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Title

Diagnostic yield of pleural fluid cytology in malignant effusions: an Australian tertiary centre experience

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Abstract

Background: Timely diagnosis of malignant pleural effusions is critical to guide prognosis and management decisions. Cytologic analysis of pleural fluid has been the first-line diagnostic test for many decades, with highly variable reported sensitivities of 40 to 90%. Its diagnostic accuracy in modern practice in Australia needs to be understood.

Aims: To determine the diagnostic yield of pleural fluid cytology for the detection of malignant pleural effusions, and to determine the aetiologies of pleural effusions at our centre.

Methods: Retrospective chart review of all pleural fluid samples submitted for cytologic analysis at a tertiary referral centre in Melbourne, Australia, over a 12-month period. Aetiology of all effusions was determined, and sensitivity, specificity, negative predictive value and diagnostic accuracy for the detection of malignant pleural effusions were calculated. We also examined diagnostic yield based on tumour cell type.

Results: Of the 153 cases analysed, 61 (39.9%) were malignant. Lung cancers accounted for 44.3% of malignant effusions, followed by mesothelioma (18%), ovarian carcinoma (11.5%) and lymphoma (8.2%). The commonest single causes of a benign effusion were cardiac (16.3%) and parapneumonic (13%). Sensitivity for diagnosis of malignant effusions was 67.2% overall, but 87.9% for adenocarcinomas and only 45.5% for mesothelioma.

Conclusions: Tumour type is an important determinant of pleural fluid cytology diagnostic yield. Cytology has good sensitivity and specificity for the diagnosis of adenocarcinoma, but if another tumour type is suspected, particularly mesothelioma, clinicians should be aware of the limitations.

Key words: Malignant pleural effusion, thoracentesis, cytology, diagnosis, cancer

Introduction

Malignant pleural effusion (MPE) is proven by the discovery of malignant cells in pleural cavity fluid. The diagnosis carries a poor prognosis, with an average survival of 3-9 months and 1 year mortality of nearly 80%, depending on the primary tumour type.[1-4] Management following MPE detection is therefore palliative, with treatment goals shifted from potentially curative to symptom-based.[5] Timely identification of MPE allows patients with a limited lifespan to avoid unnecessary hospitalisation and often toxic treatment.[6,7] Recent data suggests that pleural effusion due to a benign cause, such a congestive heart failure or renal failure, is also a poor prognostic sign that has so far been under-recognised.[8]

Cytologic analysis of pleural fluid is often the first-line diagnostic test performed after an effusion is detected. Biochemical analysis is also routine, but at best can only add weight to the suspicion of

malignancy in the given clinical context. Thoracentesis to obtain a fluid sample is a simple bedside procedure with low complication rates.[9] It is therefore more accessible and cost-effective than potentially higher yield but more invasive methods such as thorascopy. International literature over the last three decades describes a range of 40-90% sensitivity of pleural fluid cytology for detection of MPE, in various locations and clinical settings.[1,9-16] This also varies with tumour histopathology – sensitivity for adenocarcinoma has been reported as 60% in one study versus only 30% for mesothelioma, and MPE due to adenocarcinoma is more readily diagnosed than squamous cell carcinoma, sarcoma and lymphoma.[9,11] There is increasing interest in the role of molecular testing for increasing accuracy of MPE diagnosis, however this is still an experimental investigation.

We reviewed the outcomes of pleural fluid cytology in all patients attending our tertiary health service over a 12-month period, with the goal of assessing sensitivity and diagnostic yield of this test for the detection of MPE. Underlying cause of all effusions, both benign and malignant, was also examined to gain an understanding of pleural effusion aetiology in our patient population.

Material and Methods

This study was approved by the Melbourne Health Human Research Ethics Committee (HREC/14/MH/369) and the Cancer Council for Victoria Human Research Ethics Committee (HREC 1510).

One hundred and fifty-three consecutive patients who underwent pleural fluid sampling with cytologic analysis over a 12-month period (January-December 2014) at a tertiary referral centre in Melbourne, Australia were included.

Retrospective review of case files was performed to determine the final diagnosis for every pleural effusion, where possible. The minimum follow-up period was 18 months to capture all cases of difficult to diagnose malignant effusions, given an expected survival of less than 12 months in patients with MPE.[2] Patient details were submitted to a state-wide cancer registry (Victorian Cancer Registry) to verify diagnostic conclusions. Where data was missing or incomplete, clinical discussion with a Respiratory Physician experienced in the diagnosis of malignancy was used to determine if the cause was likely malignant, paramalignant, or benign. In cases where pleural fluid analysis was performed on multiple occasions, results were calculated based on the outcome of the first sampling episode.

