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Diagnosis of Malignant Pleural Effusion Using CT Scan and Pleural-Fluid Cytology Together. A Preliminary Case–Control Study

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Abstract. *Background/Aim: The purposes of this study were to evaluate the usefulness of chest computed tomographic (CT) scan plus pleural fluid cytology (PFC) together in patients with malignant pleural effusion (PE), and to compare the results of these diagnostic tools in patients with malignant PE due to non-small-cell lung cancer and pulmonary metastases from other malignancies. Patients and Methods: The medical records of 185 patients with PE, who underwent chest CT, PFC and video-assisted thoracoscopy (VATS) thoracentesis followed by VATS-guided biopsy for diagnostic purpose, were reviewed. At the final diagnosis, 123 (66.5%) patients had malignant PE (cases), and 62 (33.5%) had benign PE (controls). Results: Overall, the sensitivity, specificity, and accuracy of CT and PFC were 65.0% vs. 67.5% 98.4% vs. 98.4%, and 76.2% vs. 77.8%, respectively. The combination of CT plus PFC significantly improved sensitivity (86.2%, p=0.003) and accuracy (90.8%, p=0.02). Conclusion: CT and PFC used together may lead to approximately 100% specificity and >90% sensitivity in distinguishing between benign and malignant PE.*

Malignant pleural effusion (PE) is defined as that containing cancer cells. It represents the direct result of the action of malignant cells on the pleural wall, and may affect patients with lung cancer or other malignancies with pulmonary metastases, including of breast, renal and colorectal carcinoma, and lymphoma (1, 2). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 85% of cases, and approximately 70% of patients with lung cancer present with advanced disease at the time of diagnosis (3, 4).

When chest computed tomographic scan (CT) shows pleural thickening or nodules or cancer cells are found in pleural fluid cytology (PFC), the malignant origin of the PE should be considered. Unfortunately, the sensitivity of both CT and PFC is usually low and thus only a video-assisted thoracoscopic surgery (VATS)-guided biopsy may lead to the correct diagnosis of malignant PE. The purposes of this study were (i) to evaluate the usefulness of CT plus PFC together in patients with malignant PE, and (ii) to compare the results of these diagnostic tools in patients with malignant PE due to NSCLC and pulmonary metastases.

Patients and Methods

Design and study population. The medical records of consecutive patients with PE, who underwent chest CT, PFC and VATS-thoracentesis followed by VATS-guided biopsy for diagnostic purpose over a period of 5 years were retrospectively reviewed. Patients with inadequate samples, both cytological (*i.e.* scanty cellularity, obscuring blood) and histological (*i.e.* insufficient tissue), were excluded from the study, as well as those with other types of lung cancer, with the aim of having a more homogeneous study population (5-7). In the evaluation of PFC, the presence of atypical reactive mesothelial cells, suspicious for malignancy on PFC, was considered as a false-positive (FP) result. According to the above-mentioned criteria, the data of 185 patients were recorded and analyzed. There were 102 (55.1%) men and 83 (44.9%) women with an overall median age of 69 years (range=40-87 years). To confirm the correct final diagnosis, all patients were followed-up for at least 4 months (range=4-6 months). The study population was divided into two groups of sex- and age-matched patients, according

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Key Words: Malignant pleural effusion, differential diagnosis, pleural-fluid cytology, lung cancer, pulmonary metastases.

Table I. *Results of chest computed tomography (CT), pleural fluid cytology (PFC) and CT combined with PFC, and analysis of differences between diagnostic tools in the overall population.*

Parameter	CT (95% CI)	PFC (95% CI)	CT+PFC (95% CI)	Phi	χ^2	*p*-Value
Sensitivity	65.0% (56.8-73.3)	67.5% (58.5-75.6)	86.2% (78.5-91.5)	+0.22	9.01	**0.003**
Specificity	98.4% (90.2-99.9)	98.4% (90.2-99.9)	100% (92.7-100)	-	-	0.99
Probability of positive test	43.8% (36.5-51.3)	45.4% (38.1-52.9)	57.3% (49.8-64.4)	+0.12	2.42	0.12
Probability of negative test	56.2% (48.7-63.4)	54.6% (47.1-61.9)	42.7% (35.5-50.2)	–0.11	2.01	0.16
Positive predictive value	98.7% (92.4-99.9)	98.8% (92.6-99.9)	100% (95.6-100)	-	-	0.99
Negative predictive value	58.7% (48.6-68.0)	60.5% (50.1-69.8)	78.5% (67.5-86.6)	+0.19	6.70	**0.009**
Diagnostic accuracy	76.2% (69.4-82.2)	77.8% (71.1-83.6)	90.8% (85.7-94.6)	+0.18	5.50	**0.02**
Disease prevalence	66.4% (59.1-73.1)	66.5% (59.2-73.2)	66.5% (59.2-73.2)	-	-	1

