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MEETING REPORT

# Current state and future directions of pleural mesothelioma imaging

**KEYWORDS**
Mesothelioma;
Tumor response assessment;
PET/CT;
Tumor staging;
Computer-aided diagnosis;
mAb K1;
Total glycolytic volume

**Summary** The diagnosis, staging, and response assessment of mesothelioma pose unique challenges to radiologic imaging. No single, conventional imaging approach captures the information necessary to direct all aspects of patient management. Instead, the complexities of this unique disease demand the integration of elements cleverly adapted from different modalities. Imaging-based studies presented at the 8th International Conference of the International Mesothelioma Interest Group (IMIG) in October 2006 sought to further define the current practice and future potential of radiology for the mesothelioma patient. The imaging studies selected through a peer-review process for presentation at the 2006 IMIG Conference were intended to frame this research in the context of the unique imaging challenges presented by mesothelioma while stimulating dialogue on the future resolution of these challenges. This communication conveys the pitfalls and potential of pleural mesothelioma imaging based on work presented at the Conference. From diagnosis to response, PET/CT to molecular bioprobes, volumetric analysis to computerized tumor assessment, imaging promises to provide valuable insight for patients with mesothelioma and the physicians who treat them.

## 1. Introduction

Radiologic imaging is essential to the diagnosis, staging, and clinical management of patients with malignant pleural mesothelioma. X-ray imaging techniques (chest radiography and computed tomography (CT)), magnetic resonance (MR) imaging, positron emission tomography (PET), and, most recently, multimodality PET/CT all have been used to evaluate this disease, although the relative importance of these imaging modalities has changed over time. Imaging-based studies presented at the 8th International Conference of the International Mesothelioma Interest Group (IMIG) in October 2006 sought to further define the current practice and future potential of radiology for the mesothelioma patient. The intent of this communication is to highlight the imaging research reported at the 2006 IMIG Conference, to frame this research in the context of the unique imaging challenges presented by mesothelioma, and to stimulate dialogue on future resolution of these challenges.

## 2. Clinical applications and challenges

Malignant pleural mesothelioma is a tumor of the pleural lining of the lung. A large majority of patients will die within a year of diagnosis, and only a very small minority will survive 5 years. Mesothelioma has a very strong association with exposure to asbestos and is exceedingly rare in its absence. The geographic incidence is linked with the pattern of use of asbestos and any subsequent ban. Mesothelioma in Western Europe is predicted to rise to 9000 deaths per annum in around 2018, with a total of about one-quarter of a million deaths over the period of the epidemic [1]. In the United States, 2000 deaths per year result from mesothelioma, a number that is likely to decline after a two-decade increase [2].

Mesothelioma, which behaves quite differently from lung cancer, is a challenging disease to image with any modality. Modern multidetector row CT following intravenous contrast allows for evaluation of the entire pleural and

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diaphragmatic surfaces when the patient is scanned contiguously from the thoracic inlet to the level of the L3 vertebral body [3]. Pleural enhancement is best demonstrated with a more delayed scan time of 45—60 s. CT provides a detailed evaluation of the pleura, allowing differentiation of benign from malignant pleural disease [4] in the majority of cases; differentiation can be difficult in very early disease or when previous surgery or intervention has occurred. These limitations of CT are well recognized, and a definitive diagnosis often requires histological sampling. Image-guided percutaneous biopsy is an established technique for sampling the pleura with a higher diagnostic yield and lower complication rate than a reverse bevelled needle, such as the Abram's needle [5]. Even with adequate sampling and the use of immunocytochemistry, histological diagnosis is known to be difficult; diagnosis may require a combination of clinical presentation, time, and radiological and histological appearances. Consequently, diagnosis is best determined in the context of a multidisciplinary team.

