A Web-Based Response-Assessment System for Development and Validation of Imaging Biomarkers in Oncology

Hao Yang, Xiaotao Guo, Lawrence H. Schwartz, and Binsheng Zhao

Department of Radiology, Columbia University Medical Center, New York, NY

Corresponding Author:
Hao Yang, MA
Department of Radiology, Columbia University Medical Center,
710 West 168th Street, B26, New York, NY 10032, USA;
E-mail: yh2588@cumc.columbia.edu

ABSTRACT

Quantitative imaging biomarkers are increasingly used in oncology clinical trials to assist the evaluation of tumor responses to novel therapies. To identify these biomarkers and ensure smooth clinical translation once they have been validated, it is critical to develop a reliable workflow-efficient imaging platform for integration in clinical settings. Here we will present a web-based volumetric response-assessment system that we developed based on an open-source image viewing platform (WEASIS) and a DICOM image archive (DCM4CHEE). Our web-based response-assessment system offers a DICOM imaging archiving function, standard imaging viewing and manipulation functions, efficient tumor segmentation and quantification algorithms, and a reliable database containing tumor segmentation and measurement results. The prototype system is currently used in our research lab to foster the development and validation of new quantitative imaging biomarkers, including the volumetric computed tomography technique, as a more accurate and early assessment method of solid tumor responses to targeted and immunotherapies.

INTRODUCTION

The use of imaging biomarkers to monitor responses of tumors to treatment has attracted increasing interest in recent years. Despite the accelerated pace of new drug discoveries, and the availability of treatment options in oncology, methods for assessing tumor responses remain almost unchanged over the past few decades, that is, using tumor diameter to gauge tumor change with therapy (1, 2). This is particularly challenging for targeted and immune therapies, as efficiencies of these therapies may be better reflected by tumor density changes than by tumor size shrinkage.
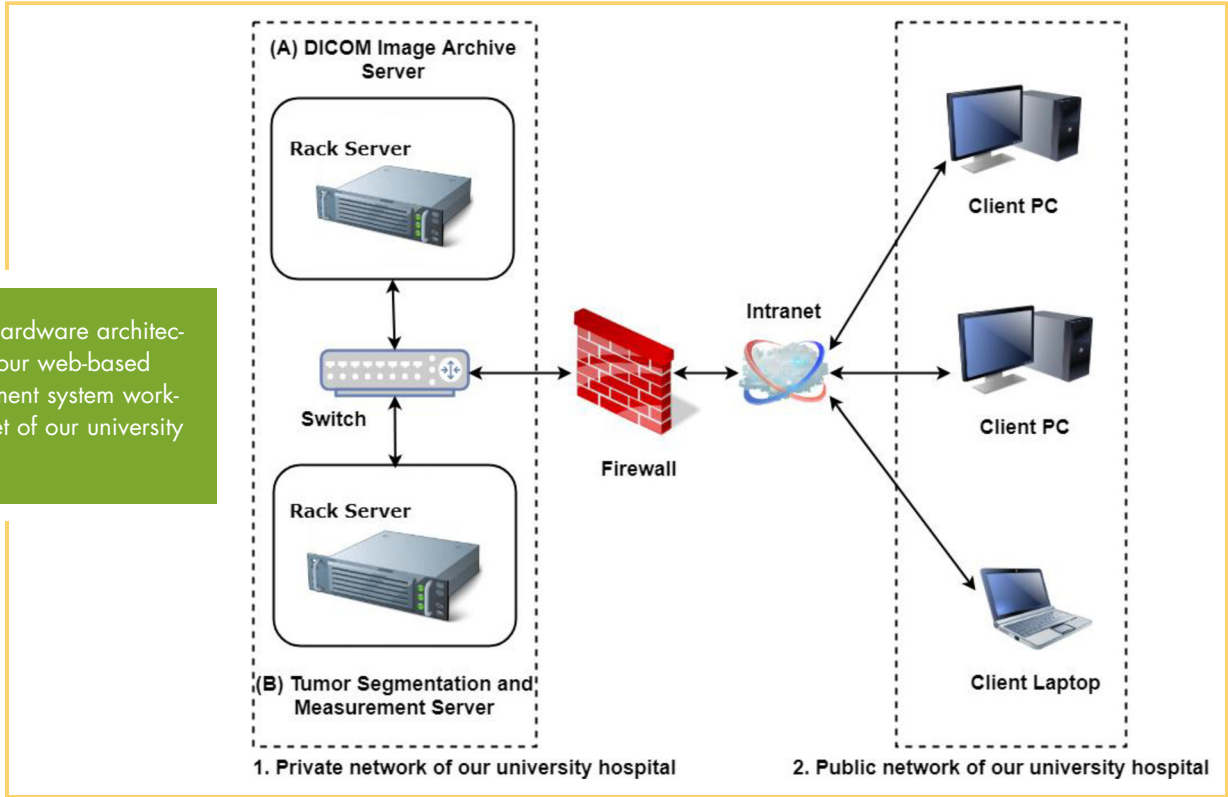
Researchers, including us, have been developing novel quantitative response-assessment methods including volume measurements and the use of more complex radiomic features to measure tumor changes (3). To foster the development and validation of quantitative imaging biomarkers, we developed a portable response-assessment system, based on an open-source WEASIS (4, 5). This system has a PACS-like user interface, which allows radiographic images to be viewed and manipulated efficiently. We integrated our homegrown segmentation tools into this system to facilitate efficient and accurate tumor segmentation and quantification.

