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Review

Imaging in pleural mesothelioma: A review of Imaging Research Presented at the 9th International Meeting of the International Mesothelioma Interest Group

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ABSTRACT

Imaging of malignant pleural mesothelioma (MPM) poses many challenges for imaging specialists and clinicians due to the anatomic location and unique growth pattern of this tumor. Nevertheless, imaging in MPM plays a critical role in diagnosis, prognostication, prediction or measurement of response to therapy, and monitoring of disease recurrence after aggressive surgical management. Imaging-based studies presented at the 9th International Conference of the International Mesothelioma Interest Group (IMIG) in October 2008 sought to further define the current practice and future potential of imaging for the mesothelioma patient. The Imaging Session was dominated by presentations that addressed the use of fluorodeoxyglucose positron emission tomography (FDG-PET), a clear indication of the expanding role of this modality. These uses included FDG-PET imaging at the point of diagnosis, in prognostication, and in the assessment of response to chemotherapy. Often FDG-PET studies were combined with computed tomography (CT) scans in an attempt to overcome limitations associated with either imaging modality alone. At diagnosis, FDG-PET parameters had a high sensitivity and specificity for differentiation of benign from malignant pleural disease. The use of FDG-PET to extract quantitative features from metabolically active tumor volume was shown to be a significant factor in the prediction of patient survival. The prognostic value of FDG-PET was not confounded by prior talc pleurodesis, despite the inflammatory response associated with the procedure. Metabolic response based on FDG-PET was found to be significantly correlated with progression-free survival. CT-based assessment of mesothelioma was determined to be inconsistent with spherical-model-based criteria so that changes in tumor area, a presumably more complete assessment of tumor burden, exhibited a 46% concordance rate with changes in linear measurements.

1. Introduction

Imaging of malignant pleural mesothelioma (MPM) poses many challenges for imaging specialists and clinicians due to the anatomical location and unique growth pattern of this tumor. The growth of many solid tumors approximates a sphere, enlarging concentrically from a central nidus before involving regional lymph nodes with later development of metastatic disease; MPM, however, usually grows around and within the pleural cavity, with concentric thickening and contraction of the pleura, involvement of the interlobar fissures, and infiltration of the mediastium, chest wall, and diaphragm. Where 'spherical' disease is present, it may not be representative of the bulk of the tumor, creating difficulties in assessment of treatment response by conventional criteria [1,2]. The presence of simultaneous pleural effusion, atelectasis, and chest wall invasion creates difficulties in distinguishing tumor from uninvolved adjacent tissue. Furthermore, in early stage disease, the tumor rind may be difficult to visualize, thus complicating tumor measurements and the exclusion of adjacent chest wall invasion. Nevertheless, imaging in MPM plays a critical role in diagnosis, prognostication, prediction or measurement of response to therapy, and monitoring of disease recurrence after aggressive surgical management. This paper synthesizes current research directions in imaging of MPM as orally presented at the imaging session

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of the October 2008 International Mesothelioma Interest Group meeting in Amsterdam, The Netherlands. All session participants were invited to contribute; five of the eight presentations from that session are summarized and further developed herein. All work reported complied with the Declaration of Helsinki and was approved by an appropriate institutional Human Research Ethics Committee.

2. Imaging at diagnosis

Despite suggestive clinical symptoms, historical asbestos exposure, and indicative findings on imaging, malignant mesothelioma can often prove difficult to diagnose with certainty. A diagnosis of MPM is usually obtained by careful assessment of clinical and radiological findings in addition to a confirming tissue biopsy or cytological examination of pleural fluid. Key reasons for early diagnosis are to select patients for aggressive surgical procedures and trimodality therapy, to utilise systemic treatment before performance status declines, and to keep clinical trial participation available as an option for patients. Nevertheless, only around 5% of patients are eligible for potentially curative surgery at the time of diagnosis.

Most symptomatic or asbestos exposed patients will first have plain chest radiography (CXR), which may suggest a diagnosis of MPM on showing pleural effusion, pleural thickening, nodularity, pleural-based mass contraction and fixation of the chest as well as mediastinal shift towards the volume loss [3]. Concerns on CXR should be followed by contrast-enhanced thoracic CT, with findings of "rind-like pleural involvement", "mediastinal pleural involvement", "pleural nodularity" and "pleural thickness more than 1 cm" potentially differentiating malignant from benign pleural disease with sensitivity/specificity values of 54/95%, 70/83%, 38/96%, and 47/64%, respectively [4]. Imaging may be used to guide selection of sites for tissue diagnosis. Whilst blind biopsy may be diagnostic in less than 50% of patients [5], ultrasound-guided pleural biopsy has a sensitivity of 77% and a specificity of 88% [6] and there are several studies reporting high diagnostic yield of CT-guided biopsy, with overall diagnostic sensitivities of 83–86% [7,8]. Use of imaging guided techniques may avoid the use of more accurate but more invasive techniques such as medical thoracoscopy, video-assisted thoracoscopic surgery or open thoracotomy [9]. Subsequent magnetic resonance imaging (MRI) may be superior to CT in diagnosing chest wall invasion and extension through the diaphragm [10].

