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Review

Imaging in pleural mesothelioma: A review of the 12th International Conference of the International Mesothelioma Interest Group

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ABSTRACT

Imaging of malignant pleural mesothelioma is essential to patient management, prognostication, and response assessment. From animal models to clinical trials, the gamut of research activities and clinical standards relies on imaging to provide information on lesion morphology and the growing number of physiologic characteristics amenable to capture through imaging techniques. The complex morphology, growth pattern, and biological mechanisms of mesothelioma, however, present challenges for image acquisition and interpretation. Nevertheless, novel approaches to image acquisition and subsequent image analysis have expanded the opportunities for (as well as the need for) imaging in this disease. This paper summarizes the imaging-based research presented orally at the 2014 International Conference of the International Mesothelioma Interest Group (iMig) in Cape Town, South Africa, October 2014. Presented topics include the imaging of hypoxia in a murine model through positron emission tomography (PET), the use of diffusion-weighted magnetic resonance imaging (MRI) to assess the histologic composition of biphasic mesothelioma and to assess early response to chemotherapy, the correlation of CT-based tumor volume with the volume of the post-surgical tumor specimen, the development of volumetric tumor response criteria, and pre-treatment tumor volume growth considerations for tumor response assessment.

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1. Introduction

The International Mesothelioma Interest Group (iMig) (www.imig.org) is a community of physicians, basic researchers, clinician-scientists, care providers, and social advocates that is engaged in understanding the underlying genetics, molecular mechanisms, proteomics, and epidemiologic factors associated with mesothelioma. The goal of those involved with iMig is to improve patient survival and quality of life through the development of new treatment strategies, enhancements to the efficacy of current therapeutic options, definitions of best practices, and supportive services. From animal models to clinical trials, the gamut of research activities and clinical standards relies on imaging to provide information on lesion morphology and a growing number of physiologic characteristics amenable to being captured through imaging techniques. This paper summarizes imaging-based research presented at the 2014 International Conference of the International Mesothelioma Interest Group in Cape Town, South Africa, October 2014.

Preclinical models are an important mechanism for the development and validation of advanced imaging methods. These models also have utility for imaging approaches that have been implemented in clinical practice but for which further understanding of the biological mechanisms of action and the means through which these mechanisms may be manipulated for prognostic (or, potentially, therapeutic) advantage is desired. The imaging of hypoxic regions within mesothelioma tumor through 18F-misonidazole (F-MISO) positron emission tomography (PET) has been the subject

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of previously reported clinical trials. Now, a preclinical model of hypoxia in mesothelioma is being investigated to test the effects of hypoxia modulation as a means to direct clinical interventions.

Functional imaging such as PET is generally considered an adjunct to imaging modalities that capture tumor structure and changes in that structure as a means to assess tumor progression or response to therapy. Although structural imaging for mesothelioma is dominated by computed tomography (CT), magnetic resonance (MR) imaging has been used as a complementary modality due to its improved soft-tissue contrast, more reliable depiction of chest wall and diaphragmatic extension of mesothelioma tumor, and ability to distinguish pleural effusion from tumor [1]. MR also offers functional imaging capabilities through diffusion-weighted imaging (DWI), which is an MR image-acquisition protocol that captures water molecule diffusion within tissues; since cell membranes restrict water diffusion, a quantity known as the apparent diffusion coefficient (ADC) may be computed from DWI data to represent tissue cellularity, which has been used to differentiate epithelioid and sarcomatoid histologic subtypes in mesothelioma [2]. The ability of the ADC to identify the predominant histologic subtype in *biphasic* MPM tumors is being investigated with prognostic implications. DWI is further being investigated to separate long- and short-term survivors as a means of assessing early response to therapy.

The role of tumor volume in staging, the impact of volume on tumor response assessment, the correlation between tumor volume and patient survival, and computerized extraction of these volumes have been investigated for a range of tumors. Despite the demonstrated potential benefits of tumor volume for these tasks, volume has not been generally adopted in clinical practice, predominantly due to the practical burden involved in the computation of image-based volume. Mesothelioma, with its unique morphology and complex growth pattern, presents an even greater challenge for tumor volumetrics derived from images. Work is being done to evaluate the validity of image-based mesothelioma tumor volume against the physical volume of the tumor ex vivo in surgical specimens.

