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Automated Tracking of Quantitative Assessments of Tumor Burden in Clinical Trials[1]

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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.

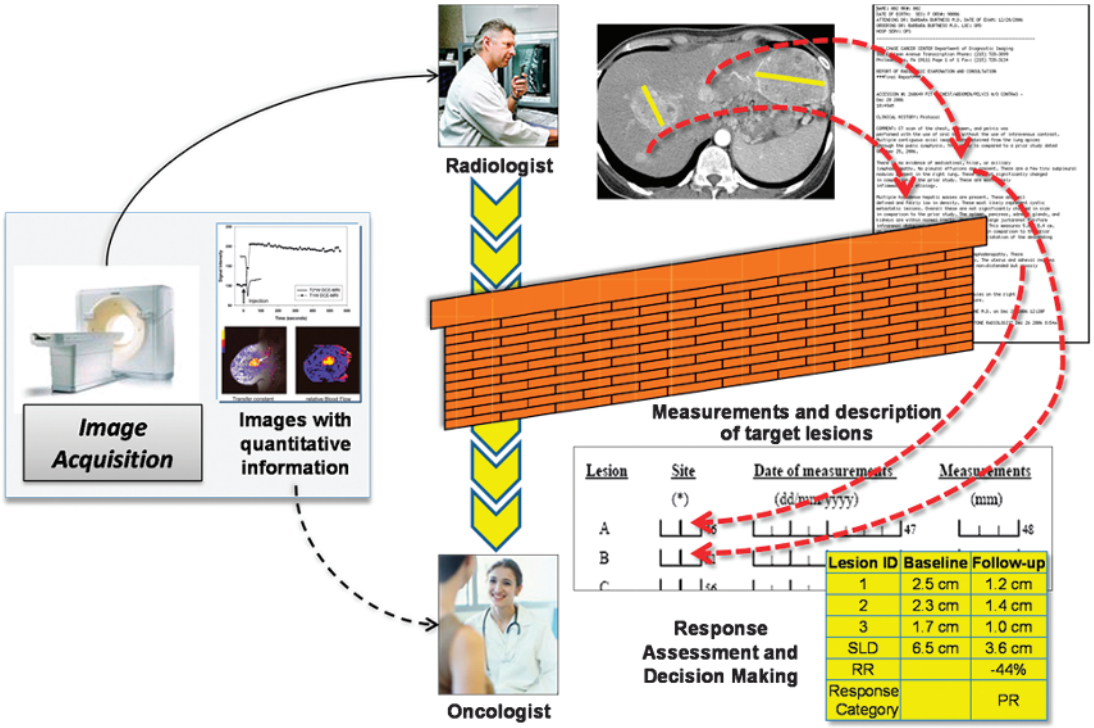


Figure 1. Challenges in collecting, recording, coordinating, and communicating quantitative imaging information in cancer research. Radiologists interpret images from oncology trials as part of the routine radiology workflow, recording their observations both in reports and as image annotations (top). Oncologists acquire quantitative information from the radiology report (bottom), which may not provide the necessary information about each measurable lesion as an image annotation or specific description in the report (dotted arrows, top). It can be difficult for the oncologist to assess all the quantitative information from the radiology report needed to apply criteria for response assessment (dashed arrows, bottom).

In this manuscript, we describe our work to produce a software tool that can be incorporated into the clinical trial imaging viewing workflow and that could facilitate lesion measurement. This tool could meet the aforementioned challenges, because radiologists generally embrace image analysis tools if using them is intuitive and quick [23], particularly if such tools could calculate and report tumor measurements with minimal mouse clicks [25]. At the same time, our tool will help the oncologists' workflow by summarizing lesion measurements and longitudinal changes in tumor burden in tabular and graphical formats, enabling them to quickly assess treatment response and to make patient management decisions.

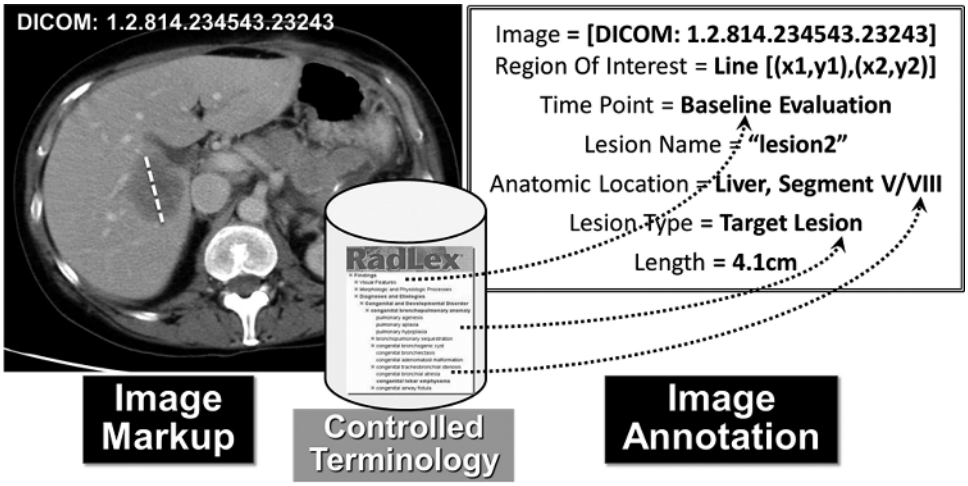


Figure 2. AIM. Image annotations convey the regions drawn on images to measure lesions, the anatomic location of lesions, their type (target or nontarget), and other data as shown.

Materials and Methods

We first describe the design and implementation of the electronic Physician Annotation Device (ePAD; http://epad.stanford.edu). We describe how it uses AIM to store image measurements to enable interoperability, and we outline its core components and features. We then describe a pilot evaluation study we carried out to investigate the potential impact of ePAD on the radiology interpretation workflow.

Annotation and Image Markup

A primary design consideration in creating ePAD was the storage of image annotations and markups. Annotations describe the results of image interpretation. For cancer studies, these annotations include the imaging time point, the name, type, anatomic location, and measurement of target lesions, the coordinates of the line drawn to make the measurements, and the identifier of the image measured. Image markups are the visual representation of the annotations (e.g., a line drawn on the image indicating a lesion measurement) (Figure 2).