The portable response-assessment system consists of a database server and a response-assessment application. The database server stores and manages tumor segmentation and measurement results, whereas the application consists of the following key components: (1) a WEASIS viewer module that allows the program's user to open, display, and manipulate radiological images, (2) an algorithm module that integrated our tumor segmentation algorithms and editing tools, and (3) a database module that allows users to communicate with the database server. The WEASIS response-assessment application is installed on each of the PCs in the lab.

However, shortcomings of the portable response-assessment system are obvious: (a) the application is hard to maintain, upgrade, and distribute and (b) (deidentified) DICOM images need to be transferred to and stored in each PC for tumor measurements. To address these 2 shortcomings of the portable response-assessment system, we upgraded our response-assessment system by tuning the response-assessment application so that it was web-based, and by adopting DCM4CHEE as the DICOM image archive. DCM4CHEE is a free, stable, feature-rich DICOM image archive (6). In the Methods section of this report, we will explain in detail how we designed and implemented our web-based response-assessment system.

Figure 1. Web-based response assessment system with integrated tumor segmentation and quantification algorithms (A). Lung, liver, and lymph node segmentation algorithms integrated into the WEASIS response assessment system (B).

METHODS

Segmentation Algorithms and Editing Tools

As shown in Figure 1, our web-based response-assessment system has several segmentation algorithms, such as: a lung nodule segmentation algorithm (7); a liver tumor segmentation algorithm (8); a lymph nodule segmentation algorithm (9); and a brain tumor segmentation algorithm (10). The initialization procedure for each algorithm has been implemented and integrated into the system. The system also provides editing tools that are designed to efficiently modify and optimize the segmentation contours. It consists of some basis operators, such as refine, smooth, expand, and shrink functions, which can automatically modify the segmentation contours based on energy-minimization segmentation methods. It also provides propagation functions, which can propagate a segmentation result from 1 slice to the neighboring slices while automatically finding the optimal contour for each slice.

All the algorithms are written in C++ or Matlab computer language and compiled into dynamic link libraries (DLLs). Because the WEASIS platform is programmed in JAVA language, we use the Java Native Interface (JNI) to call these algorithms/functions in the libraries.

