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Review

Imaging in pleural mesothelioma: A review of the 13th International Conference of the International Mesothelioma Interest Group

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ABSTRACT

Imaging plays an important role in the detection, diagnosis, staging, response assessment, and surveillance of malignant pleural mesothelioma. The etiology, biology, and growth pattern of mesothelioma present unique challenges for each modality used to capture various aspects of this disease. Clinical implementation of imaging techniques and information derived from images continue to evolve based on active research in this field worldwide. This paper summarizes the imaging-based research presented orally at the 2016 International Conference of the International Mesothelioma Interest Group (iMig) in Birmingham, United Kingdom, held May 1–4, 2016. Presented topics included intraoperative near-infrared imaging of mesothelioma to aid the assessment of resection completeness, an evaluation of tumor enhancement improvement with increased time delay between contrast injection and image acquisition in standard clinical magnetic resonance imaging (MRI) scans, the potential of early contrast enhancement analysis to provide MRI with a role in mesothelioma detection, the differentiation of short- and long-term survivors based on MRI tumor volume and histogram analysis, the response-assessment potential of hemodynamic parameters derived from dynamic contrast-enhanced computed tomography (DCE-CT) scans, the correlation of CT-based tumor volume with post-surgical tumor specimen weight, and consideration of the need to update the mesothelioma tumor response assessment paradigm.

Contents

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1. Introduction

The International Mesothelioma Interest Group (iMig) (www.imig.org) holds a biennial conference to which advances in imaging research and clinical applications of imaging technologies have made key contributions [1–4]. Researchers, clinicians, and radiologists continue to seek ways to expand the capabilities of imaging with the intent of extracting as much anatomic or physiologic information from mesothelioma patients as possible and to apply imaging technologies most appropriately to patient management in both routine practice and clinical trials research. This paper summarizes research presented in the "Imaging and Endpoint Evaluation" session of the 2016 International Conference of the International Mesothelioma Interest Group in Birmingham, United Kingdom, May 2016.

Key clinical goals of imaging in malignant pleural mesothelioma are early detection of disease, optimising sensitivity and specificity for anatomic involvement of unresectable planes to identify patients who are suitable for surgical resection, improving prognostication, and assessing response to treatment as a surrogate for therapeutic benefit. The imaging reported in the context of mesothelioma typically includes computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans; these scans may be acquired during initial tumor diagnosis and staging, treatment response assessment, or patient surveillance, depending on the clinical question being asked. Optical imaging, using electromagnetic radiation in (or near) the visible light region of the spectrum, has been an active area of research for a wide range of medical applications [5] and is now being applied in the intraoperative setting for mesothelioma. Initial results indicate the potential for optical imaging to aid surgeons in their attempt to achieve a macroscopic complete resection.

The advancement of MRI for the benefit of mesothelioma patients continues to attract the attention of clinical investigators. Tumor contrast enhancement in MRI has long provided information about tumor vascularity, but new evidence suggests that the clinically conventional time delay between contrast injection and initiation of image acquisition might be too short for optimal assessment of mesothelioma. Juxtaposed with the potential need for longer delay times in standard MRI is a perfusion-based MRI technique designed to capture *early* contrast-enhancement features of the pleura that might be characteristic of early-stage mesothelioma, thus enabling a possible tumor detection role for MRI in this setting. MRI also offers functional imaging capabilities through diffusion-weighted imaging (DWI), which is being used to compute tumor volume and parameters of the tumor pixel-value histogram in an attempt to differentiate between patients with long- and short-term overall survival.

Imaging of tumor perfusion with computed tomography (CT) has become routine for some tumors; however, dynamic contrast-enhanced computed tomography (DCE-CT) has only recently been applied to mesothelioma [3]. Investigation of this imaging technique continues with the computation of hemodynamic parameters designed to capture physiologic changes in the tumor that are not necessarily reflected in tumor thickness change. The ultimate goal of this approach is an earlier assessment of pharmacodynamic endpoints and tumor response.

The potential role of image-based mesothelioma tumor volume in staging [6], the impact of volume on tumor response assessment [7–10], the correlation between tumor volume and patient survival [7–9,11], and the computerized extraction of mesothelioma tumor volume from CT scans [12] have all been the subject of recent investigation. Mesothelioma, however, presents a unique challenge for image-based tumor volumetrics; before mesothelioma tumor volume can be adopted for clinical application, it is essential to understand the correlation between tumor volume derived from images and the actual, physical tumor bulk that the images represent. Although physical tumor weight and volume have been shown to relate to patient survival [13], the reliability of extrapolating physical tumor volume from imaging has been questioned in previous studies [14]. Ongoing work in this regard continues to demonstrate only moderate correlation between image-based mesothelioma tumor volume and both the physical weight of the resected tumor and the pathologic T stage.

Objective radiologic response rate is the key efficacy endpoint in early development of new therapies. In phase II trials, response rate is often the primary study endpoint, and even in randomised phase III studies, response rate may be used as a correlative measure of efficacy. The morphology and growth characteristics of mesothelioma, however, differ from many other solid tumors in that the disease often forms a rind around the pleural cavity, with a sheet-like rather than spherical growth pattern. The RECIST (Response Evaluation Criteria in Solid Tumors) guidelines [15] use unidimensional measurements, which are ostensibly better suited for measurement of mesothelioma rind thickness; however, RECIST requires measurement of a tumor's longest diameter, and the underlying assumption is of a spherical growth pattern. The poor suitability of RECIST for measurement of mesothelioma and discrepancies between patient response based on RECIST and the earlier World Health Organization (WHO) guidelines [16] were soon revealed [17,18]. Modified RECIST for mesothelioma [19] was developed to address this deficiency. Discrepancies in the practical implementation of modified RECIST, however, have led to confusion and inconsistent approaches to tumor measurement and response assessment. This concern, along with the update to RECIST that was provided by RECIST 1.1 [20], indicate that a revision to modified RECIST is needed.

2. Imaging with indocyanine green for intraoperative detection of residual disease

A subset of patients with epithelioid malignant mesothelioma limited to the hemithorax may benefit from an approach that includes surgery involving extrapleural pneumonectomy or a lung-preserving operation such as pleurectomy/decortication [21]. Regardless of the approach, the goal of surgery is macroscopic complete resection. Despite aggressive multimodality therapy for "resectable" mesothelioma, prognosis remains poor, potentially in part due to residual disease. At the conclusion of surgery, it can be challenging to discriminate residual disease from scar and normal tissue [22]. Keating and colleagues used near-infrared (NIR) molecular imaging using indocyanine green (ICG) for the intraoperative localization of tumors, lymph nodes, and metastases [23–25] and, more specifically, for the evaluation of margins following mediastinal tumor resection [26]. ICG is a non-targeted, near-