We previously developed the AIM data model as part of an effort by the cancer Biomedical Informatics Grid project of the National Cancer Institute (Bethesda, MD) [34,35,38–41]. AIM is an information model for storing and sharing image metadata [34,40,41]. It focuses on the metadata needed to support cancer research, such as lesion identification, location, size measurements, regions of interest, radiologist observations, anatomic locations of abnormalities, calculations, and qualitative/quantitative image features. AIM annotations are stored in a standardized extensible markup language (XML) file format. The AIM format enables interoperability and repurposing of imaging data, because the image results necessary for quantitative imaging are accessible in machine-interpretable format [42]. AIM annotations permit useful queries that would not be possible without such explicit representation, such as "find all images that contain a target lesion and get the measurements of those lesions." AIM also enables linking of measurements and other image results directly to the source image regions from which they were derived.

AIM has gained substantial traction in the academic and commercial sectors. A number of diverse research projects have embraced and have been enabled by AIM [43–54]. An increasing number of tools are supporting AIM, including open-source projects such as OsiriX [55], ClearCanvas [56,57], and Slicer [58–60]. There are also several commercial applications using AIM that are in development [61,62]. Accordingly, we designed ePAD to save the results of quantitative imaging studies in AIM format.

ePAD Platform

The ePAD platform comprises five main components (Figure 3): 1) the ePAD viewer, a Web-based image viewer and AIM annotation

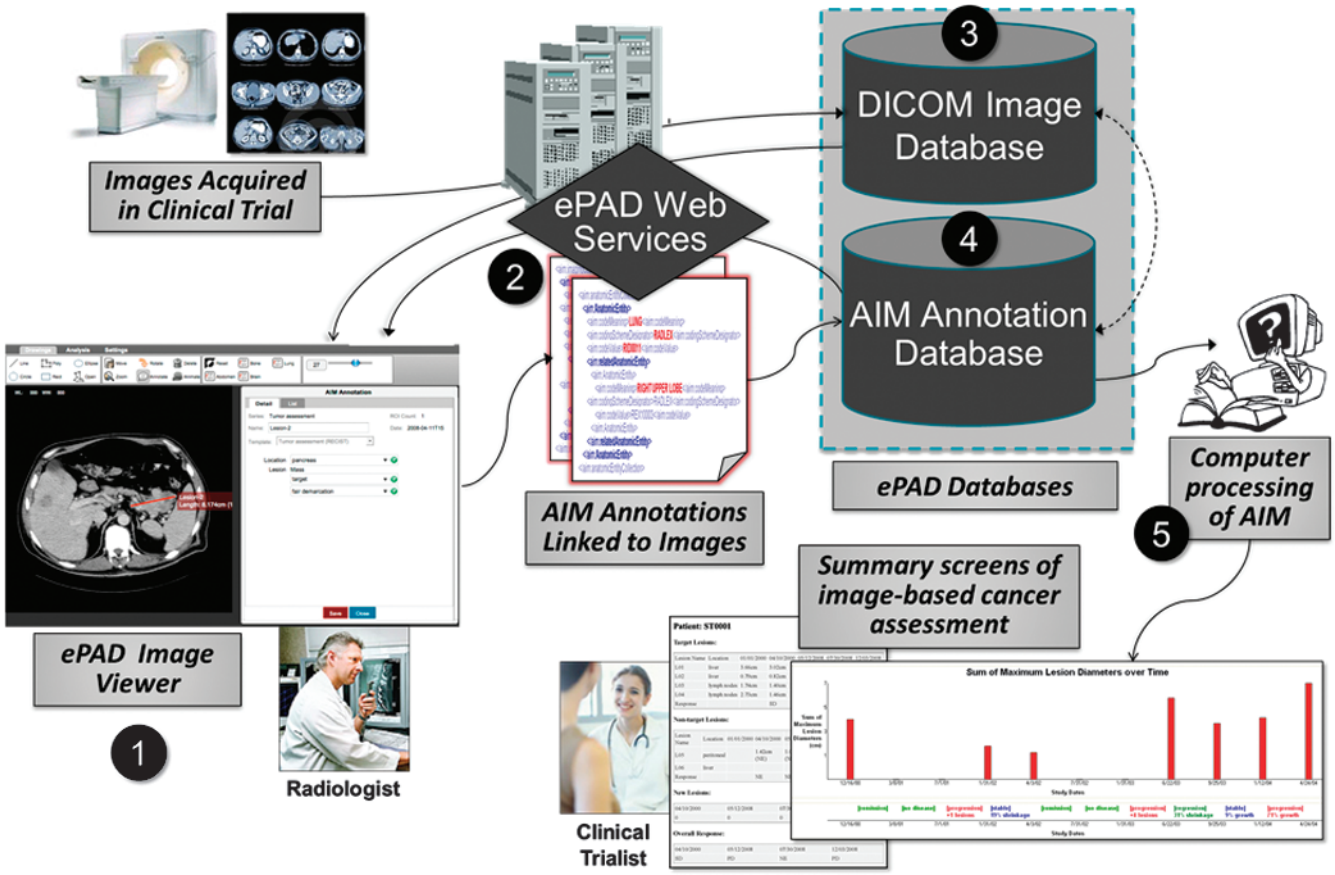


Figure 3. The ePAD platform. (1) Images are acquired and stored in the hospital PACS, (2) the radiologist uses ePAD to review the images and to make measurements on cancer lesions, (3) the images are stored in ePAD's DICOM database, (4) the image measurements (saved as AIM XML in ePAD) with links to the images are stored by the AIM annotation database, and (5) a variety of software applications can use the AIM annotation database to access the image metadata for different purposes, such as listing the lesion measurements or generating a summary of patient response assessment.

editor that provides a graphical user interface for viewing and recording image interpretations, measurements, and other metadata (Figure 4), 2) the ePAD Web Services application, which provides a programming interface to the ePAD platform resources, 3) an image database, 4) an AIM annotation database, and 5) analytical plugin modules for processing image annotations.

ePAD viewer. The ePAD viewer is implemented as a "rich Web application," a software program that runs in a Web browser and provides the core features to permit users to view images and to collect and summarize lesion measurements and other aspects of the results of imaging studies. The ePAD viewer was written using HTML5 [63], Java, JavaScript, and the Google Web Toolkit (http://www.gwtproject.org), which provide libraries and capabilities for creating self-contained applications that can be run entirely within the Web browser. HTML5, in particular, provides the Canvas object, which supports image rendering with all the customary controls for image display (e.g., zooming, panning, and window/level) within the Web browser, a core need for the ePAD viewer. Drawing and editing image annotations are accomplished with HTML5 Scalable Vector Graphics.

