

Automated Tracking of Quantitative Assessments of Tumor Burden in Clinical Trials¹

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Abstract

There are two key challenges hindering effective use of quantitative assessment of imaging in cancer response assessment: 1) Radiologists usually describe the cancer lesions in imaging studies subjectively and sometimes ambiguously, and 2) it is difficult to repurpose imaging data, because lesion measurements are not recorded in a format that permits machine interpretation and interoperability. We have developed a freely available software platform on the basis of open standards, the electronic Physician Annotation Device (ePAD), to tackle these challenges in two ways. First, ePAD facilitates the radiologist in carrying out cancer lesion measurements as part of routine clinical trial image interpretation workflow. Second, ePAD records all image measurements and annotations in a data format that permits repurposing image data for analyses of alternative imaging biomarkers of treatment response. To determine the impact of ePAD on radiologist efficiency in quantitative assessment of imaging studies, a radiologist evaluated computed tomography (CT) imaging studies from 20 subjects having one baseline and three consecutive follow-up imaging studies with and without ePAD. The radiologist made measurements of target lesions in each imaging study using Response Evaluation Criteria in Solid Tumors 1.1 criteria, initially with the aid of ePAD, and then after a 30-day washout period, the exams were reread without ePAD. The mean total time required to review the images and summarize measurements of target lesions was 15% ($P < .039$) shorter using ePAD than without using this tool. In addition, it was possible to rapidly reanalyze the images to explore lesion cross-sectional area as an alternative imaging biomarker to linear measure. We conclude that ePAD appears promising to potentially improve reader efficiency for quantitative assessment of CT examinations, and it may enable discovery of future novel image-based biomarkers of cancer treatment response.

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Introduction

Assessing cancer treatment response in both research and clinical practice depends critically on the results of imaging, which provides detailed information about tumor burden. Objective assessment of cancer burden on imaging studies is the foundation of treatment response assessment in cancer clinical trials. Lesion measurements on radiologic images enable objective assessment of changes in the tumor burden, and they can potentially predict patient outcomes earlier and more accurately than serologic or clinical parameters [1–5]. For most response criteria, such as the Response Evaluation Criteria in Solid Tumors (RECIST) [6–8], Cheson [9,10], and Rano

[11], lesion measurements are made in a selected set of cancer lesions (“target lesions”). A calculated value derived from target lesions, such as the sum of the linear dimension (SLD) of target lesions, is

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produced to provide a quantitative imaging biomarker that is followed on longitudinal imaging to evaluate cancer treatment response. Such linear measurements are the most widely used radiologic method of measuring tumor response in clinical trials supporting drug applications to the US Food and Drug Administration to document response in clinical trials [12,13]. Though there is controversy about whether simple linear measures are the best proxy for tumor activity and treatment response [14–19] and alternative criteria have been proposed (even current criteria have been recently modified [8,20,21]), some form of quantitative assessment of radiologic imaging is critical for deciding the degree to which a patient has responded to treatment in clinical trials. The benefit of quantitative assessment of cancer lesions in patients with cancer is that it provides a clear-cut way of categorizing patients into categories of disease response, and it reduces variation of such assessments in practice.

Although the current response criteria rely primarily on linear measurement of selected cancer lesions, there is much interest in the emerging field of “quantitative imaging” to provide better objective, reproducible assessments of image features (“imaging biomarkers”) of cancer treatment response than the current imaging criteria. Novel quantitative imaging biomarkers have the potential of detecting response to new treatments with great sensitivity so that incremental benefits provided by new cancer treatments are not overlooked. Quantitative imaging techniques provide information about the functional and molecular characteristics of cancer that may be more sensitive to changes during treatment than linear size. Such image-based characteristics of tumor burden may be better surrogates for clinical benefit and improve assessment of the therapeutic response to treatment compared with current criteria.