A malignant effusion was defined as the finding of malignant cells in the pleural space, on either cytology or tissue biopsy. In 6 cases where patients were palliated and/or deceased before histological diagnosis was confirmed, a clinical scenario highly consistent with a malignant aetiology of effusion was considered a positive case.

Effusions were considered paramalignant if the patient had a cancer diagnosis but there was no finding of malignant cells in the pleural space, and no evidence of another more likely benign cause.[17] For example, a later wedge resection might confirm a primary lung malignancy but there was no histological or cytological evidence of disease spread to the pleura.

In cases where the cause was unclear, but follow-up showed resolution of the effusion without reaccumulation and no subsequent detection of malignancy, the aetiology was considered benign.

We also reviewed whether immunohistochemistry, which can assist in confirming malignancy and pathological classification, was able to be performed on cohort samples. Volume of fluid sent in all cases of malignant effusion was recorded and mean sample volumes in those with successful

diagnosis of malignancy ('true positives') were compared to those with a missed malignant aetiology ('false negatives').

Statistical analysis was performed using GraphPad Prism 7.02 software. Fischer's exact test and the two-tailed unpaired t-test, and the Wilson/Brown hybrid method, were used to calculate p values and confidence intervals respectively, as appropriate.

Results

Patients

Of the 153 patients who underwent cytological analysis of pleural fluid at our hospital, 91 (59%) were male and the average age was 67±16 years (Table 1.). Sixty-one (40%) were found to have a malignant pleural effusion (MPE), and of these, 31 (51%, p value = 0.093) were male. Patients with a MPE were older that those with a benign aetiology (71±13 versus 65±17 years, respectively, p=0.017). Final diagnoses for all patients are recorded in Table 2.

Aetiology of effusions

Of the 92 patients with a benign effusion due to a single aetiology, the commonest diagnoses were cardiac in 15 (16.3% of benign), parapneumonic in 12 (13.0%), traumatic (7, 7.6%) and paramalignant (6, 6.5%) (Table 2). One third (31, 33.7%) of all benign cases, however, were determined to be multifactorial or of unclear cause.

In the 61 patients with MPE, lung cancer was the commonest cause, identified in 27 (44.3%), followed by mesothelioma (11, 18.0%), ovarian carcinoma (7, 11.5%), lymphoma (5, 8.2%) and breast carcinoma (4, 6.6%). In males, the commonest causes of MPE were lung carcinoma (16, 51.6%) and mesothelioma (6, 19.4%). In females, lung cancer was also the primary aetiology (11, 36.7%), followed by ovarian carcinoma (7, 23.3%), mesothelioma (5, 16.7%) and then breast carcinoma (4, 13.3%). By tumour type alone, adenocarcinoma was by far the commonest as it accounted for 54.1% (33/61) of all MPEs, followed by mesothelioma and then lymphoma as described.

Of all 27 cases due to lung cancers, 21 (77.8%) were adenocarcinomas. There were only 2 MPEs due to squamous cell carcinoma and 1 due to small cell lung cancer.

Three cases were assumed to have a malignant cause due to highly suspicious clinical and/or imaging findings, as cytological diagnosis was not made in 2 and 1 was lost to follow-up.

Diagnostic yield of pleural fluid cytology

Cytologic analysis of pleural fluid identified malignancy in 41 of 61 patients with a final diagnosis of MPE (sensitivity 67.2%, negative predictive value (NPV) 82.1%, positive predictive value (PPV) 100%, diagnostic accuracy 85.9%) (Table 3). Accuracy of diagnosis was much higher in those with lung adenocarcinoma, with a sensitivity of 85.7%, NPV 99.8% and diagnostic accuracy of 98.0%. Similar numbers were true for all lung cancer and adenocarcinoma of any type. Sensitivity for MPE due to mesothelioma was lower at only 45.5%.

Of all patients with MPE, 49 out of 61 cases had immunohistochemistry (IHC) performed or didn't need it because the diagnosis was already made. Insufficient number of cells in the cell block precluded IHC in only 1 case of lung adenocarcinoma, but this did not result in missed diagnosis of malignancy. In 11 cases there were no malignant cells seen in the cell block.