Accurate staging is required to ensure patients are triaged to the best treatment option. In many institutions, multidetector row CT has superseded MRI as the primary modality for the evaluation of T status in patients prior to radical surgical treatment, although MRI can provide additional diagnostic information when equivocal findings exist with regard to chest wall, diaphragmatic, or pericardial invasion. The TNM staging system proposed by the International Mesothelioma Interest Group (IMIG) [6] is used for patients with potentially resectable disease, but this system was designed as a surgical tool and, consequently, is not completely applicable to imaging. The accurate determination of N status remains difficult with CT, which exhibits poor correlation between nodal size and tumor involvement. Metabolic imaging with [$^{18}$F]-fluoro-2-deoxy-D-glucose (FDG) PET exhibits difficulties in differentiating mediastinal nodal metastases from adjacent mediastinal pleural involvement; combined PET/CT, however, may have a role in detecting N3 or M1 disease [7] and in determining possible biopsy sites following previous indeterminate sampling.

Conventional imaging techniques are disadvantaged by the fact that the pleural surface is not a solid organ and that this lining has a complex shape, thus often complicating the differentiation of tumor from adjacent pleural effusion or collapsed lung. Furthermore, many patients have undergone pleurodesis and/or debulking surgery, and subsequent inflammatory or fibrotic changes can mimic the appearance of the disease. Mesothelioma remains a difficult tumor to assess following chemotherapy. Axial measurements adapted from solid organ tumors [8] have limitations. CT volume techniques and metabolic uptake and volume using FDG PET are promising techniques and will be discussed in detail. The most common primary endpoints for phase II trials in mesothelioma are response or progression-free survival, while the most common endpoint for phase III trials is overall survival; to ensure the reliable and expedient identification of treatment regimens that warrant phase III clinical trials, the development of imaging-based response assessment techniques is required to establish an accurate surrogate endpoint for phase II trials.

## 3. Tumor measurement and response assessment

The acquisition and comparison of temporally sequential imaging studies is standard practice for the evaluation of tumor response. While CT is the dominant study for this application, complementary roles are being developed for other imaging modalities. CT provides essential information on tumor morphology at any one time point so that CT-based response may be assessed on the basis of change in morphology between multiple time points. ''Morphology'' broadly encompasses lesion ''shape,'' which is a complex concept that operationally must be reduced to distinct numeric features to allow for quantitative comparison. The most obvious such feature is size; however, the manner in which lesion size information is captured has evolved over the years. Ultimately, tumor volume is the most complete representation of size, since this measure captures the magnitude of a lesion in three dimensions (subject to limitation of the physical imaging device) and, consequently, can be used to estimate the number of cells that comprise the lesion. In practice, however, tumor volume and change in tumor volume is never measured to assess tumor response to therapy; rather, change in two-dimensional cross-sectional area based on the World Health Organization (WHO) bidimensional measurement approach [9] and, more recently, change in longest diameter based on the Response Evaluation Criteria in Solid Tumors (RECIST) unidimensional measurement approach [10,11] have been used as more efficient and manageable surrogates of change in three-dimensional tumor volume.

The mathematical relationship among diameter, cross-sectional area, and volume is direct for spherical objects. As an object deviates from a sphere, however, the relationship between diameter and volume begins to fail [12]. Mesothelioma is a tumor that is not compact, not intraparenchymal, and not uniformly growing; the implication of these attributes is that mesothelioma is distinctly non-spherical and, accordingly, is beyond the domain for which conventional response assessment approaches have been developed.

The RECIST approach, like the WHO approach before it, consists of two components: (1) a procedure for the acquisition of tumor measurements within medical images (the measurement protocol) and (2) a set of numeric thresholds to convert quantitative differences in tumor measurements acquired from temporally sequential images to discrete response categories (the tumor response criteria). The RECIST measurement protocol requires measurement of the longest diameter of a tumor in the single CT section that demonstrates the greatest tumor extent. The RECIST response criteria then categorize change in tumor diameter between two CT scans as progressive disease if this change reflects an increase in diameter of at least 20%, partial response if this change reflects a decrease in diameter of at least 30%, and stable disease if the change is between these two thresholds.

Direct application of the RECIST measurement protocol to mesothelioma is complicated by the unique morphology of this tumor, and the shortcomings of this approach for mesothelioma have been confirmed [8,13,14]. The alterna-