Change in mesothelioma tumor volume is under investigation as an indicator of tumor progression or response to therapy. Current tumor response classification categories defined by modified RECIST (response evaluation criteria in solid tumors) are based on relative changes in linear tumor thickness measurements on CT scans [3]. The possibility that tumor volume may eventually replace linear measurements necessitates the development of response criteria specific to changes in volume. Optimized survival-based mesothelioma volumetric response criteria are being developed to meet this anticipated future need. Another on-going investigation of tumor volume change for response assessment involves the comparison of tumor volume growth rate during a patient's pre-treatment period and during the patient's initial on-treatment period. This study of "change in tumor volume change" between time periods aims to discern a possible therapeutic effect even in the absence of substantial tumor volume regression when the alternative would have been a continued increase in tumor burden at the natural growth rate.

2. Imaging hypoxia in a murine model

Hypoxia is common in solid tumor masses. In normal tissue, oxygen supply is matched to metabolic requirements; in large masses, however, the oxygen consumption of tumor and stroma may exceed the ability of the vasculature to supply oxygen, resulting in hypoxic areas. Factors contributing to tumor hypoxia in mesothelioma may include abnormalities in tumor vasculature, diffusion distance from the vascular supply, anemia from disease or treatment, and respiratory hypoxia [4]. Hypoxia has long been recognized as a predictor of poor treatment outcomes, in particular for radiotherapy. Early work used invasive techniques such as implantable oxygen electrodes to demonstrate hypoxia [5,6], with 50–60% of solid tumors shown to contain hypoxic regions ($pO_2 \leq 5$ mmHg); however, the invasive nature of these measurement techniques prevented widespread clinical use. More recently, non-invasive imaging with nitroimidazole agents has almost entirely supplanted invasive measurement techniques and is more tractable for clinical application and murine studies.

F-MISO is a PET tracer that allows non-invasive estimation of the level, intensity, and regional variation of hypoxia in solid tumors [7]. F-MISO enters cells by passive diffusion, where it is reduced by nitroreductase enzymes. In normally oxygenated cells, the parent compound is quickly regenerated by re-oxidation, and metabolites do not accumulate; however, in hypoxic cells, low oxygen partial pressure prevents re-oxidation of F-MISO metabolites, resulting in tracer accumulation [8]. Importantly, F-MISO only accumulates in hypoxic cells with functional nitroreductase enzymes, so accumulation in necrotic cells is not possible.

A previous pilot clinical study of F-MISO PET-CT imaging in mesothelioma demonstrated detectable hypoxia in bulky pleural masses. The presence of hypoxia in bulky tumor masses may be clinically important in mesothelioma, as these areas, often of painful chest wall invasion or bulky compressive lymphadenopathy, are the most likely to require palliative radiotherapy. This finding raised the hypothesis that hypoxia in bulky tumor masses may be a potential determinant of radioresistance and chemoresistance in mesothelioma. Robinson, Nowak, and colleagues developed a preclinical model of hypoxia in mesothelioma to test the effects of hypoxia modulation with the future aim of directing clinical interventions.

AB1 mesothelioma tumor cells were implanted into the flank of BALB/c mice. Subcutaneous AB1 tumor has characteristics similar to human mesothelioma and forms roughly spherical flank masses (Fig. 1). The route and timing of F-MISO injection and scanning protocols were optimized, with the optimal protocol comprising intravenous injection of F-MISO with a 90-min uptake phase before imaging when tumors measured at least 5×5 mm. F-MISO uptake signifying central hypoxia could be readily visualized and quantified and subsequently manipulated. Three hypoxia modulation interventions were tested: nitroglycerine, O_2 therapy, and tirapazamine. The presence of hypoxia was confirmed using the immunohistochemical hypoxyprobe assay, in which mice were injected antemortem with hypoxyprobe and tumor tissues were then examined postmortem for staining indicative of hypoxia [9].

Prominent physiologic intra-abdominal F-MISO activity was seen with both intraperitoneal and intravenous administration routes. Mild F-MISO activity was detected in tumors of 5–7 mm, with reliable hypoxia seen in larger tumors (7–10 mm diameter). Preliminary results of the modulation experiments showed a visual reduction in F-MISO intensity compared with untreated mice following administration of intraperitoneal nitroglycerine. A reduction in F-MISO activity of borderline statistical significance was measured semi-quantitatively after treatment with hyperbaric oxygen conditions. No significant change in hypoxia was seen with tirapazamine, as expected, given that tirapazamine is a radiation sensitizer in hypoxic conditions but does not modulate the presence of hypoxia.

In summary, a preclinical model of hypoxia imaging in mesothelioma has been developed using F-MISO PET-CT in subcutaneous flank tumors. This model may be useful to test potential hypoxia modulation strategies before clinical application, which may have a future role in radiosensitisation during palliative treatment of bulky chest wall masses.

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