ORIGINAL ARTICLE

North American Multicenter Volumetric CT Study for Clinical Staging of Malignant Pleural Mesothelioma: Feasibility and Logistics of Setting Up a Quantitative Imaging Study

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Received 29 January 2016; revised 30 March 2016; accepted 7 April 2016
Available online - 12 May 2016

ABSTRACT

Background: Clinical tumor (T), node, and metastasis staging is based on a qualitative assessment of features defining T descriptors and has been found to be suboptimal for predicting the prognosis of patients with malignant pleural mesothelioma (MPM). Previous work suggests that volumetric computed tomography (VolCT) is prognostic and, if found practical and reproducible, could improve clinical MPM classification.

Methods: Six North American institutions electronically submitted clinical, pathologic, and imaging data on patients with stages I to IV MPM to an established multicenter database and biostatistical center. Two reference radiologists blinded to clinical data independently reviewed the scans; calculated clinical T, node, and metastasis stage by standard criteria; performed semiautomated tumor volume calculations using commercially available software; and submitted the findings to the biostatistical center. Study end points included the feasibility of a multi-institutional VolCT network, concordance of independent VolCT assessments, and association of VolCT with pathological T classification.

Results: Of 164 submitted cases, 129 were evaluated by both reference radiologists. Discordant clinical staging of most cases confirmed the inadequacy of current criteria. The overall correlation between VolCT estimates was good (Spearman correlation 0.822), but some were significantly discordant. Root cause analysis of the most discordant estimates identified four common sources of variability. Despite these limitations, median tumor volume estimates were similar within subgroups of cases representing each pathological

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**See Appendix for the members of the Malignant Mesothelioma Volumetric Computed Tomography Study Group.*

Disclosure: Dr. Rusch reports grants from the Mesothelioma Applied Research Foundation during the conduct of the study. Dr. Gill reports grants from the Mesothelioma Applied Research Foundation during the conduct of the study. Dr. Armato III reports grants from the Mesothelioma Applied Research Foundation and grants from Cancer Research and Biostatistics during the conduct of the study, as well as personal fees from Aduro Biotech, Inc., outside the submitted work. In addition, Dr. Armato III has patents issued (U.S. Patent No. 6,577,752 and No. 6,813,375). The remaining authors declare no conflict of interest.

Presented at the 12th International Mesothelioma Interest Group Conference, Cape Town, South Africa, 21-24 October, 2014.

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ISSN: 1556-0864
http://dx.doi.org/10.1016/j.jtho.2016.04.027

T descriptor and increased monotonically for each reference radiologist with increasing pathological T status.

Conclusions: The good correlation between VolCT estimates obtained for most cases reviewed by two independent radiologists and qualitative association of VolCT with pathological T status combine to encourage further study. The identified sources of user error will inform design of a follow-up prospective trial to more formally assess interobserver variability of VolCT and its potential contribution to clinical MPM staging.

Key words: MPM; Mesothelioma; Tumor volume; Volumetric CT; Clinical staging

Introduction

Staging of solid tumors using tumor, node, and metastasis (TNM) criteria is important for estimating prognosis, selecting among available treatment strategies, and stratifying patients for clinical trials of new therapies. Pathological stage (PS), determined by microscopic analysis of tissue or cytologic specimens, provides an accepted standard. Clinical staging (CS) using one or more imaging modalities is often used to predict T, N, and M status before confirmation by invasive procedures. For patients with malignant pleural mesothelioma (MPM), CS does not accurately predict either PS or prognosis, limiting its utility for disease management and suggesting the need for revision of CS methodologies and/or criteria.[1]

T classification of many solid tumors is based on quantitative assessment of tumor size combined with binary determination of direct invasion into specific tissue planes or adjacent structures. Tumor size in lung cancer and other tumors can be reliably measured in one or more planes owing to round or spheroidal structure; however, the diffuse and irregular anatomy of MPM precludes consistent single- or two-dimensional measurement of tumor size,[2–4] which is therefore not included among T classification criteria. Clinical T classification of MPM is instead based entirely on qualitative binary assessment of tumor invasion into adjacent anatomical structures at a level of resolution insufficient for making such predictions accurately or consistently.

Tumor volume derived from volumetric computed tomography (VolCT) scans may represent a practical means of quantitatively assessing tumor burden in MPM. Two decades ago, Pass et al. showed that VolCT correlated with overall survival among patients with MPM. At that time, however, it required specialized equipment and was too labor-intensive and time-consuming to be clinically practical.[5] Technological advances and improvements in radiology workflow with the availability of hybrid workstations now allow for efficient calculation of tumor volume at the time of reporting. A recent study using this technology confirmed a strong association of VolCT with overall survival, controlling for other prognostic factors, in patients with epithelioid MPM.[6]

In preparation for designing an international study to evaluate VolCT in the context of TNM staging, a pilot study was undertaken to determine parameters required to optimize reproducibility of volume estimates. A North American multicenter network was established to electronically acquire and de-identify preoperative CT scans of retrospective MPM cases and distribute them for blind analysis by two reference radiologists. The objectives were to compare their independent volume estimates and identify logistical, technical, and disease, and observer-related parameters associated with the most discrepant estimates. Data obtained from this pilot will assist in determining optimal methods of assessing interobserver variability of VolCT. The pitfalls identified and lessons learned will help refine the current radiological methodology, inform the design of the international study, and guide training and credentialing of participating radiologists in the use of image analysis tools.

Materials and Methods

The North American Multicenter Volumetric CT Study for Clinical Staging of Malignant Pleural Mesothelioma is a prospective, multi-institutional feasibility study. Central standard TNM staging evaluation and volumetric analysis were performed using de-identified CT scans submitted by institutions already participating in the International International Association for the Study of Lung Cancer (IASLC)/International Mesothelioma Interest Group (IMIG) database for MPM project.[1] The sites submitting scans and data had institutional review board approval from their institutions and appropriate data transfer agreements were in place. An institutional review board waiver was obtained at the sites analyzing the scans.

Figure 1 depicts the flow of scans and data among the submitting sites, the biostatistical center (BC), and the reference radiologists. The International IASLC/IMIG database for MPM comprises retrospective cases submitted by members of the IASLC and IMIG. Detailed information was obtained, including clinical and pathological tumor staging, patient history, demographics, treatment, and outcome of patients with clinical stage I to IV MPM who were deemed candidates for surgical resection with intent to treat. The database was formed with the intent of recommending revisions to the current Union internationale contre le cancer and American Joint Committee on Cancer (AJCC) staging system for MPM. A subset of cases that were submitted from six participating North