Review Article

Role of total-body computed tomography and 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography scan in malignant pleural effusion patients with unknown primary tumor site

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Abstract: Malignant pleural effusion (MPE) is defined by the presence of neoplastic cells in the pleural fluid, and it can occur during multiple malignancies; lung and breast cancer are the main responsibles. However, about 11% of MPE are determined by cancer of unknown primary (CUP) site. CUP is a malignant widespread metastatic disease without an identified primary site despite sweeping medical and radiological evaluation. It is known that CUPs are related to poor prognosis with a low life expectancy. The management of MPE from unknown primary tumor site represents an important medical challenge also because there are no protocols or "*ad hoc*" guidelines. Total body positron emission tomography/computed tomography (PET/CT) and CT scan in the diagnostic path of CUP has been well-defined, but the Literature is poor regarding their use in the evaluation of MPE associated with CUP. This review tries to achieve a conclusion on the role of CT scan and PET/CT in MPE with CUP by comparing the most recent clinical studies.

Keywords: Malignant pleural effusion (MPE); cancer of unknown primary (CUP); total-body computed tomography; 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT)

Received: 14 May 2020; Accepted: 10 July 2020; Published: 25 September 2020.

doi: 10.21037/jxym-20-56

View this article at: http://dx.doi.org/10.21037/jxym-20-56

Introduction

Malignant pleural effusion (MPE) occurs in advanced-stage cancer, accounting for the 15% to 35% of all pleural effusions (1). It is defined by the presence of neoplastic cells in the pleural fluid, and it can occur during multiple various type of malignancies: lung cancer (37.5%), breast cancer (16.8%) and lymphoma (11.5%) are the main responsibles (2). Supposed causes are an increased permeability of the pulmonary capillaries or a direct invasion of the lymphatic vessels by the tumor cells. The most common clinical signs of massive pleural effusion are dyspnoea, cough and chest pain. Nevertheless about 25% of patients with MPE show no symptoms and a moderate/important ipsilateral pleural effusion (0.5–2 L) is often found on radiological images. In 10–13% of cases it can be bilateral (3).

Generally, it is diagnosed through the cytological examination of the pleural fluid collected through a thoracentesis. However, the sensitivity of thoracentesis is low, with an accuracy of 60% and it is often necessary to perform a diagnostic thoracoscopy with pleural biopsy. Furthermore, the primary lesion is difficult to identify

histologically even in cytologically positive specimens (4). In fact, MPE can be secondary to what is called cancer of unknown primary (CUP) site which is defined by an identification of a metastatic disease with no underlying detectable primary lesion at multiple radiological and clinical investigations; CUP accounts for the 4–5% of all invasive cancers. The reported incidence of CUP in MPE patients is about the 10.2% (5). Patients with MPE associated with CUP have poor prognosis with a low life expectancy, less than 1 year. Site of metastasis and histology are two essential factors in the prognosis of CUP (6). The incidence of CUP is highest in patients of age between 60–75 years (7).

However, not all patients with cancer and pleural effusion have an MPE but may have a para-malignant pleural effusion (PPE). In particular in PPE direct pleural infiltration is absent and malignant cells are not present in the pleural fluid (8). Therefore, for optimal patient management and ensuring adequate treatment, it is essential to distinguish MPE versus PPE (9). As described by the current guidelines, the diagnostic path to reach the diagnosis of CUP requires an extensive clinical and laboratory evaluation and also recommend a computed tomography (CT) scan of thorax, abdomen and pelvis. CT is important in the search for a primary site of the malignancy, for staging and remission assessment 18-fluorine-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) imaging which displays tissue metabolism, is frequently additionally employed in CUP to identify malignant lesions, typically integrated PET/CT is used. Total-body PET/CT are the first choice to assess the whole-body status in a single examination (10), and may aid the identification of the primary site, hence positively affecting the management algorithm. Unfortunately, little is found in the literature regarding the specific use of the total-body CT and PET/CT in the evaluation of MPE associated with CUP. Despite the significant progresses in the oncological field, the diagnosis and treatment of MPE from CUP remains a hard-to-manage "black hole" with no clear guideline. Few studies have described the usefulness of PET/CT and CT in differentiating benign and malignant pleural diseases with reported huge variability between sensitivity/specificity parameters. Given the potential contribution of the total body CT and PET/CT to MPE and differential diagnosis, we aimed to investigate the role of these radiological techniques in patients with unknown primary tumor site. An update critical review of the available literature is thus presented.