Two additional design goals of the ePAD viewer were to 1) to capture the minimum information needed to create image annotations, ensuring they are complete and 2) to check for errors in user input. The ePAD viewer ensures that the following minimum information necessary to create a meaningful quantitative imaging report are collected from the radiologist: the lesion name, the lesion type (target, nontarget, new lesion, or resolved lesion) and the anatomic location of the lesion, and the study time point (baseline or follow-up). The ePAD viewer automatically labels each lesion with a name (e.g., "Lesion1") to enable unambiguous determination of the same lesion on serial imaging studies [44]. The default label name can be overridden by the user. To ensure that the minimum information is collected, ePAD uses a mechanism called "AIM templates" [64]. AIM templates specify an electronic data collection form, analogous to an electronic case report form, containing data elements whose values are specified by the user while viewing the images. The data elements in AIM templates specify the type(s) of valid values, cardinality, and whether values are required. Each template is used to ensure that the minimal required set of data elements is collected for a particular type of annotation.

A template for recording image metadata needed for tumor burden assessment in the RECIST 1.1 is shown in Figure 4. In addition to the preceding minimal necessary information, this template captures (automatically without user intervention) the coordinates of lines drawn on the image to measure lesions and lesion size.

To provide error-checking capability, the ePAD viewer leverages the ability of AIM templates to specify constrained choices of controlled terms [40]. All answer choices in ePAD templates are controlled terminology lists provided by the RadLex ontology [65]. The ePAD viewer prompts the user if certain values in the templates are inconsistent or incomplete [40]. Text entered into ePAD's templates is matched to controlled terminologies such as RadLex to prevent spelling errors and to ensure that legal terms are recorded in AIM documents. This ensures compliance with data standards and interoperability with other image metadata collected in cancer research. It also helps to facilitate comparability of radiology results reported using the templates.

The ePAD viewer also provides a summary panel of annotations designed to streamline the time-consuming task of the radiologist reviewing the numerous prior measurements and images in prior

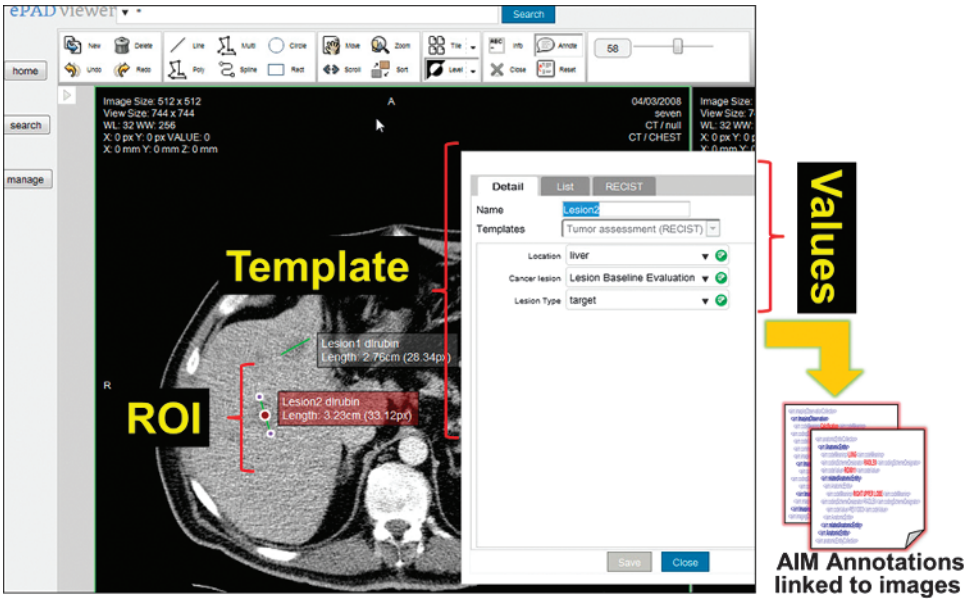


Figure 4. ePAD user interface and annotation template. The ePAD Web-based tool allows users to create cancer lesion measurements as part of routine image-viewing/interpretation workflow. A template window captures additional information needed for quantitative lesion assessment (the template shown is for capturing information required for RECIST criteria). The user has drawn a line to measure a lesion in the liver seen in a CT image (left), designated it as a target lesion, and indicated that it is identified as "Lesion2" and that it is located in the liver (right). The user also has recorded that the image is from the baseline study. ePAD stores all of this information, in addition to the coordinates of the line drawn and the lesion measurement, in the AIM standard format, which can be later queried and analyzed computationally.

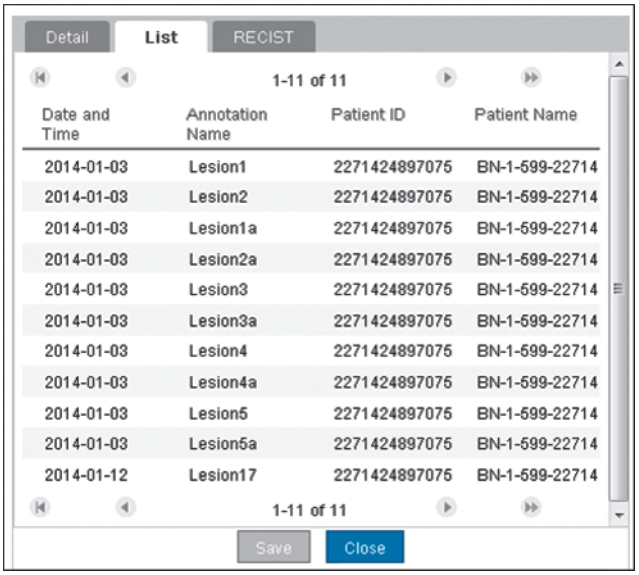


Figure 5. Annotation worklist view in ePAD. ePAD produces a "flow sheet" summary of target lesions that have been annotated using the tool to help guide the radiologist as to the image measurements already made and that need to be made.

studies to become aware of the lesions previously measured and that need to be measured on the current study. The ePAD viewer queries the AIM annotation database (described below) to summarize, for the radiologist, all the lesions from the prior exams in a summary table (Figure 5). In essence, this comprises a radiology worklist of the measurements needed to be made in each imaging study. It also links each measurement to the image from which it was obtained. When the radiologist clicks on a measurement, the corresponding image is retrieved, and the measurement is displayed as a graphical overlay.

ePAD Web Services. The ePAD viewer uses a set of Web services to provide functionalities requiring persistence of data or more heavy-duty processing than can be handled by a Web application, such as authenticating user credentials, retrieving image data from the image database (see below), storing and retrieving annotations, and invoking image calculation methods that are too time consuming to be performed within the client Web-based application. The ePAD Web Services were written using standard open-source Java Web application technologies.