CI: Confidence intervaI; Phi: *phi* coefficient, χ^2: chi-square. Significant differences are shown in bold.

to the histopathology of the VATS-guided specimens: 123 (66.5%) patients (age=68.3±21.4 years) with malignant PE (cases), and 62 (33.5%) controls (age=61.9±22.8 years) with benign PE. Two further subgroups of patients with malignant PE were considered, according to the etiology of PE: (i) Patients with NSCLC (N 72, 58.5%); and (ii) patients with PE due to pulmonary metastases from other malignancies (N=51, 41.4%), including breast and ovarian cancer (N=29, 56.9%), colorectal cancer (N=14, 27.4%), and lymphoma (N=3, 5.9%).

Statistical analysis. The reported data are expressed as median (range) or mean±standard deviation (SD). Assuming that the data were not normally distributed, the Mann-Whitney *U*-test was used to compare continuous variables (*i.e.* age of the patients). Sensitivity was defined as true-positives (TP)/[TP + false-negatives (FN)], specificity as true-negatives (TN)/(TN + FP), positive predictive value (PPV) as TP/(TP + FP), negative predictive value (NPV) as TN/(TN + FN), accuracy as (TN + TP)/overall population. The 95% confidence interval (95% CI) was reported for all results. Comparisons between the data were obtained using contingency tables and the chi-square test corrected by Yates for continuity. The *phi* coefficient (Phi) was also calculated, for measuring the degree of association between variables (8, 9). The differences were considered significant at a *p*-value of less than 0.05. The software used for the analysis was SPSS Statistics, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

The age of the patients did not differ significantly between men and women (69.3±23.1 *vs*. 62.5±24.8 years; $p=0.055$) nor between those with malignant PE and benign PE ($p=0.062$).

Overall, the sensitivity, specificity, NPV and accuracy of CT and PFC were 65.0% *vs*. 67.5% ($p=0.89$), 98.4% *vs*. 98.4% ($p=0.99$), 58.7% *vs*. 60.5% ($p=0.77$) and 76.2 *vs*. 77.8 ($p=0.85$), respectively. However, the combination of CT plus PFC significantly improved the sensitivity ($p=0.003$), NPV ($p=0.009$) and accuracy ($p=0.02$) (Table I).

As displayed in Tables II and III, the usefulness of PFC alone and with CT did not differ significantly ($p>0.05$) between subgroups, although in patients with malignant PE due to pulmonary metastases, the sensitivity (90.2% *vs*. 81.9%, $p=0.11$), NPV (92.5% *vs*. 82.5%, $p=0.09$) and accuracy (95.6% *vs*. 90.3%, $p=0.09$) were higher than that in those with NSCLC.

Discussion

The presence of malignant cells in PE is a relatively common occurrence in patients with advanced cancer. It has been reported that malignant PE may develop in up to 30% of patients with lung cancer and 10% of women with breast cancer (2, 10, 11). According to the 2012 National Inpatients Sample, more than 126,000 patients were hospitalized for malignant PE in the USA, accounting for 0.35% of all admissions; the origin of PE was lung (37%) breast (15%), gastrointestinal tract (11%) and gynecological (9%) cancer, while 10% of cases were related to malignancies of unknown origin (11, 12). Para-malignant PE, not directly related to malignant cell involvement of the pleura, is also reported (13).

The usefulness of radiological investigations in differentiating between benign and malignant PE has long been reported (14-16). However, the reliability of chest CT varies widely, according to the different radiological findings considered; in any case, sensitivity is usually lower than specificity (Table IV). The use of a scoring system that takes into account the characteristics of the pleural lesion together with the presence or lack of lung, abdominal or liver masses, pericardial effusion or cardiomegaly, may increase both sensitivity and specificity (18). The advantages of dual-energy spectral CT has also been reported, showing that in selected patients, the sensitivity and specificity may reach 100% and 71%, respectively (19). In a group of patients who underwent CT scan-guided Abram's needle pleural biopsy, the sensitivity of this minimally invasive procedure ranged from 90.2% to 95.2%, according to the CT findings (20).