Mean volume of fluid sent in cases of successfully diagnosed MPE versus those with a false negative result were 352mL and 372mL respectively, and this difference was not statistically significant (p value = 0.9034). Similarly, when analysed by primary tumour type (all adenocarcinoma, lung adenocarcinoma, mesothelioma etc.), there was no statistically significant difference in volume of fluid sent for analysis between cases of true positive and false negatives.

The means of MPE diagnosis and aetiology of cases not diagnosed on initial cytology are summarised in Figure 1. Of the 61 cases of MPE, 41 (67.2%) were positive for malignancy on the first tap and another 5 cases of MPE were detected on a second sample, bringing the overall sensitivity to 75.4% and diagnostic accuracy to 90.2%. The underlying aetiology in these 5 cases were mesothelioma, B-cell lymphoma, Hodgkin lymphoma, lung adenocarcinoma, and breast adenocarcinoma. No new cases were detected on third or fourth samples. Of the 15 cases that were diagnosed as MPE by another means (i.e. 'false negatives'), 7 were found to have pleural disease on biopsy, 6 were assessed clinically to be MPE without histological confirmation, 1 case of lymphoma had evidence of pleural involvement on PET and a clinical course consistent with MPE, and 1 case of MPE due to lymphoma was confirmed on flow cytometry of the pleural fluid sample. We did not include the latter sample with the 'true positive' cohort as this is not a routine test performed on every pleural fluid sample sent for cytology.

Discussion

We found that cytological analysis of pleural fluid has a very good sensitivity with regards to diagnosis of MPE due to adenocarcinomas, but is relatively poor at excluding non-epithelial-type malignancies. Timely diagnosis of MPE is important as it guides prognostication and management decisions. In non-small cell lung cancer, it qualifies the patient as having Stage IV disease.[18] The presence of an exudate or high-risk features such as massive volume, haemorrhage or lymphocyte predominance may suggest malignancy but these are not definitive.[19,20] For example, 3-10% of MPEs are transudates, and transudates due to congestive cardiac failure may be misclassified as exudates if the patient is on diuretic medication.[9,17,21] While cytologic diagnosis is highly specific, clinicians need to appreciate the limitations of this investigative method and the risk of false negative results.

In our study, accuracy of pleural fluid cytology for the diagnosis of malignancy was 85.9% and overall sensitivity was 67.2%. Our sensitivity was higher than other literature from the past fifteen years in which sensitivities range from 39-63%.[1,10,11,13,15,16,22] The largest and most recent of these studies examined 3077 consecutive patients in a single Spanish hospital and found a sensitivity of 51% for the diagnosis of MPE.[15] The higher sensitivity found in our study may in part be due to the experience of laboratory staff and pathologists at our large tertiary teaching hospital, which influences the yield of cytologic analysis as a diagnostic test, or recent improvements in the use of immunohistochemistry to aid diagnosis of MPE. Population differences, such as prevalence of smoking affecting relative frequencies of lung cancer types, may also contribute.

An important outcome of our study was that the tumour cell type determined the diagnostic accuracy of pleural fluid cytology. Adenocarcinoma was much more readily detected than mesothelioma, as we found sensitivities of 87.9% and 45.5% respectively. Non-adenocarcinoma

NSCLC (NSCLC not specified, NSCLC with neuroendocrine differentiation and squamous cell carcinoma) also demonstrated high sensitivity, however with only 5 cases in our cohort this should be interpreted with caution. Cytologic diagnosis of mesothelioma is feasible for MPE, with a study from Western Australia, a region with the highest per capita incidence of malignant mesothelioma worldwide, reporting 73% accuracy for diagnosis of mesothelioma with an experienced laboratory and cytopathologist.[23] Our finding regarding sensitivity is consistent with other studies reporting significantly lower sensitivity for detection of mesothelioma (range 27 – 48%).[15,24] Another study which included over 1200 cases of epithelioid mesothelioma demonstrated no difference in survival between those diagnosed by cytology versus those with histologic-derived diagnosis.[25] Cytologic diagnosis thus appears to have a high positive predictive value for detection of mesothelioma, but is limited by a poor negative predictive value. Clinicians may therefore be fairly confident in excluding MPE in patients presenting with known adenocarcinoma and negative pleural fluid cytology, however further investigation must be considered in those with known or suspected non-adenocarcinomatous malignancy. The latter is in keeping with current practice guidelines that mandate pleural biopsy in cases of suspected mesothelioma where cytology is non-diagnostic, as distinction between reactive and malignant epithelioid mesothelial cells on cytology can be difficult.[26,27]