The ePAD Web Services provide programmatic access to the image database and AIM annotation database (described below). The ePAD Web Services are hosted on a CentOS VMware virtual machine. A typical configuration has 100 GB of disk storage and 16 GB of random access memory (RAM), though more storage or RAM can be exploited if needed. The ePAD Web Services are typically hosted on a server that resides within an institution's firewall so that all traffic between the ePAD viewer and the ePAD Web Services reside within the institution's Intranet. Thus, users can use ePAD to evaluate image data containing protected health information, provided the network on which ePAD is hosted is secure. Another model for hosting ePAD is a centralized hosted version, which could provide publicly available images (e.g., those disseminated publicly in national databases) to build national databases of image annotations. The ePad platform supports both environments.

The ePAD Web Services are implemented as a set of RESTful Web services [66] that other applications use to access and modify the resources of the ePAD platform. Developers can use the ePAD Web Services to access annotations and images in their own applications or to provide extensions to the ePAD platform.

Image database. Medical images in Digital Image Communications in Medicine (DICOM) format are managed by an open-source Picture Archiving and Communication System (PACS) called dcm4chee [67]. This PACS contains a DICOM image receiver and a programming interface that permits the ePAD Web Services to manage imaging studies within ePAD (Figure 3). The advantages of using dcm4chee are interoperability with other open-source projects and its robust support for open standards, such as the Integrating Healthcare Enterprise [68]. The ePAD platform can alternatively use other types of PACS.

The DICOM image database supports the following two mechanisms for importing images into ePAD: direct upload (from the local computer workstation) and the "DICOM send" method from any DICOM-compliant image workstation (e.g., a commercial PACS). The concept of the DICOM image database is that of an "image cache," a temporary storage depot for images, which are kept sufficiently long for image display and annotation. Because AIM annotations reference DICOM identifiers and the latter are universally unique and persistent, deleting images from the DICOM image database does not inviolate the corresponding AIM files (which are stored in ePAD's AIM database). The AIM annotations can be displayed once again if the associated DICOM images are loaded into ePAD or some other AIM-compliant workstation.

A challenge with creating a Web-based image viewer such as ePAD is that DICOM images are typically large. CT studies typically have hundreds of DICOM images, and transmitting all of them from the dcm4chee database to the ePAD viewer would hamper performance significantly. We thus designed a lossless compressed Portable Networks Graphics (PNG) image object ("packed PNG") to convey the DICOM data in compressed format. This compression mechanism takes each 16-bit pixel in a DICOM image and packs it into a PNG color channel before returning it to the ePAD viewer, where it is unpacked. The packed PNGs provide a Web-friendly, lossless approach to compressing the DICOM data and significantly reduce the volume of data provided by the server. Using the PNG format is advantageous for Web display of DICOM images, because it allows for faster upload and browser caching of image data; if the image has already been loaded in the Web browser, it is retrieved from the browser's cache and not reloaded. The ePAD Web Services preprocess the DICOM files so that the packed PNG files are available when the user opens the ePAD viewer. The DICOM image database thus maintains two parallel image stores, the original DICOM images and the packed PNGs. The ePAD Web Services manage the packed PNGs, creating them when the DICOM database receives new images and deleting them when a DICOM study is deleted from the DICOM database.

To further speed image display performance, ePAD makes use of a feature of dcm4chee called the Web-Accessible DICOM Objects [69] protocol to retrieve lossy Joint Photographic Experts Group (JPG) images while the lossless packed PNGs are initially loading. Using this strategy, the image slices are scrollable quickly after the user first opens a study. If the user stops at a JPG image to start inspecting it in detail, that image is prioritized by the ePAD Web Services, which load its packed PNG and the corresponding packed

PNGs in its vicinity. The ePAD viewer clearly tells users when they are viewing lossy images by displaying a prominent "lossy" flag on the image.

AIM annotation database. As the user makes annotations on images, ePAD creates AIM files appropriate to the data entry template selected. All AIM annotations are stored in an XML database (eXist [70]). The ePAD Web Services manage annotations in the AIM annotation database using a programming interface called the AIM API (http://www.stanford.edu/group/qil/cgi-bin/mediawiki/index.php/AIM_API). The latter has functions for creating, storing, and retrieving AIM files from the AIM annotation database. As described below, the AIM annotation database is the key resource that ePAD queries for lesion tracking and summarizing longitudinal changes in cancer treatment response (Figure 3).

Analytical modules for processing image annotations. Using the ePAD Web services, we built a query engine to retrieve AIM annotations and their associated images to enable analyses of image measurements for tracking target lesions and for evaluating cancer treatment response. The query engine interrogates the AIM annotation database to retrieve annotations on a given patient for one or more imaging studies, processes the annotations, and displays the results (Figure 3). This query engine also accesses the DICOM image database to retrieve images associated with the corresponding annotations to permit displaying the images and their annotations as overlays in the ePAD viewer (Figure 4). Because the AIM files contain the DICOM unique identifiers of the source images from which they were derived, queries to the AIM annotation database can retrieve the image(s) associated with any AIM annotation.

We created the following two application modules: 1) summary of lesion measurements across longitudinal imaging studies, to help radiologists to review the measurements made in prior imaging studies when interpreting a follow-up imaging study, and 2) calculation and analysis of aggregate imaging data, to help oncologists to understand patient response assessment and cohort evaluation.

Summary of lesion measurements. When the user opens a patient study, the ePAD Web Services query the AIM annotation database to populate a panel in the ePAD viewer that shows the user all of the lesions from the prior imaging studies for the patient in a Patient Lesion Summary Table (Figure 6). It also links each measurement to the image from which it was obtained. When the user clicks on a measurement in the ePAD viewer, the corresponding image is retrieved, and the measurement is displayed as a graphical overlay.

In addition to summarizing each lesion and its measurement across all imaging time points, the ePAD Web Services also perform automated calculations and inferences in accordance to response criteria. For example, for RECIST, it sums the long axis of the lesions for which the lesion type is "target lesion" (producing the SLD), as well as an image-based response rate (the percentage of change in the SLD compared with baseline). It then applies the RECIST rules to classify the response rate to determine the response category (i.e., stable disease, partial response, complete response, and progressive disease). This information is displayed with the lesion measurements in the ePAD viewer (Figure 6).

