CHEST

Original Research

NEOPLASTIC DISEASE

Prospective Study To Determine the Volume of Pleural Fluid Required To Diagnose Malignancy

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Background: **The optimal volume of pleural fluid to diagnose a malignant effusion is unknown. Our study was designed to demonstrate if a minimum pleural fluid volume (10 mL) is equivalent to a large volume thoracentesis to make a cytopathologic diagnosis of malignancy.**

Methods: **A total of 121 thoracentesis samples were obtained from 102 patients with suspected or known malignant effusions. Pleural fluid was collected in three aliquots for cytologic examination (10 mL, 60 mL, ≥ 150 mL). The pathologist was blinded to patient identifiers and aliquot volume. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated for each volume for the diagnosis of malignancy.**

Results: **Pleural malignancy was diagnosed in 90 patient encounters (74.4%). For direct smear/cytospin, there was increased sensitivity and NPV for 60 mL ($P = .0058$ and $P = .045$, respectively) and for ≧150 mL ($P < .001$ and $P = .009$, respectively) compared with 10 mL. For combined direct smear/cytospin and cell block preparations, statistical significance for sensitivity and NPV existed only between the 10 mL and ≥ 150 mL specimens ($P = .0099$ and $P = .033$, respectively). No statistical difference existed for specificity or PPV for any aliquot volume.**

Conclusions: **The sensitivity for diagnosis of pleural malignancy is dependent on the pleural fluid volume extracted during thoracentesis. Volumes of 10 mL do not perform as well as larger volumes. When both direct smear/cytospin and cell block preparations are used, we recommend ≥ 150 mL, whereas when only direct smear/cytospin is used, 60 mL is adequate for the diagnosis a malignant pleural effusion.**

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Abbreviations: NPV = negative predictive value; PPV = positive predictive value

Pleural effusions are a common finding in patients with cancer. The diagnosis of a malignant pleural effusion is important both in the management of the effusion and in the prognosis of the malignancy.[1-4] Although many studies have looked at the diagnostic yield comparing cytology from thoracentesis, needle biopsy, and thoracoscopy, few have evaluated the optimal pleural fluid volume needed to make the diagnosis of a malignant pleural effusion.[5-13] A previous retrospective study done at our institution suggested a minimal amount of fluid is needed to determine if a malignancy exists.[14] A recent smaller prospective study demonstrated that 50 mL of pleural fluid is equivalent to larger volumes of pleural fluid to diagnose a malignant pleural effusion.[15] The purpose of

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our study was to prospectively reevaluate these findings regarding the pleural fluid volume needed to make a cytopathologic diagnosis of a malignant effusion.

Materials and Methods

This was a single-center prospective study to determine the amount of pleural fluid needed to make the diagnosis of a malignant pleural effusion. The study was performed at Henry Ford Hospital in Detroit, Michigan, and received Institutional Review Board approval. Between September 1, 2001, and August 31, 2007, 102 patients (60 women and 42 men) underwent diagnostic thoracentesis yielding 121 pleural fluid samples. Eligible patients included those suspected of having a malignant pleural effusion (n = 94) or patients with a known malignant pleural effusion undergoing a subsequent thoracentesis (n = 8). The definition of "suspected malignancy" was left to the clinical judgment of the senior attending pulmonologist who ordered the thoracentesis. Criteria typically included a history of a known malignancy, chest pain, weight loss, cigarette smoking, and the absence of symptoms or findings that would suggest an infection or congestive heart failure as the cause of the effusion. In addition, all patients had a moderate to large pleural effusion, defined as greater than or equal to one-third of a hemithorax.