Repeated cytologic analysis with a second sample only modestly improved the accuracy (by 4.3% to 90.2%) and sensitivity (by 7.7% to 75.4%) of pleural fluid cytology for MPE diagnosis, with most cases diagnosed on a second sample being less common tumour types. Third and fourth samples did not detect any new cases. The yield of repeated samples remains unclear; some guidelines suggest that more than one sample is unlikely to be useful, whereas some studies report benefit from sending up to 3 separate samples for cytologic analysis.[27,286] Our findings suggest that one pleural fluid sample is

adequate for detecting MPE due to lung adenocarcinoma, but repeated samples may increase sensitivity for detection of other cancer types. Clinicians should consider more definitive investigations, such as pleuroscopy and/or biopsy, following negative cytology where clinical suspicion remains high.

Volume of fluid sent for analysis in our study was not significantly different between malignant cases correctly diagnosed on pleural fluid cytology and those that were false negatives. The question of ideal volume, or minimal volume, of fluid required for accurate diagnosis of MPE has been addressed by numerous studies with varying results. While some authors report no benefit from sending small amounts (<10mL) versus much larger fluid volumes, others have found that sensitivity is increased by greater volumes, and current guidelines acknowledge that the answer is unclear. [7,9,16,29]

In terms of underlying aetiology of pleural effusions in our cohort, MPE accounted for 39.9% of cases. Including paramalignant effusions, cancer was the cause of 44.8% of all effusions. These results are at the higher end of the spectrum of international reports of MPE incidence of 25-40%.[1,13,15,16,19] This may reflect the fact that our hospital is a tertiary referral centre with established diagnostic Respiratory Medicine and Cardiothoracic Surgery services. Consistent with cohorts in non-TB-endemic areas, cardiac and then parapneumonic were the foremost single causes of benign effusions (16.3% and 13.4% of benign cases respectively).[15,19] Tuberculosis was the cause of only 3.3% of benign effusions, whereas in TB-endemic areas and in younger populations it is often the commonest non-malignant cause of pleural effusions.[13,30]

Lung cancer, particularly adenocarcinoma of the lung, was the commonest cause of MPE, which is in keeping with international and Australian data.[15,22,31-33] It accounted for 18% of all effusions and 44% of all MPE. Mesothelioma was the second commonest malignant pathology (18.0% of MPE) followed

by ovarian carcinoma (11.5%), lymphoma (8.2%) and breast carcinoma (6.6%). Previous reports state that 75% of MPE are due to cancer of the lung, breast, ovary or lymphoma.[12,17] In our study, however, and other more recent reports, mesothelioma is one of the commonest diagnoses after lung cancer, along with breast cancer and lymphoma.[11,22]

A limitation of our study was that we did not differentiate unilateral effusions, which are inherently more suspicious for a malignant diagnosis, from bilateral effusions. Instead we included all pleural fluid samples submitted for cytology during the study period. Regardless, we found a robust proportion of effusions were malignant in aetiology. This is probably due to our role as a tertiary referral centre with a strong practice in pulmonary diagnostics, and the fact that clinicians would have had a reasonable pre-test suspicion of malignancy to request cytologic analysis. The latter is also important when considering relative proportions of pleural effusion aetiologies in our cohort. It is likely that a significant number of pleural effusions occurred in our hospital without cytology being sent for analysis. This may have been due to high clinical suspicion of a benign cause, already known MPE, and no other indication for pleural fluid sampling or therapeutic removal. Our data therefore better reflects aetiology and diagnostic yield of cytology in cases where there is diagnostic uncertainty.

Conclusion

Our study shows that underlying tumour type is an important determinant of diagnostic yield of pleural fluid cytology for the diagnosis of MPE, and that overall sensitivity in our centre appears to be slightly higher than international literature from recent years. Cytology has good sensitivity and specificity when it comes to the diagnosis of MPE due to adenocarcinoma and NSCLC, including lung

adenocarcinoma which is also the commonest cause of MPE. Sensitivity is lower for MPE due to non-epithelial cancer types, particularly mesothelioma, which in our experience required pleural biopsy to make nearly half of the diagnoses.

Development of new methods to improve diagnostic accuracy, such as specific biomarkers or molecular testing of pleural fluid, may improve detection of MPE, but further study in this area is required.