Calculation and analysis of imaging data for response assessment. We created a module that uses the ePAD Web Services to query the AIM annotation database to produce automated

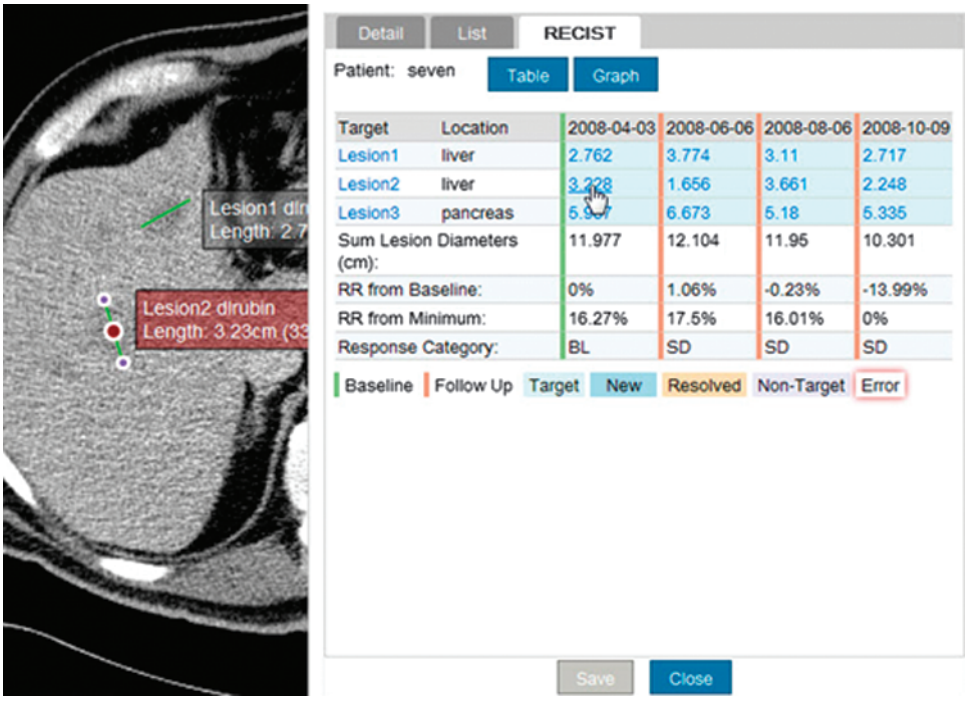
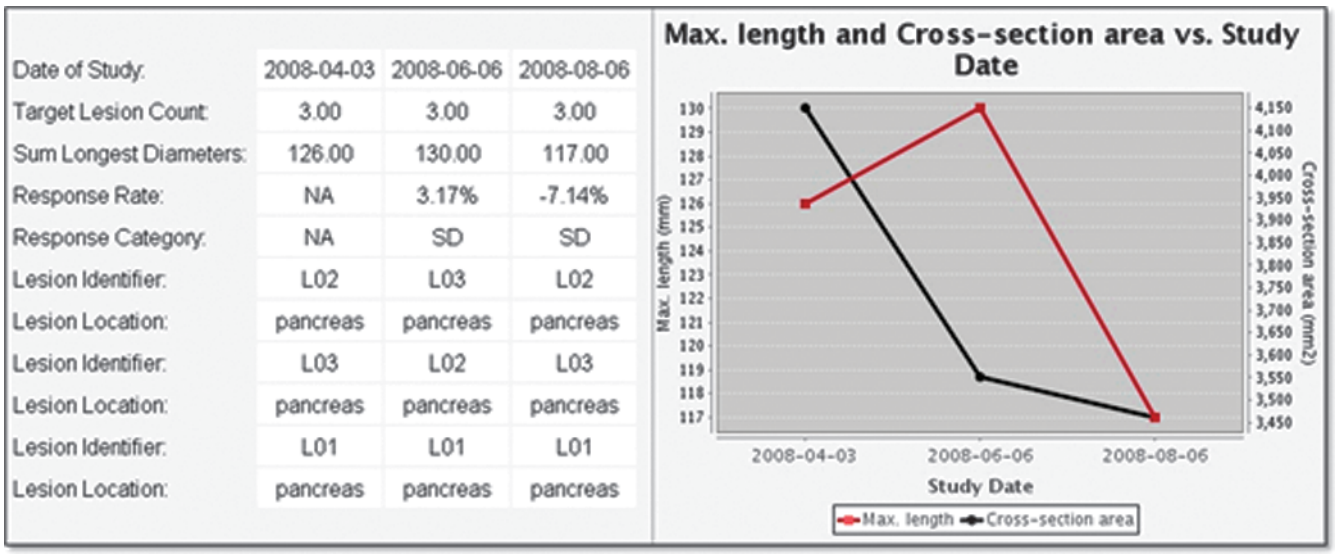


Figure 6. Patient Findings Table in ePAD. When a patient exam is opened for viewing, ePAD queries the AIM annotation database to show the measurements made on all previous imaging studies. The user can navigate directly to any of the prior images to view the corresponding measurements by clicking on the measurement as shown.



Date of Study:	2008-04-03	2008-06-06	2008-08-06
Target Lesion Count:	3.00	3.00	3.00
Sum Longest Diameters:	126.00	130.00	117.00
Response Rate:	NA	3.17%	-7.14%
Response Category:	NA	SD	SD
Lesion Identifier:	L02	L03	L02
Lesion Location:	pancreas	pancreas	pancreas
Lesion Identifier:	L03	L02	L03
Lesion Location:	pancreas	pancreas	pancreas
Lesion Identifier:	L01	L01	L01
Lesion Location:	pancreas	pancreas	pancreas

Figure 7. ePAD quantitative imaging report. This report is generated automatically by the ePAD Web Services, which query its AIM annotation database to produce a tabular and graphical summary of patient response. The table includes calculations of the SLD and response obtained from ePAD's analysis of the image annotations/measurements that were made by the radiologist (left). The changes in SLD over times are summarized in a graph, facilitating understanding of treatment response by the oncologist (right). The report can include display of alternative response measures to SLD (red line) such as lesion cross-sectional area (black line).

summaries of lesion measurements at each study time point [71]. These summaries comprise a quantitative imaging report, which can help the oncologist quickly amass the measurements on target lesions and the changes in tumor burden in a patient across longitudinal imaging studies. This application, implemented as a separate Web application in the ePAD platform, was designed to address the needs that oncologists have in assessing treatment response, which we previously described [22]. The application generates the following two summaries (Figure 7): 1) a Patient Findings Table, showing all imaging findings in a given patient, and 2) a Graphical Timeline, showing the patient's image-based measurement of disease (i.e., SLD) and the response classification at each time point.

The ePAD Web Services also calculate other measures, such as the lesion cross-sectional area (Figure 7), and they are extensible to calculate other image-based measures such as the metabolic tumor burden in PET images.