Several studies confirmed that the sensitivity of PFC to range from 40% to 95%, being lower in patients with

Table II. *Comparison of results of pleural fluid cytology in patients with non-small cell lung cancer (Group A) and those with other malignancies (Group B).*

Parameter	Group A	Group B	Phi	χ^2	*p*-Value
No. of patients (%)	72 (58.5%)	51 (41.4%)	-	-	-
Sensitivity (95% CI)	65.3% (53.1-75.8)	76.5% (62.2-86.7)	+0.13	2.94	0.06
Specificity (95% CI)	98.4% (90.2-99.9)	98.4% (90.2-99.9)	-	-	1
Probability of positive test (95% CI)	35.8% (27.8-44.6)	35.4% (26.8-45.0)	–0.01	0	0.99
Probability of negative test (95% CI)	64.2% (55.4-72.1)	64.6% (55.0-73.2)	+0.01	0	0.99
Positive predictive value (95% CI)	97.9% (87.5-99.9)	97.5% (85.3-99.8)	–0.03	0	0.99
Negative predictive value (95% CI)	70.9% (60.0-80.0)	83.6% (72.6-90.9)	+0.14	3.42	0.06
Diagnostic accuracy (95% CI)	80.6% 72.9-86.9)	88.5% (81.1-93.7)	+0.11	1.82	0.17
Disease prevalence (95% CI)	53.7% (44.9-62.4)	45.1% (35.7-54.8)	+0.09	1.28	0.26

CI: Confidence intervaI; Phi: *phi* coefficient, χ^2: chi-square.

Table III. *Comparison of results of computed tomography plus pleural fluid cytology together in patients with non-small cell lung cancer (Group A) and those with other malignancies (Group B).*

Parameter	Group A	Group B	Phi	χ^2	*p*-Value
No. of patients (%)	72 (58.5%)	51 (41.4%)	-	-	-
Sensitivity (95% CI)	81.9% (70.7-89.7)	90.2% (77.8-96.3)	+0.13	2.58	0.11
Specificity (95% CI)	100% (92.7-100)	100% (92.7-100)	-	-	1
Probability of positive test (95% CI)	44.0% (35.5-52.8)	40.7% (31.7-50.4)	–0.04	0.18	0.67
Probability of negative test (95% CI)	55.9% (47.1-64.4)	59.3% (49.6-68.3)	+0.03	0.08	0.78
Positive predictive value (95% CI)	100% (93.4-100)	100% (90.4-100)	-	-	1
Negative predictive value (95% CI)	82.7% (71.8-90.0)	92.5% (82.7-97.2)	+0.14	2.93	0.09
Diagnostic accuracy (95% CI)	90.35 (84.0-94.7)	95.6% (90.0-98.5)	+0.14	2.96	0.09
Disease prevalence (95% CI)	53.7% (44.9-62.4)	45.1% (35.7-54.8)	–0.09	1.28	0.26

CI: Confidence intervaI; Phi: *phi* coefficient, χ^2: chi-square.

hematological malignancies and higher in women with ovarian cancer, with a mean of approximately 46% (21). Another reported that it may reach 67.2%, ranging between 87.9% and 45.5%, in patients with adenocarcinoma and mesothelioma, respectively (22). Woo *et al*., in a retrospective study of 862 patients, evaluated the benefits of PFC compared with cell block preparation in malignant PE, showing that the sensitivity and specificity of PFC and cell block preparation were 81.3% *vs*. 94.3% (p=0.010), and 99.4% *vs*. 98.7%, respectively. The combined use of cell block preparation and carcinoembryonic antigen immunostaining improved the diagnostic accuracy (6). A recent systematic review showed that overall the specificity of PFC was higher (99.9%) than its sensitivity (73.1%) (23). In our study, we obtained similar results (100% specificity, 86.2% sensitivity), with no significant differences between subgroups. We also found that using PFC plus pleural chemiluminescence immunoassay for carcinoembryonic antigen better results might be achieved (5). Other diagnostic tools, such as ^{18}F-fluorodeoxyglucose positron-emission tomography- and CT-guided pleural biopsy are expensive or invasive, offering similar outcomes (1, 20).

Table IV. *Reported sensitivity and specificity of computed tomographic (CT) scan in patients with malignant pleural effusion, according to Hallifax et al. (17).*

Pleural thickening on CT	Sensitivity	Specificity
Nodular	87-100%	18-53%
Mediastinal	68-87%	14-74%
Parietal	64-98%	7-47%
Circumferential	63-100%	7-54%

Talc pleurodesis and indwelling pleural catheter are the procedures available to treat malignant PE; the latter may result in a reduction of the hospital stay (24). In any case, before any treatment, the use of non-invasive diagnostic procedures is always recommended, with the aim of treating all symptomatic patients early (25).

In conclusion, the results of our preliminary study suggest that CT and PFC are simple and accurate procedures, which together may lead to approximately 100% specificity and >90% sensitivity, and should be suggested for all patients with PE who undergo thoracentesis. Further studies will hopefully confirm these preliminary results.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

SMMB, FL and PU designed the study. SMMB and FL wrote the article, analyzed the data and interpreted the results. SMMB, ADC, SS and FM acquired the data. All the Authors finally revised and approved the article.

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