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Figure legends

Figure 1. Method of Malignant Pleural Effusion (MPE) diagnosis. Forty-six cases of MPE were diagnosed on pleural fluid cytology, of which 5 required a second sample to detect malignant cells. No diagnoses were made on third or fourth samples. Fifteen cases of MPE were diagnosed by another means other than pleural fluid cytology. Seven diagnoses were made on pleural biopsy, of which 5 cases were malignant mesothelioma. Six cases were deemed most likely to be due to MPE based on expert review of the clinical scenario, and in 3 of these cases the primary malignancy was unknown. One case of lymphoma was detected by flow cytometric analysis of pleural fluid – we did not include this with the rest of the cases diagnosed on pleural fluid cytology as this test is not routinely performed on all samples. In one case a patient with known lymphoma and recurrent pleural effusions was diagnosed with MPE based on PET imaging showing pleural involvement. *PET: Positron Emission Tomography.*

Tables

Table 1. Baseline characteristics

	Total number (%) n=153	Benign n = 92 (%)	Malignant n = 61 (%)
Gender: n (%)			
Male	91 (59%)	60 (65%)	31 (50.8%)
Female	62 (41%)	32 (34.8%)	30 (49.2%)
Age: years			
Mean ± SD (range)	67 ± 16 (26-95)	65 ± 13 (26-95)	71 ± 17 (34-95)*

SD: standard deviation

**P value for age of cases with benign versus malignant effusions = 0.017*

Table 2. Pleural effusion aetiology

Aetiology	Female	Male	Total (n=153)	% overall (% of benign)
Benign effusions	32	60	92	60.1
Cardiac	4	11	15	9.8 (16.3)
Parapneumonic	7	5	12	7.8 (13.0)
Trauma	2	5	7	4.6 (7.6)
Paramalignant	2	4	6	3.9 (6.5)
Empyema	0	4	4	2.6 (4.4)
Tuberculosis	1	2	3	2.0 (3.3)
Hepatic/chronic liver disease	1	2	3	2.0 (3.3)
Pleuro-peritoneal fistula due to peritoneal dialysis	2	1	3	2.0 (3.3)
Renal (fluid overload)	1	2	3	2.0 (3.3)
Benign not specified/ multiple aetiologies	10	21	31	20.3 (33.7)
Other benign[†]	2	3	5	3.3 (5.4)
Malignant pleural effusions	30	31	61	39.9 (% of MPE)

Lung	11	16	27	17.7 (44.3)
Adenocarcinoma	*9*	*12*	*21*	*13.7 (34.4)*
Squamous cell carcinoma	*0*	*2*	*2*	*1.3 (3.3)*
NSCLC NOS/other[‡]	*2*	*1*	*3*	*2.0 (4.9)*
Small cell carcinoma	*0*	*1*	*1*	*0.7 (1.6)*
Mesothelioma	5	6	11	7.2 (18.0)
Ovarian carcinoma	7	0	7	4.6 (11.5)
Lymphoma[§]	1	4	5	3.3 (8.2)
Breast carcinoma	4	0	4	2.6 (6.6)
Other malignancy[¶]	2	5	7	5.2 (13.1)
All adenocarcinoma	21	12	33	21.6 (54.1)