Evaluation

We obtained 20 CT imaging studies of chest, abdomen, and/or pelvis from a university-based (University of Pennsylvania, Philadelphia, PA) clinical trial of a chemotherapeutic agent. Each case consisted of a baseline imaging study and three follow-up imaging studies. A board-certified radiologist with experience in oncological imaging reviewed each imaging study, identifying target lesions and measuring them using RECIST 1.1 criteria. The radiologist was unblinded as to the time order of the follow-up imaging studies. Nontarget lesions were not identified or measured for purposes of this pilot evaluation. The reader indicated the presence of new lesions on follow-up studies, as well as areas where lesions have responded completely.

The time (in minutes) required to perform the lesion assessments on each imaging study and the time needed to make the response determinations were recorded. The radiologist completed the RECIST assessments for each study in both ePAD and again manually without the use of automated assistance of ePAD, with a 30-day washout period to reduce case recall bias. For reading without automated assistance, the radiologist used ePAD like a conventional PACS workstation, recording the measurements by hand but not being able to access the automated lesion summarization and tracking features. A training set of two cases was reviewed by the radiologist to become familiar with the ePAD tool and the study tasks before commencing the evaluation study. The primary measurement variable was the time required to perform the RECIST assessment in each case. Across all of the different cases, target lesions occurred in different organs in the chest and abdomen.

The workflow was as follows. First, the radiologist opened a case by selecting it from among the list of cases that was loaded into ePAD. The reader viewed axial images in ePAD, adjusting the image window/level display as needed for making measurements. For each target lesion identified, the radiologist drew a line to measure the longest linear diameter (or short axis in the case of lymph nodes) according to RECIST 1.1 criteria. The radiologist then filled out the electronic template to complete the annotation of the lesion, indicating the lesion name (e.g., "Lesion1"), the location of the lesion, and the lesion type (target, nontarget, new lesion, or resolved lesion) and time point (baseline or follow-up study). At the conclusion of annotating the lesions in the baseline and all follow-up imaging studies in the patient, the radiologist calculated the SLD for each imaging study and the response category [partial response (PR), progressive disease (PD), complete response (CR), or stable disease (SD) according to RECIST 1.1 criteria]. The radiologist was able to bring up any of previously annotated target lesions by consulting the Patient Findings Table in the ePAD viewer (Figure 6). When doing the read during the session without ePAD, they had to bring up the images and locate the previous measurements by hand to determine which target lesions were measured previously.

The radiologist's reading time for the assisted and unassisted reading of the imaging studies for each patient, as well as the mean, median, and SD of the reading times for all patients, was calculated for assisted and unassisted reading sessions. Significance of the differences in the

reading times for the assisted and unassisted reading sessions was tested using the two-tailed paired Student's *t* test, assuming a threshold of significance of $P < .05$. Overall percentage in time savings for using ePAD was also computed.

Results

ePAD Usage Workflow

We provide the results of our ePAD implementation by describing the workflow of radiologists in interpreting imaging studies in ePAD and by illustrating its capabilities. Radiologists open a study in ePAD, view the images, and make measurements in a manner akin to their routine workflow on a commercial PACS workstation (Figure 4). In addition, ePAD shows a data collection template so that radiologists can designate the anatomic location of the lesion and its type. They can learn that, for example, there were three target lesions previously measured by viewing the Patient Findings Table in ePAD (Figure 8). This table also permits them to quickly view the measurements of the target lesions on the prior imaging studies by clicking either on a measurement or on the lesion name. This functionality provides a simple workflow for radiologists to make lesion measurements, clicking on each measurement made on the prior study, so that a similar measurement can be facilitated on the current study.

Repurposing Imaging Data for Research

To evaluate the ePAD platform's ability to enable repurposing of data collected previously for new research, we selected a subset of existing cases that had been annotated by the radiologist as part of the RECIST reader study. We extracted the AIM files corresponding to the annotations produced during that reader study and processed them to explore lesion cross-sectional area as an alternative quantitative imaging biomarker of response. The AIM files contained the endpoints of lines that were drawn to make the long axis measurements of target lesions for the original RECIST assessments. We processed the AIM files and the source images in a commercial automatic segmentation algorithm (provided by Siemens AG, Erlangen, Germany) to obtain a region of interest that circumscribed each target lesion, and from that, we obtained the cross-sectional area of each target lesion. These analyses were completely automated.

We created AIM files that captured the output of the automated calculation of the lesion cross-sectional area and input those into the