The patient underwent a diagnostic thoracentesis in which the initial 10 to 30 mL was sent for biochemical and microbiologic studies if desired by the attending physician performing the procedure. Subsequently, aliquots of 10 mL, 60 mL, and ≥ 150 mL were obtained and placed in separate specimen containers and labeled as such. These specimens were hand delivered by a research team member to the cytopathology laboratory. All the samples were processed by one cytotechnologist as per Henry Ford Hospital cytopathology laboratory protocol.[16] The entire volume of each aliquot sample was centrifuged. Direct smears were prepared from the visible sediment. If the centrifuged sample was clear, cytospin preparations were made. Cell blocks were performed if the specimen contained clot or if the visible sediment remaining after making the smears was sufficient to make the block.

All the direct smears/cytospins were stained by Papanicolaou smears and cell blocks were stained by hematoxylin and eosin.[16] No immunostains were used on any of the samples. These were initially reviewed as nonblinded, nonstudy slides by a senior staff pathologist to determine if malignancy existed, and the result was reported as positive or negative for malignancy. This initial reading was only used to compare interobserver reliability between the pathologist reading the initial specimen the day it was delivered to the laboratory and the pathologist later reading the blinded study slides.

Upon completion of the enrollment process and reaching the target number of participants for our study population, all study slides were obtained and blinded as to pleural fluid volume and patient information. These blinded slides were analyzed by a single attending pathologist (S.K.) for the presence or absence of malignancy. Charts were reviewed to obtain patient demographics and cytopathologic and clinical diagnoses. The gold standard for diagnosis was the cytologic or histologic confirmation of a malignant pleural effusion within 6 months of the initial thoracentesis, or CT scan findings of pleural thickening or nodularity in a patient with a known underlying malignancy that had been pathologically confirmed.

The objective of this study was to compare the sensitivities, specificities, negative predictive value (NPV), and positive predictive value (PPV) for three different fluid volumes (10 mL, 60 mL, and ≥ 150 mL). Logistic regression models using generalized estimating equations methods were used to compare the four measures between the fluid volumes, taking into account the correlation among volumes (10 mL, 60 mL, and ≥ 150 mL) within the same pleural fluid sample. Pairwise comparisons of the three volumes were done within each logistic model. The testing level was set at 0.05. No adjustments were done for multiple comparisons because all three pairwise comparisons for each of the four outcomes were set *a priori* and of equal importance. Direct smear/cytospin alone and the combination of direct smear/cytospin and cell blocks were considered. χ^2 tests were done to assess the relationship of demographics/past medical history information and malignancy diagnosis.

The initial sample size calculations were based on seeing a 10% difference in sensitivities between any two volume levels. This was the observed difference between the first and fourth quartiles in our previous retrospective study.[14] It was assumed that the proportion of discordant pairs would be around 12%. With these assumptions and power set at 80%, α at 0.05, and two-sided testing, a sample size of 77 patient encounters with malignant pleural effusions would be required. Hence, the total number of patient encounters estimated was 130, which assumed that 60% of the patient encounters would be positive for malignancy. The increased number of malignant effusions obtained in our patient encounters (90 instead of 77) enabled us to perform the analysis within the power calculations for the total number of patient encounters we are reporting (121).

Results

There were 102 patients (42 men and 60 women) in our study population. Table 1 shows our patients' demographic data and past medical history. The average age of our patients in the study was 67.8 years with an SD of 11.6. The difference in the mean age between patients with and without a malignancy was not significant. The mean age of patients with malignancy was 67.4 years (SD, 12.9), whereas the mean age of patients without a malignancy was 68.7 years (SD, 8.0), $P = .55$. No differences in the rate of diagnosed malignancies were detected for gender, race, age, and past history of malignancy ($P > .05$ for all). The difference between smokers and nonsmokers was significant, with smokers having a lower positivity rate than nonsmokers (62.5% vs 84.2%, $P = .02$). Malignant pleural effusions were present in 90 of the

Table 1—*Demographics of Study Patients*

Demographic Variable	No. of Patients	No. Positive for Malignancy (%)	*P* Value[a]
Gender			
Male	42	28 (66.7)	0.467
Female	60	44 (73.3)	…
Race			
White	64	43 (67.2)	0.466
Black	36	27 (75.0)	…
Other	2	2 (100)	…
History of smoking			
Yes	64	40 (62.5)	0.020
No	38	32 (84.2)	…
Previous history of any malignancy			
Yes	67	49 (73.1)	0.434
No	35	23 (65.7)	…

[a]*P* values from χ^2 tests.