Methods

Search strategy

A systematic MEDLINE literature review was performed on the PubMed platform with the following search terms in all fields: "Malignant pleural effusion"; "cancer of unknown primary"; "Positron Emission Tomography/Computed Tomography"; "Computed Tomography". Results were then limited by "English language" and "2010-2019" published papers.

Study selection

All the titles and abstracts concerning the usefulness of CT scan and PET/CT in the differential diagnosis between malignant and benign pleural effusion by CUP were deemed eligible. Inclusion criteria were as follows: original studies reporting on diagnostic parameters of PET/CT and CT on MPE, articles within the field of CUP.

Data extraction

For each included study, information was collected on the basis of the study construct (authors, journal, study design and country), sample and patient characteristics and technical aspects (sensitivity and specificity of PET/CT and CT).

PET/CT

PET and PET/CT is a non-invasive radiological investigation, that allows to evaluate presence and extension of the disease in cancer patients. The positron emission tomography reveals the metabolically active tissue, by an increased uptake of a radio-labelled glucose isotope ^{18}F-FDG. Usually malignant lesions present a higher glucose metabolism avidly concentrating FDG when compared to normal tissue (11). Substantial data exist to support the use of PET/CT in the work up of CUP because it helps to identify the primary tumor site (3) with a diagnostic accuracy of 78%, a sensitivity of 80% and a specificity of about 74% (12). The indications for FDG PET/CT for CUP include primary tumor site localization and disease staging. PET with ^{18}F-FDG was first reported in the 1997 as an effective tool in the evaluation of pleural disease (13) Since then, several studies have been conducted to evaluate the effectiveness of PET/CT in the differential diagnosis of MPE with different results on sensitivity and specificity. Treglia *et al.* (14) published a systematic review

and meta-analysis on the diagnostic accuracy of PET/CT. They evaluated 11 studies (212 patients) demonstrating that PET/CT has a high sensitivity (95%) and good specificity (82%) in evaluating MPE. However, the authors draw attention to the possibility of false positive (e.g., inflammatory disease) and false negative (some epithelioid subtypes of mesothelioma) results and they underlined the need for further studies on the usefulness of PET/CT in this setting. Another meta-analysis on the diagnostic accuracy of PET/CT imaging in differential diagnosis of benign from MPE was published by Porcel *et al.* (15); presented data were processed from 14 studies with more than 600 patients, of whom 407 had MPE and 232 had a benign pleural disease. Results showed that when the PET image analysis was performed applying qualitative criteria (visual analysis) sensitivity and specificity values were of 96% and 76% respectively. Instead using a semiquantitative method [based on the calculation of standardized up-take value (SUV)] for identifying MPE, sensitivity went to the 81% and specificity to the 74%. According to the authors the best sensitivity provided by the visual interpretation compared to the SUV-based methods is to be attributed to many biological and technological factors. Based on their data Porcel *et al.* concluded that PET/CT, although of some value, could not change the probability of pleural malignancy and that it should be avoided in the medical routine to rule out differential diagnosis. On the other hand, a retrospective study conducted by Nakajima *et al.* (16) concluded that it could be of use in the differential diagnosis as a non-invasive method. The study was run on 36 patients with tumor and pleural effusion (mesothelioma was excluded) and evaluated the maximum standardized uptake values (SUVmax) of pleural effusion and the target-to-normal tissue ratio (TNR), calculated as the ratio of the pleural effusion SUVmax to the SUVmean of the normal tissues [liver, spleen, 12th thoracic vertebrae (th12), thoracic aorta and spinalis muscle]. The authors report that the cut-off TNR (th12) value of >0.95 on PET images was the most accurate parameter to detect MPE with specificity, sensitivity and accuracy of 68%, 93% and 75% respectively (16). The SUV can be influenced by many factors that can be related to the patient (for example body weight) but also to the technical aspects (e.g., scan protocols; scan time and FDG injection activity); thus, SUV alone should not be used for differentiating a benign disease from MPE. The main limitation of the study was a low number of patients and a larger cohort would be needed to validate the results. Sun *et al.* (17) evaluated the effectiveness of PET/CT in identifying MPE from benign pleural effusion. This retrospective study included 176 patients, of whom 108 with histologically confirmed MPE. PET/CT integrated imaging has demonstrated a sensitivity of 93.5% and a specificity of 92.6%; CT imaging can improve the specificity and reduce the false positive findings. A recent study developed a scoring system to assess the diagnostic accuracy of PET/CT (18); a derivation cohort of patients (n=199) was employed to develop a PET/CT score and then the identified score was validated on an independent prospective cohort (n=74). Twenty-nine parameters were used to discriminate the quality of the pleural effusion and after multivariate analysis, 5 of these parameters showed the ability to forecast MPE.