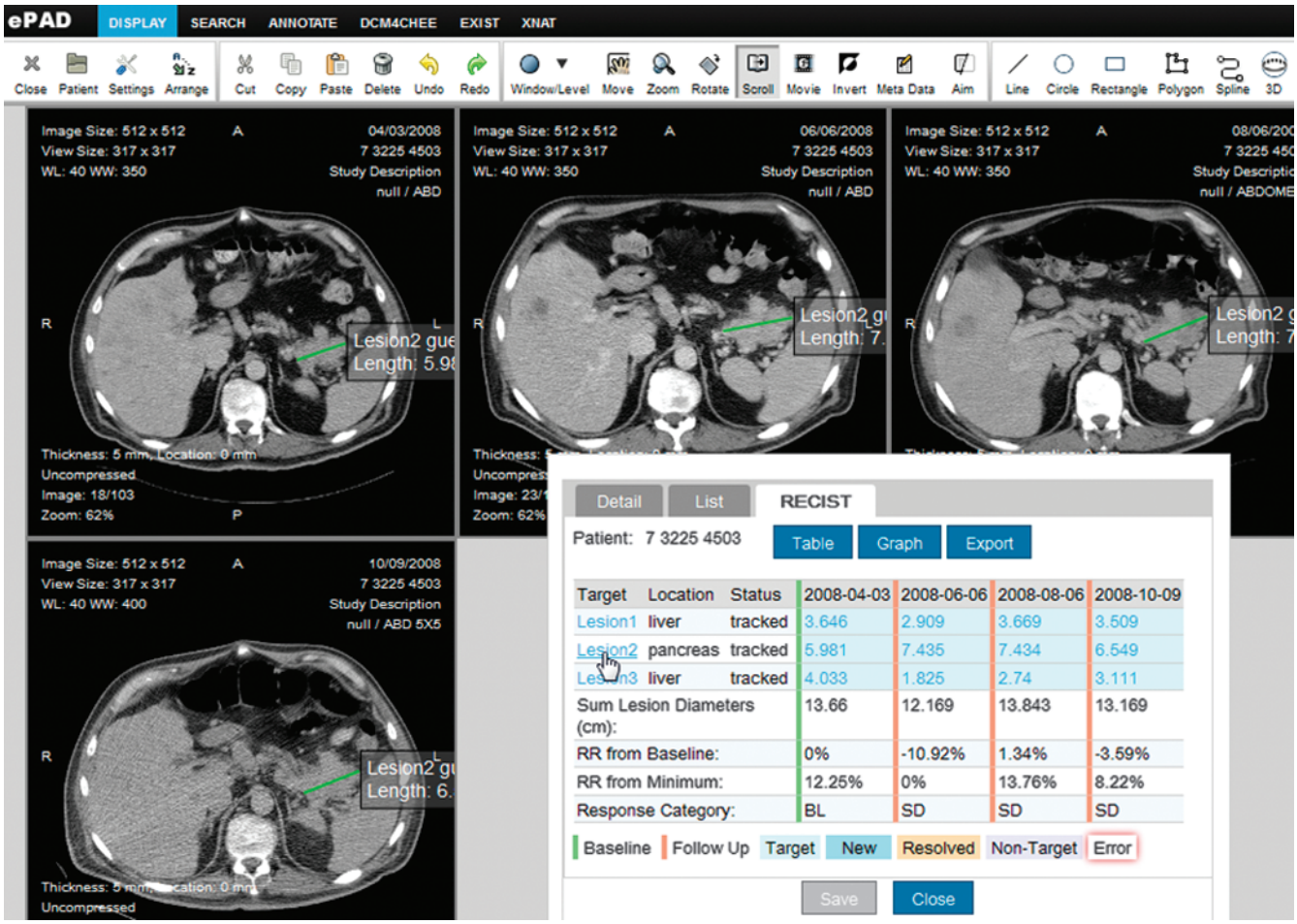


Figure 8. Reviewing prior measurements using the ePAD Patient Findings Table. Radiologists can quickly review the prior lesion measurements in the different imaging study time points by clicking on individual measurements, or they can view all measurements on a lesion by clicking on the lesion name. The result of clicking on "Lesion2" is shown. This helps the radiologist identify the lesions measured previously and to confirm the axis of measure that was used. It also provides a means of performing quality assurance on lesion measurements. All the information shown in the Patient Findings Table is also exported in the quantitative imaging report provided by ePAD (Figure 7).

ePAD platform, so that it could compare RECIST-based measurement with cross-sectional area in assessing treatment response. For purposes of this demonstration, we did not systematically evaluate lesion cross-sectional area as an alternative quantitative imaging biomarker; however, we noticed differences in the patient treatment response assessed using RECIST and cross-sectional area (Figure 7). We thus demonstrated that it is possible to efficiently reanalyze the images for new research, specifically, comparing an alternative biomarker (lesion cross-sectional area) to linear dimension (RECIST).

Reader Study Evaluation

As shown in Table 1, in all except for five of the cases, the reading time for the assisted readings was faster than for the unassisted reads. The mean (SD) review time per patient for the radiologist for unassisted reading was 8.8 (0.10) minutes, whereas for the ePAD-assisted reads, the mean (SD) time required for the radiologist was 7.5 (0.10) minutes, an average time savings of 15%. The difference was statistically significant ($P < .039$). The savings in time ranged from 4% to 87% across the cases. For the cases in which the unassisted reading was faster, it was faster from between 3.5% to 42.6% in reading time.

Adoption and Availability

The ePAD platform (and a desktop-based predecessor called iPAD [55]) has been successfully deployed in the workflow to support many research studies [22,43–52,54,72]. The system is distributed as a VMware virtual machine that can be deployed within an institution's internal network so as to avoid the need to transmit protected health information outside the institutional firewalls. Deployment requires installing the VMware player application on a server within the institution to host the ePAD virtual machine. The ePAD project collects feedback from the user community to enable iterative improvement. The ePAD system and the RECIST template described in this paper are freely available for research use (http://epad.stanford.edu).

Table 1. Reading Times (min:s) for Assisted and Unassisted Reading Sessions in 20 Patients by the Radiologist.

Case No.	Time to Read		% Difference
	Assisted	Unassisted	
1	6:27	9:20	44.7%
2	6:49	10:12	49.6%
3	4:48	8:57	86.5%
4	10:32	6:03	–42.6%
5	4:41	10:02	114.2%
6	5:11	7:27	43.7%
7	13:13	16:33	25.2%
8	6:46	8:39	27.8%
9	7:18	6:00	–17.8%
10	9:34	7:03	–26.3%
11	5:47	10:25	80.1%
12	6:49	7:13	5.9%
13	4:34	5:33	21.5%
14	6:04	9:13	51.9%
15	8:16	8:36	4.0%
16	9:30	6:47	–28.6%
17	11:09	11:36	4.0%
18	4:21	7:49	79.7%
19	9:00	10:11	13.1%
20	9:07	8:48	–3.5%
Total time	149:56	176:27	
Mean	7:29	8:49	26.7%
Median	6:49	8:43	23.4%

The reading times for the assisted and unassisted reading sessions are shown. The assisted reading sessions were significantly faster ($P < .039$) in terms of differences in time for reading the cases on the basis of a paired two-tailed t test. In five cases, the reading time for unassisted reading was faster than assisted reading.

Discussion

We believe that our work addresses two major challenges hindering effective use of imaging in support of cancer treatment response. The first challenge our ePAD platform addresses is improving the ability of radiologists to produce a more explicit summary of target lesion measurements. This provides advantages to both the radiologist and the oncologist. Oncologists receive a quantitative imaging report, comprising a flow sheet and patient response graph that obviate the need to cull through radiology text reports and image annotations to understand how much lesion measurements are changing over time. ePAD provides an imaging viewing interface similar to that which radiologists are accustomed to in doing routine radiology interpretation, while at the same time capturing measurements (Figures 5 and 6). ePAD helps the radiologist in carrying out cancer lesion measurements, showing them the measurements made previously and enabling them to quickly navigate to the images on which those measurements were made previously (Figure 8). The visual guidance and automated summary of lesion measurements provided by ePAD greatly accelerate the task of identifying and measuring target lesions and may reduce the subjectivity and ambiguity in reporting cancer imaging studies. The quantitative imaging report is generated from the original measurements made by the radiologist and provides a view of the measurements that helps the oncologist to rapidly amass the target lesion measurements and patient response (Figure 7). Ultimately, ePAD could also facilitate the analysis of imaging data in clinical trials by automatically generating waterfall plots of patient cohorts, as these are derived from analysis of the response graphs in each patent.