121 thoracentesis encounters (74.3%) by all methods described above.

The cancer cell types of our study population are shown in Table 2. Study pleural fluid samples were positive in 61 patient encounters. An additional 29 patient encounters were determined to be positive by pleural biopsy (n = 7), subsequent nonstudy thoracentesis (n = 6), or unequivocal evidence of malignancy on CT examination (n = 16). The most common cancer cell type was lung adenocarcinoma in 31 of 90 patient encounters (34.4%) followed by metastatic breast carcinoma in 24 of 90 patient encounters (26.7%) and undifferentiated non-small cell carcinoma in nine of 90 patient encounters (10%).

There were three patient encounters for which there were no direct smear/cytospin or cell block information for any of the three volumes (10 mL, 60 mL, and ≥ 150 mL; slides were lost prior to blinding). These three patient encounters were not considered in the following analyses (all were initially read as negative for malignancy by the clinical attending pathologist), leaving the final sample size at 118 patient encounters with 87 (73.7%) positive.

Direct Smear/Cytospin Only

For the following analyses, only patient encounters with direct smear/cytospin information for all three fluid volumes were included. The sample size was 107 pleural fluid specimens, of which 78 (72.9%) were positive. Table 3 contains the numbers of samples and positive results, together with the sensitivities, specificities, PPV, and NPV for the three fluid volumes using direct smear/cytospin results. The differences between 10 mL and 60 mL and between 10 mL and ≥ 150 mL were significant for sensitivity and NPV. No significant differences for sensitivity and NPV value were observed between 60 mL and ≥ 150 mL. Also, no significant differences were detected between any of the fluid volumes for specificity and PPV.

Table 2—*Cancer Cell Type for all Patients With a Malignant Pleural Effusion*

Cancer cell Type	Diagnosed by Study Thoracentesis (n = 61) No. (%)	Diagnosed by Other Methods (n = 29) No. (%)	Total (n = 90) No. (%)
Lung carcinoma			
Adenocarcinoma	30 (49.2)	1 (3.4)	31 (34.4)
Undifferentiated NSCLC	5 (8.2)	4 (13.7)	9 (10)
Small-cell carcinoma	2 (3.3)	2 (6.8)	4 (4.4)
Breast carcinoma	17 (27.9)	7 (24.1)	24 (26.7)
Mesothelioma	0	6 (20.7)	6 (6.7)
Endometrial carcinoma	2 (3.3)	0	2 (2.2)
Renal cell carcinoma	0	5 (17.2)	5 (5.6)
Ovarian carcinoma	1 (1.6)	0	1 (1.1)
Primary peritoneal carcinoma	1 (1.6)	0	1 (1.1)
Lymphoma	2 (3.3)	0	2 (2.2)
Papillary carcinoma (thyroid)	1 (1.6)	0	1 (1.1)
Cholangiocarcinoma	0	1 (3.4)	1 (1.1)
Rectal carcinoma	0	1 (3.4)	1 (1.1)
Lymphoma	0	1 (3.4)	1 (1.1)
Unknown carcinoma cell type	0	1 (3.4)	1 (1.1)

NSCLC = non-small cell lung carcinoma.