FDG-PET/CT has an emerging role in the early diagnostic workup of patients with MPM. Applications for FDG-PET/CT at this time point include differentiation between malignant and benign lesions in asbestos-exposed patients, classification of stage, and identification of candidates for aggressive surgical management. Duysinx et al. have previously demonstrated a sensitivity of FDG-PET of 97% in the differential between benign and malignant pleural lesions [11]. In a prospective study, Kramer et al. studied 32 patients, and also concluded that qualitative assessment of pleural thickening with PET accurately discriminates between malignant and benign pleural thickening, with a high accuracy and negative predictive value, suggesting that patients with pleural thickening on CT and negative PET findings may be followed up using only CT instead of pathologic diagnostic procedures [12].

At IMIG 2008, Yildirim and colleagues reported on 42 consecutive patients, 18 with MPM, 15 with benign asbestos-related pleural disease, and 9 with diffuse pleural fibrosis. The median age was 60 years (range 39–82 years). All patients underwent PET/CT as part of diagnostic workup for known or suspected neoplasms. PET images were first reviewed by nuclear medicine physicians without corresponding clinical information. Subsequent diagnosis was made on the basis of thoracoscopy or image-guided pleural biopsy and/or clinical follow up for at least 2 years. ROC analyses for standardized uptake value adjusted to body weight (SUV) were calculated between benign and malignant pleural disease. FDG-PET imaging correctly detected malignant disease in 17 of 18 patients, giving a sensitivity, specificity and accuracy of 94.4%, 91.7%, and 92.3% respectively. FDG-PET imaging correctly identified 22 of 24 cases of benign pleural disease. Two patients with benign pleural disease demonstrated pleural uptake on FDG-PET; however, malignant lesions accumulated significantly more FDG than benign lesions, with mean SUV values of 7.8 ± 3.3 and 0.4 ± 0.8 respectively ($p < 0.001$). In this group, a cut-off value of SUV 3.0 gave a sensitivity and specificity of 100% for differentiation between benign and malignant disease. Therefore, FDG-PET imaging is a highly accurate and reliable non-invasive test to differentiate benign from malignant pleural disease. However, these findings require further validation in larger, multicentre series.

3. Using FDG-PET scan to assess prognosis

Prognostic information at diagnosis is important for patients, clinicians, and in clinical trials. Patients require such information to help them make treatment and lifestyle decisions and to plan for a limited future, whilst clinicians may use this information to guide management recommendations. In clinical trials, the description of prognostic groups assists clinicians to judge how study results may be applicable to their patient, and randomized trials should stratify for important prognostic variables. The most well known prognostic scoring systems for MPM are the EORTC and CALGB prognostic models [13–15]. The CALGB model is complex, with a regression tree leading to 11 groups with are then combined for six prognostic groups. Whilst the EORTC model is simpler, it includes "definite" versus "probable" diagnosis, in an era when a definitive diagnosis should be achievable and would certainly be required for patients enrolled in clinical trials. However, since the development of these models, the use of combination systemic chemotherapy has become widely accepted, and FDG-PET imaging has become more available. Furthermore, more robust statistical methods for prognostic models have been developed. A recently published nomogram includes such statistical methods, however the contribution of imaging to this nomogram is confined to staging information [16].

Tumor size has prognostic implications in many other cancers, for example, in non-metastatic breast and non-small cell lung cancer. Nevertheless, it is unclear whether size is a surrogate for metastatic potential and opportunity in these diseases, where tumor resection is the primary therapy for localized disease. Although advanced MPM is not usually treated surgically, the disease is commonly more locally aggressive than metastatic during progression. It is possible that disease volume at diagnosis may be prognostically important. FDG-PET can be used to quantify both metabolic activity and tumor volume in mesothelioma using a semi-automated, iterative, region-growing algorithm [17], deriving the parameter total glycolytic volume (TGV), a composite measure of both volume and standardized uptake value (SUV)/metabolic activity. Changes in TGV following treatment with chemotherapy have been shown to predict overall survival better than objective response on cross-sectional imaging [18]. The study presented by Nowak and colleagues assessed whether FDG-PET scanning added information to clinical prognostic variables with or without prior pleurodesis.

In the prospective study presented at IMIG 2008 by Nowak and colleagues, participants were all consenting, newly-referred, untreated patients with a confirmed diagnosis of MPM at a single tertiary referral centre. Patients were not excluded by age or performance status, and the study was approved by the Insti-