Editorial

Imaging for malignant pleural effusions—still no routine role of positron emission tomography

David T. Arnold, Nick Maskell

Academic Respiratory Unit, University of Bristol, Bristol, UK

Correspondence to: David T. Arnold. Academic Respiratory Unit, Level 2, Learning and Research Building, Southmead Hospital, Southmead Road, Bristol BS105NB, UK. Email: arnold.dta@gmail.com.

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Malignant pleural effusions (MPEs) are a common diagnostic challenge for the respiratory physician. Their incidence is increasing with an estimated 150,000 new cases in the USA annually (1). As well as an increasing incidence, patients with MPE are presenting older due to ageing population and improved survival from primary cancer. The survival from diagnosis of all-cause MPEs is poor at around 5 months (2). Therefore, a clear and minimally invasive pathway for investigating these patients is essential. Currently, the mainstay of early investigation is computed tomography (CT) scanning and pleural fluid sampling for cytological analysis.

Computed tomography is recommended on all patients with an undiagnosed unilateral exudative pleural effusion as a quick and non-invasive method of imaging the pleura (3). Various studies have assessed the sensitivity of CT for detecting malignant pleural disease. Hallifax *et al.* in 2015 performed a retrospective review of 370 thoracoscopy procedures where the patient had a CT scan prior to the procedure (4). This analysis involved interpreting the radiologists reporting of the scan as to their certainty of malignancy. The sensitivity and specificity of CT was calculated using the thoracoscopic biopsy results as gold standard and was 68% and 78% respectively. Several further analyses have been performed and apart from a known false negative rate, especially for certain tumours (e.g., mesothelioma), the utility of CT scanning is unequivocal.

Pleural fluid cytology is another cornerstone in the investigation of malignant pleural disease and again is recommended in all patients with undiagnosed unilateral pleural effusions. The sensitivity of cytology to detect malignant disease varies depending on the population studied and the immunohistochemical techniques used. A recent UK based prospective study found the overall sensitivity for detecting malignancy was 46% (95% CI, 42–58%) with a considerable number of mesothelioma cases, in whom cytological yield was just 6% (5). When this analysis was limited to just lung carcinomas, sensitivity rose to 56%, and higher still in lung adenocarcinomas (82%). The downsides of pleural fluid cytology include the time taken for immunohistochemical analysis, up to 5–7 days, during which the patient may be symptomatic without definitive management of their effusion. Additionally, it is still an invasive test and may not be immediately possible in those on anticoagulation or with only a small amount of pleural fluid.

Positron emission tomography (PET) scanning is becoming increasingly used in malignant disease given improved availability and evidence base. It has been full incorporated in the diagnostic and treatment pathway of lung cancer but without a clear translation to MPE investigation currently. In MPE most studies have focused on the ability of PET to diagnose and stage mesothelioma (6,7). The drawback of PET in all-cause effusions suspicious of malignancy are the false positives due to other causes of pleural inflammation including inflammatory pleuritis, parapneumonic effusions or previous pleurodesis. Additionally, the availability of PET scanners varies dramatically worldwide so any guidelines should take this into account.

A meta-analysis of diagnostic accuracy studies focusing

specifically on PET for MPEs, was performed by Porcel *et al.* in 2015 (8). From 14 studies (comprising 407 patients with malignant disease) the pooled test characteristics of PET imaging had a sensitivity of 81% and specificity of 74%. The studies included were highly heterogenous, and authors concluded that there was no basis for the routine inclusion of PET in the diagnosis of malignant pleural disease. Other roles for PET have been explored. The TARGET trial is currently under follow-up and explores the potential role of PET-CT to target areas of high uptake when performing a CT guided biopsy (9).

The study published in this edition of *JTD* by Brun and colleagues assesses the correlation between CT scanning and pleural fluid cytology with PET (10). They focus on a cohort of 101 patients with proven MPEs secondary to lung cancer. Their analysis is retrospective across a 7-year period in a single centre French hospital. All patients had a CT and pleural fluid analysis, with a proportion also having a PET scan as part of their diagnostic work up. Their focus on a single primary site is important as often the study of MPEs is hampered by the inclusion of many different primary malignancies.

The sensitivity of pleural fluid cytology amongst these patients was 60%, which is in keeping with previous literature for this condition. Interestingly, they also analysed the results from patients who had a repeat pleural fluid cytology sent at thoracoscopy. In those patients the cytological sensitivity was 67%. This adds value to previous literature that has recommended repeating the pleural fluid cytology (11). However, the authors of this editorial would caution against delaying thoracoscopy in patients where cytology is unlikely to give an answer e.g., males with previous asbestos exposure and no obvious primary tumour on baseline CT, or where tissue is likely to be required for targeted therapy (e.g., EGFR and ALK status).

The analysis of the CT results, performed in all 101 patients, showed that in 69 patients there was no clear evidence of malignancy (defined as pleural nodularity or thickening). A sensitivity of only 32% is lower than would be expected when compared to previous literature. The focus on lung cancers alone may have biased the study when compared to studies of all cause MPEs because a lung carcinoma can cause a reactive effusion without directly metastasizing to the pleura. Despite strict criteria for defining radiological malignancy (clear evidence of pleural nodules, masses and/or pleural thickening) CT evidence of malignancy did not translate into significantly worse overall survival in this cohort.

This study did not find any value in PET imaging for diagnosis. Unfortunately, only a minority (47/101) patients had a PET performed as it was not standard of care (these were performed for staging purposes only). From these cases 68% had pleural enhancement indicating malignancy. This correlates with published literature. This study cannot give any estimates of specificity given the lack of a control group. Additionally, there was no correlation between PET findings, CT, pleural fluid cytology or survival.

In terms of prognosticating patients with MPEs this paper has also not shown any role for PET. Patients with proven lung adenocarcinoma who present with a pleural effusion are automatically upstaged to "non-operability". There is an argument that this is inappropriate given the lung cancer may not have caused the effusion by local invasion or metastasis into the pleura. Although there was a slight survival advantage in patients with no pleural changes on CT (2 months) or PET (2 months) these were not statistically significant. Previous literature has focused on the role of PET in prognosticating mesothelioma, where CT imaging is less helpful, but the evidence is not conclusive. Depending on the PET endpoint used some studies have shown a role in baseline prognostication but no ability to monitor disease (6). The recent BTS guidelines on mesothelioma do not recommend the routine use of PET-CT except in patients "where excluding distant metastases will change management" (12). A potential future direction of study is the assessment of PET as a prognostic marker for lung cancer in patients with pleural effusions who might otherwise have been amenable for surgical resection.

What this paper has shown is that there is no single or combination of non-invasive tests that can reliably diagnose MPEs. This condition continues to require a considered approach based on a thorough assessment of risk factors, CT imaging and thorough cytological testing. Even once these have been performed, there will continue to be a significant proportion of patients who will require biopsy (for tissue confirmation and genetic testing) or interval scanning in order to make a diagnosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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