The mentioned score accounted for five variables: (I) unilateral lung nodules/or masses with increased ^{18}F-FDG up-take (3 points); (II) extrapulmonary malignancies (primary/metastatic) (3 points); (III) pleural thickening (≥3 mm) with increased ^{18}F-FDG up-take (TBR >1.8) (2 points); (IV) multiple nodules or masses (uni- or bilateral lungs) with increased ^{18}F-FDG up-take (1 points); (V) increased pleural effusion ^{18}F-FDG up-take (TBR >1.1) (1 point)]. Data showed that from a maximum sum of 10 points of PET/CT score, a mark ≥4 had to be considered suggestive for MPE. With cut-off value of 4 points sensitivity was of 83.3% and specificity 92.2%.

CT

The total body CT is an usual practice in diagnostic manage of CUP since, in addition to attempting to detect the primary site, it acts as an extension study and can identify lesions that may be target of biopsy (7), moreover, the CT scanning is firmly established in the diagnostic pathway of pleural disease. CT scan in evaluation of pleural disease should provide for thin multi-slice sections (0.5–2.0 mm) so as to allow a multiplanar reconstruction (11), and it should be done by administering intravenous contrast, with a delay of 60–90 s (“pleural phase”) (19). “Nodular pleural thickening”, “mediastinal pleural thickening”, “parietal pleural thickening” (>1 cm) and “circumferential pleural thickening” represent a pathological alteration characterizing the pleural malignancy, which can be seen on CT scanning (20). These characteristics showed a high sensitivity but a low specificity. Hallifax *et al.* (21) assessed the effectiveness of the CT investigation in identifying both primary and metastatic pleural malignancies, before getting the histological results. This is a retrospective analysis

that included 370 patients, and it reported a sensitivity of 68% and a specificity of 78% with a negative predictive value of 65%; potentially this means that about third of patients with pleural effusion has a CT scan suggestive of benign disease but in reality there is a malignancy. The authors concluded that CT alone in attempt to determine which patients with pleural effusion should undergo thoracoscopy to perform pleural biopsies should be re-evaluated. In another review article by Hallifax *et al.* (22) summarized the evidences of CT and PET/CT on their ability to identify MPEs, due to both primary and metastatic tumors; CT scan should be considered in the presence of exudative pleural effusions and CT scoring systems may allow further risk stratification. Over the last few years there has been an increasing interest in using of dual-energy spectral CT imaging for the assessment of pleural effusion; dual-spectral CT imaging can generate material decomposition images as well as monochromatic images sets with fast kilovoltage switching. Zhang *et al.* (23) evaluated 29 patients with pleural effusion (14 with benign pleural effusion and 15 with MPE) showing that dual-energy spectral CT improve the diagnostic performance of differentiating benign from malignant effusion with a sensitivity of 100% and specificity of 71.4%. Porcel *et al.* (24) developed a CT scan-based scoring system to distinguish between malignant and benign pleural effusion; their study involved 80 patients with exudate pleural effusion, transudate effusion was excluded. The CT scan features evaluated for the discriminating analysis were 18, 7 of these were useful in building the score: any pleural lesion ≥1 cm (5 points); liver metastases (3 points); abdominal mass (3 points); lung mass or lung nodule ≥1 cm (3 points); absence of pleural loculations (2 points); no pericardial effusion (2 points); and non-enlarged cardiac silhouette (2 points). Thus, CT scan scores ranged from 0 to 20. With a score of 7 points, the scoring system showed a sensitivity of 88% and a specificity of 94%. CT scan scoring system increased the detection probability of malignancy in patients with pleural effusion. Recently a retrospective study (25), that included 79 patients with pleural effusion without a definite diagnosis, evaluated the CT scan scoring system developed by Porcel *et al.* (24); binary regression analysis of correlation between malignant pleural disease and CT scan score showed the odds ratio of 1.314 (95% CI: 1.119–1.543). They confirmed the usefulness of the CT scan scoring system in the diagnostic pathway and decision making for optimal treatment of pleural effusion. Short while ago, a paper (26) was published that assessed clinicians' adherence to follow the recommendations of the British Thoracic Society (BTS) guidelines with respect to CT in patients with unilateral pleural effusion. The guidelines recommend performing contrast enhanced CT only if the liquid is not a transudate and the analysis of the fluid are not diagnostic. The authors found that clinicians don't seem to follow the guidelines when deciding to perform a CT scan: about two-thirds of patients underwent a CT scan regardless of the quality of the pleural effusion and moreover the sensitivity of a non-guideline CT was superior compared to a CT performed in accordance with the BTS guideline. The superior sensitivity of non-guideline supported CT (70%) could be due to the fact that about 10% of patients with pleural transudate actually have a malignancy.

