be confirmed through larger prospective studies, which can also explore the prognostic value of first thoracentesis in the management of multiple cancer types. More specifically, discussions with patients with larger effusions may need to lean more towards palliative care where as a more aggressive treatment plan can be instituted for patients with smaller effusions.

Conclusion

Thoracentesis is a common procedure performed for diagnosis and treatment of pleural effusions. Previous studies have shown that malignant and para-malignant pleural effusions have increased mortality compared to benign etiologies [10]. This study demonstrates that the volume of pleural effusions in cancer patients is also significantly related to survival duration and mortality. Patients with smaller volume pleural effusions have statistically significant higher median survival durations, while patients with larger volume pleural effusions were noted to have increased mortality. Although there was increased mortality with increased pleural effusion size, there was no significant difference in mortality based of the type of pleural effusion, regardless of the volume. Providers encountering cancer patients with large volume pleural effusions after their first thoracentesis should be aware of the increased mortality related to the larger size effusion and direct care appropriately, including the use of palliative care services and hospice. Cancer patients with smaller pleural effusions on their first thoracentesis have increased survival duration may be better suited for more aggressive treatment plans.

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