Direct Smear/Cytospin and Cell Block (Combined)

For the following analyses, at each fluid level the result was defined as (1) positive if either the direct smear/cytospin or the cell block result was positive, and (2) negative if both the direct smear/cytospin and cell block results were negative. Results for samples that had a negative direct smear/cytospin (cell block) result and no information for the cell block (direct smear/cytospin) result were defined as not available (or missing). As in the previous analyses, only samples with information for all three fluid volumes were included. The sample size was 71 with 54 (76.1%) patient encounters positive. Table 4 contains the sensitivities, specificities, PPV, and NPV for the three fluid volumes using direct smear/cytospin and cell block results. The differences between 10 mL and ≥ 150 mL were significant for sensitivity and NPV. No significant differences were observed between 10 mL and 60 mL and between 60 mL and ≥ 150 mL. Also, no significant differences were detected between the fluid volumes for specificity and PPV.

Fourteen of 60 samples that were initially read as negative were determined to be positive by the blinded pathologist. Of these 14 samples, three were noted by the initial pathologist to be suspicious for malignancy, and eight of the patients had a subsequent diagnosis of a malignant pleural effusion by repeat thoracentesis,

Table 3—*Direct Smear/Cytospin Only Results (n = 107)*

Volume, mL	Sensitivity	Specificity	PPV	NPV
10	48.7% (38/78)	96.6% (28/29)	97.4% (38/39)	41.2% (28/68)
60	62.8% (49/78)	89.7% (26/29)	94.2% (49/52)	47.3% (26/55)
150	69.2% (54/78)	86.2% (25/29)	93.1% (54/58)	51.0% (25/49)
P Values for Pairwise Comparisons				
10 vs 60	.0058	.166	.096	.045
10 vs 150	< .001	.095	.126	.009
60 vs 150	.090	.563	.645	.304

NPV = negative predictive value; PPV = positive predictive value.

Table 4—*Direct Smear/Cytospin and Cell Block Results Combined (n = 71)*

Volume	Sensitivity	Specificity	PPV	NPV
10	75.9% (41/54)	94.1% (16/17)	97.6% (41/42)	55.2% (16/29)
60	79.6% (43/54)	94.1% (16/17)	97.7% (43/44)	59.3% (16/27)
150	87.0% (47/54)	82.3% (14/17)	94.0% (47/50)	66.7% (17/21)
		P values for Pairwise Comparisons		
10 vs 60	.090	NA	.483	.478
10 vs 150	.0099	.314	.074	.033
60 vs 150	.181	.314	.060	.117

NA = not applicable. See Table 3 for expansion of other abbreviations.

needle biopsy, or thoracoscopy. Of the 61 initial positive pleural fluid samples, two were subsequently read as negative by the blinded pathologist. Both of these patients were diagnosed with lymphoma on the initial interpretation.

Discussion

The diagnosis of a malignant pleural effusion is a poor prognostic indicator with overall mean life expectancy of approximately 6 months.[3] Multiple studies have evaluated the sensitivity of cytologic diagnosis of pleural fluid from thoracentesis fluid sample compared with needle biopsy and thoracoscopy.[5-13] A number of authors have analyzed one or more cytology samples, multiple ways to process the fluid samples for cytologic interpretation, and cytology coupled with biopsies to determine the best method or combination of methods to diagnose a malignant effusion.[17-21] However, few studies exist to determine the optimal volume of pleural fluid withdrawn during a thoracentesis to diagnose malignancy. Previous authors have suggested ranges from 2 to 3 mL of fluid to several hundred milliliters.[7,22] Sallach et al[14] from our institution performed a retrospective study, from which they concluded that 10 mL of fluid was just as likely to be positive on cytologic assessment when malignancy is present as were larger volumes of pleural fluid. A recent prospective study, in which 23 patients were diagnosed with pleural malignancy by thoracentesis, showed no difference between 50 mL of pleural fluid and larger volumes of fluid for the cytologic diagnosis of malignancy. This study did not evaluate pleural fluid volumes <50 mL.[15]

We performed our study to reevaluate the previous retrospective results from our institution in a prospective study. Our study, which was designed so that each patient served as his/her own control, does not support our earlier results. We found that for direct smear/cytospin there was increased sensitivity and negative predictive value for 60 mL as compared with 10 mL and for ≥ 150 mL as compared with 10 mL. Although there was no statistically significant difference for direct smear/cytospin preparations alone between 60 mL and ≥ 150 mL, there was an incremental positive (sensitivity) yield with increasing volume of fluid for analysis. When both direct smear/cytospin and cell block processing was done, there was a significant difference in positivity only between the 10-mL and the ≥ 150-mL volume.