Discussion

MPE is a common disease with an estimated annual incidence of 150,000 cases in the United States (8). It is believed that 15% of people diagnosed with cancer will develop pleural effusion over the course of the disease following malignant infiltration of the pleura. MPE is often associated with an unfavorable prognosis and reduced quality of life (1). The focus of treatment is inevitably palliative and aimed at alleviating symptoms by pleural fluid aspiration. About 11% of MPE are due to CUP. Overall, the management of MPE is difficult and a comprehensive and extensive medical evaluation should be considered in the initial diagnostic process. The guidelines recommend performing a diagnostic thoracentesis to differentiate the malignant from the benign pleural effusion, but the role of PET/CT and CT is not well established and even there are no consensus or guidelines on their role on the MPE during CUP. In this paper we have provided an overview of the role of PET/CT and CT in MPE, and on their sensitivity and specificity in differential diagnosis power between benign and MPE (*Table 1*). The inclusion of PET/CT in the routine test has controversies due to the lack of prospective studies. PET/CT does not currently appear to add additional diagnostic value over and above CT scanning for differentiating benign and malignant disease. In addition, clinicians should keep in mind the likelihood of getting false positive (e.g., pleural tuberculosis) and false negative (low up-take forms e.g., epithelioid mesothelioma) findings. Moreover PET/CT should be avoided in patients who have received talc pleurodesis, because PET/CT will have a high grade of ^{18}F-FDG uptake. PET/CT should not

Table 1 The efficacy of ^{18}F-FDG PET/CT integrated imaging and CT in the differential diagnosis between malignant and benign pleural effusion

Study	Country	Design	Number of patients	Device	Sensitivity	Specificity
Treglia G *et al*. 2014	Italy	Meta-analysis, systematic review	745	PET/CT	95%	82%
Porcel JM *et al*. 2015	Spain	Meta-analysis	639	PET/CT	Quantitative analysis, 81%; qualitative analysis, 96%	Quantitative analysis, 74%; qualitative analysis, 76%
Nakajima R *et al*. 2015	Japan	Retrospective	36	PET/CT	93%	68%
Sun Y *et al*. 2016	China	Retrospective	176	PET/CT	93.5%	92.6%
Hallifax RJ *et al*. 2017	UK	Retrospective	370	CT	68%	78%
Zhang X *et al*. 2018	China	Retrospective	29	CT	100%	71.4%
Porcel JM *et al*. 2015	Spain	Retrospective	80	CT	88%	94%

^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

be used as a routine examination because did not change the probability of malignancy sufficiently (15). PET/CT could provide additional information on malignant pleural disease regarding prognosis and response to therapy, and also can help find the site of the primary tumor site. CT scan is the diagnostic modality of choice in the evaluation of pleural diseases; the BTS recommends performing CT scan in all undiagnosed exudative pleural effusions. CT scan is able to image the entire pleural space, and the identification of pleural changes in CT images such as the presence of nodules and pleural thickenings hold additional diagnostic importance in characterizing a pleural effusion. Contrasted-enhanced CT scans are performed for the initial staging and follow-up in patients with carcinoma and in the diagnostic workup of pleural effusion with variety protocols. However, Arenas-Jiménez *et al.* (27) advised that the delayed phase of contrasted-enhanced should be preferable to early phase for evaluating pleural changes. CT scoring system may allow further risk stratification. Despite the increasing use of PET/CT and CT scan neither is able to establish with certainty the pleural effusion malignancy.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Duilio Divisi, Roberto Crisci) for the series "Malignant Pleural Effusion" published in *Journal of Xiangya Medicine*. The article has undergone external peer review.

Peer Review File: Available at http://dx.doi.org/10.21037/jxym-20-56

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym-20-56). The series "Malignant Pleural Effusion" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jxym-20-56
Cite this article as: Gonfiotti A, Salvicchi A, Voltolini L. Role of total-body computed tomography and 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography scan in malignant pleural effusion patients with unknown primary tumor site. J Xiangya Med 2020;5:29.