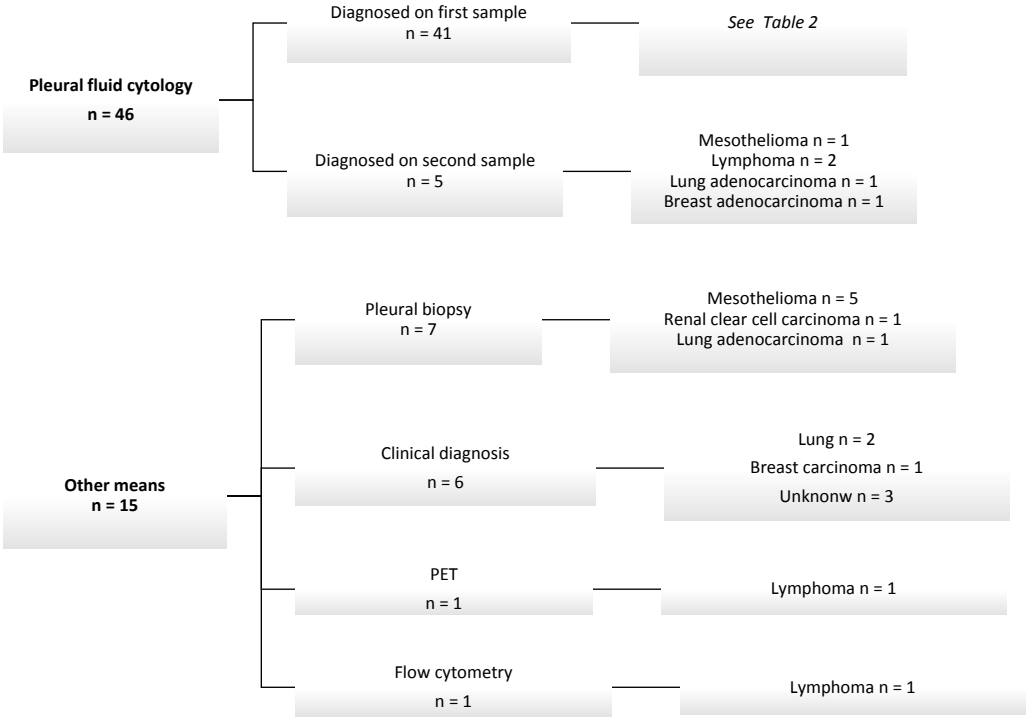
NSCLC NOS: non-small cell lung cancer not otherwise specified.
[†]*Other benign: Pulmonary embolus (1), chemotherapy (1), chylous pleural effusion secondary to intrathoracic lymph node compression (1), silicosis (1), rheumatoid (1).*
[‡]*NSCLC NOS/other: NSCLC with neuroendocrine differentiation (1), large cell neuroendocrine carcinoma of the lung (1), NSCLC NOS (1).*
[§]*Lymphoma: follicular lymphoma (2), Hodgkin's lymphoma (1), large B cell lymphoma (1), Burkitt's lymphoma(1).*
[¶]*Other malignancy: adenocarcinoma of the female genital tract (1), adenocarcinoma not otherwise specified (1), renal cell carcinoma (1), undifferentiated epithelial tumour (1), assumed MPE of unknown primary due to clinical +/- imaging findings (3).*
NB: one case of lung adenocarcinoma and one case of squamous cell carcinoma of the lung were inferred clinically based on histologically-proven primary malignancies. One case of breast cancer was presumed based on clinical history without proven histology, therefore is not included in the total adenocarcinoma count.

Table 3. Yield of pleural fluid cytology for the diagnosis of malignant pleural effusion

Malignancy type	N =	NPV	Sensitivity	Diagnostic accuracy
All MPE	153	82.1	67.2	85.9
Lung (all)	27	96.9	85.2	97.4
Lung Adenocarcinoma	21	99.8	85.7	98.0
Mesothelioma	11	96.0	45.5	96.1
Ovary	7	100	100	100
Lymphoma	5	97.4	20.0	97.4
Breast	4	98.7	50.0	98.7
All adenocarcinoma	33	96.8	87.9	97.4

MPE: malignant pleural effusion; NPV: negative predictive value

Figure 1.



Title

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Abstract

Background: Timely diagnosis of malignant pleural effusions is critical to guide prognosis and management decisions. Cytologic analysis of pleural fluid has been the first-line diagnostic test for many decades, with highly variable reported sensitivities of 40 to 90%. Its diagnostic accuracy in modern practice in Australia needs to be understood.

Aims: To determine the diagnostic yield of pleural fluid cytology for the detection of malignant pleural effusions, and to determine the aetiologies of pleural effusions at our centre.

Methods: Retrospective chart review of all pleural fluid samples submitted for cytologic analysis at a tertiary referral centre in Melbourne, Australia, over a 12-month period. Aetiology of all effusions was determined, and sensitivity, specificity, negative predictive value and diagnostic accuracy for the detection of malignant pleural effusions were calculated. We also examined diagnostic yield based on tumour cell type.

Results: Of the 153 cases analysed, 61 (39.9%) were malignant. Lung cancers accounted for 44.3% of malignant effusions, followed by mesothelioma (18%), ovarian carcinoma (11.5%) and lymphoma (8.2%). The commonest single causes of a benign effusion were cardiac (16.3%) and parapneumonic (13%). Sensitivity for diagnosis of malignant effusions was 67.2% overall, but 87.9% for adenocarcinomas and only 45.5% for mesothelioma.

Conclusions: Tumour type is an important determinant of pleural fluid cytology diagnostic yield. Cytology has good sensitivity and specificity for the diagnosis of adenocarcinoma, but if another tumour type is suspected, particularly mesothelioma, clinicians should be aware of the limitations.

Key words: Malignant pleural effusion, thoracentesis, cytology, diagnosis, cancer