However, there are presently substantial challenges that thwart the widespread, routine use of current and novel quantitative image-based assessment of cancer. The first challenge is that radiology reports do not sufficiently describe target lesions and measurements. In a recent study, the majority of radiology reports and image annotations were found to be insufficient to apply the RECIST criteria; radiology report and image annotation data were sufficient to calculate the quantitative response rate in only 26% of the studies [22]. Radiologists usually provide only qualitative descriptions of changes in cancer lesion size (i.e., “increasing” or “decreasing”), and when lesion measurements are made, they are often inconsistent across imaging studies (different radiologists usually interpret each imaging study during patient treatment). Oncologists thus find that the qualitative information they receive in radiology reports is insufficient to assess cancer response [23,24], and they frequently ask radiologists to addend the imaging report to include lesion measurements [25]. Better practices in reporting cancer lesion measurements have been advocated [24,26]. Although nearly all radiologists acknowledge that tumor measurements impact patient care [25], they are reluctant to perform these assessments [25] because of the effort entailed; dictating tumor measurements slows their workflow [25]. In addition, radiologists believe that qualitative assessment of tumor growth is sufficient [24,25]. The lack of complete and consistent measurement of lesions makes it difficult for oncologists to assess treatment response on the basis of the reported imaging results; they must review the computed tomography (CT) images themselves to locate the target lesions, and they must often measure the lesions themselves.

A second challenge is that there is poor coordination and communication between oncologists and radiologists with respect to target

lesions and their assessments (Figure 1). Oncologists or data managers record the target lesions and measurements in flow sheets that are usually not communicated to radiologists, who interpret each case as part of their routine workflow. Thus, the radiologist who happens to interpret the scans from a patient enrolled in a clinical trial may not necessarily describe and make quantitative measurements on all the lesions being tracked in the trial. Moreover, radiology results are recorded in a text report and in graphical annotations on the images, which are an inefficient (and sometimes unclear or ambiguous) way in which to communicate the quantitative imaging information. We recently found that radiology reporting is often insufficient for oncologists to apply response criteria in the clinical trial setting [27]. Radiologists do not consistently report quantitative metrics, nor they consistently identify the target lesions that are being tracked by the oncologist for response evaluation. Thus, tools that inform radiologists, during image interpretation, as to which lesions the oncologists are tracking and which measurements must be made are desperately needed. In turn, radiologists need to make oncologists aware of any new relevant observations that may need to be tracked in subsequent scans.

A third challenge is that it is difficult to mine previously acquired imaging data sets to discover alternative quantitative imaging biomarkers of cancer treatment response. Enabling such research is important because there is great interest in developing improved criteria of response assessment that exploit the rich information in quantitative imaging data. The current response criteria have limitations [8,15], as they are based only on tumor shrinkage. Whereas tumor shrinkage is the hallmark of most effective cytotoxic treatments [28], it is not always observed for noncytotoxic agents that, nonetheless, demonstrate improvements in progression-free survival [29,30]. Newer agents that are being developed and entering clinical trials may work through mechanisms unlikely to cause regression in tumor size, and some treatments can provide significant benefit to patient survival without showing substantial tumor regression [31,32].

Multiple research centers have established the Quantitative Imaging Network to develop new quantitative imaging approaches for assessing response to cancer therapies, and the National Institutes of Health Clinical Trials Working Group recommended improving tools and procedures for data capture and data sharing to catalyze this research and to enable an integrated national cancer clinical trial network [33]. Studies by Quantitative Imaging Network and other researchers to correlate quantitative imaging biomarkers with clinical outcomes are limited by the lack of tools to record the objective information derived from imaging studies (collectively referred to as *metadata*) in standard formats consistently across clinical trials. Radiologists report the results of imaging procedures in unstructured image annotations and narrative text reports. Their measurements and annotations on images that demarcate cancer lesions are not recorded in a format that enables them to be reprocessed easily. The latter are usually recorded in the form of graphical overlays, and researchers usually must manually reprocess all images using their research-specific software.

A recently developed imaging metadata standard, called Annotation and Image Markup (AIM) [34,35] from the Cancer Biomedical Informatics Grid Imaging Workspace project [36,37], provides a standardized format for recording quantitative and qualitative image information; however, few tools adopting AIM have been developed and deployed to enable quantitative imaging in clinical trials—a key goal of the work we undertook.

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