For patients diagnosed with pleural malignancy by thoracentesis, the cancer cell types were consistent with previous literature, with lung cancer the most common followed by breast cancer.[2] The cancer cell types for patients with a pleural malignancy diagnosed by means other than the study thoracentesis (subsequent nonstudy thoracentesis, pleural biopsy, CT chest findings) are listed in Table 2. Lung and breast cancer were the most common malignancies diagnosed in this group followed by mesothelioma, which is inherently difficult to diagnose by thoracentesis.

We have no explanation for the greater number of women included in our study. Previous authors have suggested that more females will have a malignant pleural effusion because breast cancer is the second most common cause of a malignant pleural effusion.[2] In our study, 17 of the 60 women who underwent thoracentesis had a diagnosis of breast cancer (28%). A previous study observed greater sensitivity of pleural fluid analysis in women.[14] However, this should have made small-volume thoracentesis more sensitive, given the larger percentage of women included in our study.

There are several potential limitations of our study. The long recruitment of patients into our study is explained by at least two factors. The attending physician had to consider study enrollment of a patient undergoing a thoracentesis and decide to notify one of the study investigators to enroll the patient. In addition, the attending physician performing the thoracentesis had to suspect malignancy to include the patient in the study. During the 6-year period of our study, 74 thoracenteses were performed on average per year in the pulmonary department. We were able to enroll 27% of the patients who had a thoracentesis performed during this time. However, we have no reason to believe that there was any selection bias

that might have confounded our observations and conclusions.

Fifteen patients underwent more than one thoracentesis in which more than one pleural fluid sample from them was included and analyzed in this study. However, the findings were similar when only the first sample from a patient was analyzed (results not given). At the time of blinded analysis, there were several patients with missing direct smear/cytospin or cell block slides that were unable to be included in our final analysis.

It is not clear what should be the optimal cut point for pleural fluid volume for the cytopathologic diagnosis of malignancy. Based on our prospectively derived data and the recent study by Abouzgheib et al,[15] we now recommend that the minimal volume of pleural fluid to facilitate the diagnosis of pleural malignancy should be 50 to 60 mL, whenever this is possible. As hypothesized in an editorial that accompanied our earlier retrospective study, "pleural fluid cells may not be homogeneously distributed within the pleural fluid. Cells may settle in a gravity-dependent gradient that creates an environment whereby a larger volume will more likely recover malignant cells. This seems feasible in patients who often have limited activity and remain recumbent for long periods due to their underlying malignancy."[23]

Conclusion

The sensitivity for the diagnosis of a malignant pleural effusion depends on the volume of pleural fluid obtained during thoracentesis. In our study, thoracentesis of at least 60 mL performed better than a 10-mL aliquot of pleural fluid to make the diagnosis of malignancy.

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Dr Donthireddy: contributed to developing initial research protocol, obtaining study participants, and helping write manuscript revisions.
Dr Surapaneni: contributed to developing initial research protocol, obtaining study participants, and helping write manuscript revisions.
Ms Jackson-Thompson: contributed by making study pathology slides and helping write manuscript revisions.
Dr Schultz: contributed to performing all statistical analysis, writing the manuscript, and helping write revisions.
Dr Kini: contributed to reading all blinded pathology slides, writing the manuscript, and helping write revisions.
Dr Kvale: contributed to overseeing the research project, developing the initial research protocol, obtaining study patients, writing the manuscript, and helping with revisions.
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