The second challenge that ePAD addresses is the repurposing of imaging data for new research. ePAD records all lesion measurements in AIM, a standardized, machine-accessible format. AIM was created specifically to enable repurposing of image data. We demonstrated an example of this by reanalyzing image data that had been originally evaluated using RECIST criteria and showing that it is possible to automatically generate alternative quantitative imaging biomarkers (lesion cross-sectional area), from the prior image data by processing the AIM annotations. Because AIM records the pertinent information about regions drawn on images, information about lesions themselves (lesion type, name, and anatomic location), and their measurements, there are many possibilities for reanalyses of prior image data. In our case, we generated the alternative imaging biomarker data by obtaining the coordinates of the lines used to measure the target lesions from the AIM files, and we used it to seed an automatic image segmentation algorithm, from which we extracted lesion cross-sectional area. Other features such as lesion texture, volume, or change over time could have been used as well. Given the limitations pointed out about RECIST and other linear measure–based criteria [14–19] and the challenge of collecting aggregate data to qualify alternative imaging biomarkers, the ePAD approach could enable collecting the necessary aggregate evidence over time.

There were a number of limitations to our work. Using ePAD for making lesion measurements requires some extra work for the radiologist, who must complete an annotation template for each lesion (Figure 4). However, ePAD provides features that streamline the process of identifying the lesions measured previously. In our preliminary evaluation of the impact of using ePAD on the radiologist

workflow, we found that ePAD improved the time efficiency of the radiologist in reading the test cases by 15%, which was a statistically significant improvement compared with doing the task without ePAD ($P < .039$). In our study design, we asked the radiologist to do the first reading session with ePAD to avoid providing positive bias to ePAD in the subsequent reading session, in case there was a carryover benefit of case recall after the 30-day washout. However, there may have been some recall of the cases during the unassisted reading session with benefit to the radiologist's speed during the unassisted reading session. This may explain why the reading time for the unassisted reading session was faster than using ePAD in five cases (Table 1). Nonetheless, there are likely improvements that could be made to ePAD in the future to further streamline the radiologist workflow in creating lesion measurements, such as automatically locating the target lesion on subsequent studies, on the basis of where lesions were found previously [73].

An additional limitation is that ePAD currently supports recording and summarizing information about only target lesions but not nontarget lesions. In addition, splitting or merging of lesions is not supported. We are currently extending our RECIST template to support collecting information about nontarget lesions and labeling lesions appropriately when they merge or split.

There were also some limitations in our evaluation study. We only had one reader, and we acknowledge that there may be variability among radiologists in their efficiency. We are currently conducting a multi-institutional multireader study. Another potential limitation of our evaluation study is that the number of test subjects was small. However, our effective data sample size, which included four time points for each patient, reflected a total of 80 imaging studies, a reasonable number for our evaluation.

There are other tools and approaches that have recently been produced for purposes of lesion tracking. In terms of tools, a few commercial image-viewing workstations have been developed for purposes of automated cancer lesion tracking (mint Lesion; Mint Medical GmbH, Dossenheim, Germany and *syngo*.via; Siemens Healthcare, Malvern, PA). These systems are "closed," storing all image data internally in a proprietary format and requiring that all patient time points be assessed using their system. In terms of alternative approaches, some organizations have developed core laboratories for providing quantitative image interpretations (e.g., American College of Radiology Imaging Network Core Laboratory, http://www.acrin.org/CORELABS.aspx; Tumor Imaging Metrics Core, http://www.tumormetrics.org/; and RadPharm, http://www.radpharm.com). Each of these groups generally uses a combination of commercial tools and handcrafted workflows to carry out quantitative imaging assessment, which can be time consuming and costly. However, ePAD provides an integrated, freely-available tool for carrying out cancer lesion assessments. In addition, because ePAD uses the AIM format for capturing the image measurements, it is possible to use ePAD for interpreting studies for which prior imaging time points were assessed using a different workstation, provided that the prior measurements were recorded in AIM format.

Having all image metadata recorded in AIM format is also crucial to being able to repurpose prior imaging data for new research. Current image-viewing platforms that record image metadata in proprietary formats cannot be leveraged for this purpose. We demonstrated that, by recording lesion measurements in AIM format, we could subsequently reanalyze those data in a largely automated manner to explore an alternative imaging biomarker of treatment response. In addition, being Web-based, ePAD offers the additional advantage of being easily accessible by radiologists anywhere for quantitative evaluation without the need to install any software on their local computers. That said, the institution providing ePAD needs to establish a server within their internal network to host the ePAD virtual machine.

ePAD uses the AIM format to promote interoperability of image metadata among cancer sites. The DICOM standard has a type of object called the DICOM Structured Report (DICOM-SR [74]), developed to convey nonimage data such as tracing, radiology results, or other nonimaging information. Tools were recently developed to interconvert between AIM and DICOM-SR (ANIVATR, https://wiki.nci.nih.gov/display/AIM/Annotation+and+Image+Markup+-+AIM), so AIM and DICOM-SR can be considered to be alternative formats for image metadata. Our choosing AIM over DICOM-SR was guided by the ease of manipulating and querying image metadata in the AIM XML format; to query DICOM-SR, applications need to unpack the data object and store it in, e.g., a relational database format.

All aspects of the ePAD functionality are based on querying AIM annotations, which contain the image data that comprise the original measurement [the region of interest (ROI) drawn to make the measurement, the value of the measurement, the designation of the measurement as being a target lesion, and other information]. Thus, all of ePAD's functionality is directly driven from the primary image data and image assessments—the AIM annotations acquired from the user who originally evaluated the images—rather than from a transcription of image-derived results onto flow sheets or case report forms (the current practice). This is a substantial advantage, because the source documentation for image measurements when using AIM is the actual measurement, rather than indirect information—the radiology report and image annotations—neither of which may consistently document all of the information about lesions required for response assessment [22].

We believe that deploying the ePAD platform in clinical research practice will greatly improve the ability of oncologists to assess the effectiveness of cancer treatments in patients enrolled in clinical trials. It will also potentially assist new research to discover novel imaging biomarkers of response or enable collection of sufficient data to enable Food and Drug Administration (FDA) qualification of alternative imaging biomarkers. Ultimately, with further enhancements to ePAD, radiologists may find our tools practical to use in routine practice to produce better reports that will help oncologists to better understand cancer treatment response in their patients.

Conclusion

We developed a freely available tool, ePAD, which provides a promising approach to enable radiologists to perform measurements on target lesions and to produce quantitative imaging reports without substantially hampering the efficiency of their workflow. Use of the ePAD platform may also enable repurposing previously acquired quantitative imaging data and promoting discovery of future novel image-based biomarkers of cancer treatment response. Stimulating such research could eventually lead to amassing the critical evidence needed to qualify novel quantitative imaging biomarkers for assessment of cancer treatment response.

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