Segmentation Results and Storage Methods

Lesions will be semiautomatically delineated using the integrated 3D lesion segmentation tools developed in our research lab. Once the lesions are segmented, lesion diameters and volumes (as well as other radiomic features once the feature extraction methods are integrated into the platform) can be computed automatically. Our tumor segmentation results are binary images in which a background voxel has a value of 0 (zero) and a lesion voxel has a value of 1 (one). The compressed binary images and tumor measurement values of UNI (the maximal in-plane diameters), BI (product of the maximal diameter and its maximal perpendicular diameter), and

Figure 2. The hardware architecture diagram of our web-based response assessment system working in the intranet of our university hospital.

volumetry are sent to and stored in a relational database that is an industry standard. The database structure we designed is published in our previous paper, which reported our portable response-assessment system (4).

System Hardware Architecture

Figure 2 shows the hardware architecture diagram of our web-based response-assessment system. It consists of the following 2 rack servers: (1) a DICOM image archive server, hosting a DCM4CHEE and a web-based response-assessment application and (2) a dedicated database server storing tumor segmentation and measurement results in a MySQL database. The web-based response-assessment system resides in the intranet of our uni-

versity hospital. The two servers are inside the private network of our university hospital, and public access is prevented by a firewall; while the client PCs, where users of the response-assessment system work, are within the public network of our university hospital. The deidentified DICOM images are stored in the image archive server and are remotely accessed by client PCs through a web browser and a web-based response-assessment application.

System Software Framework

Figure 3 shows the major components of the web-based response-assessment system, which is divided into the following 4 layers: an interface layer, an application layer, a service layer,

Figure 3. The layered software framework of the web-based response assessment system.
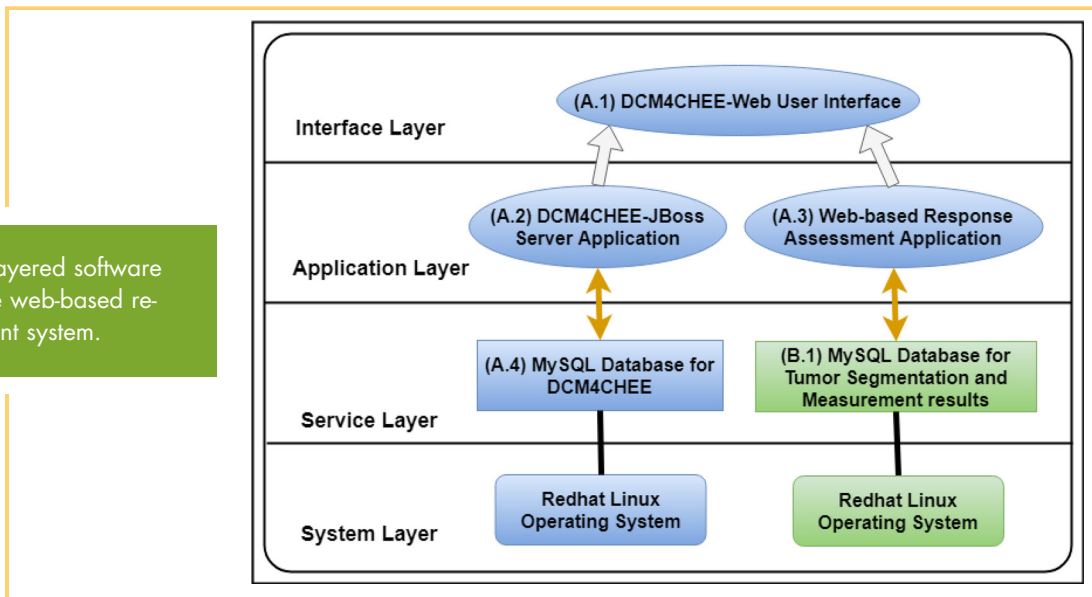
Figure 4. User interface of DCM4CHEE-Web and the link (arrow) to launch response assessment application.
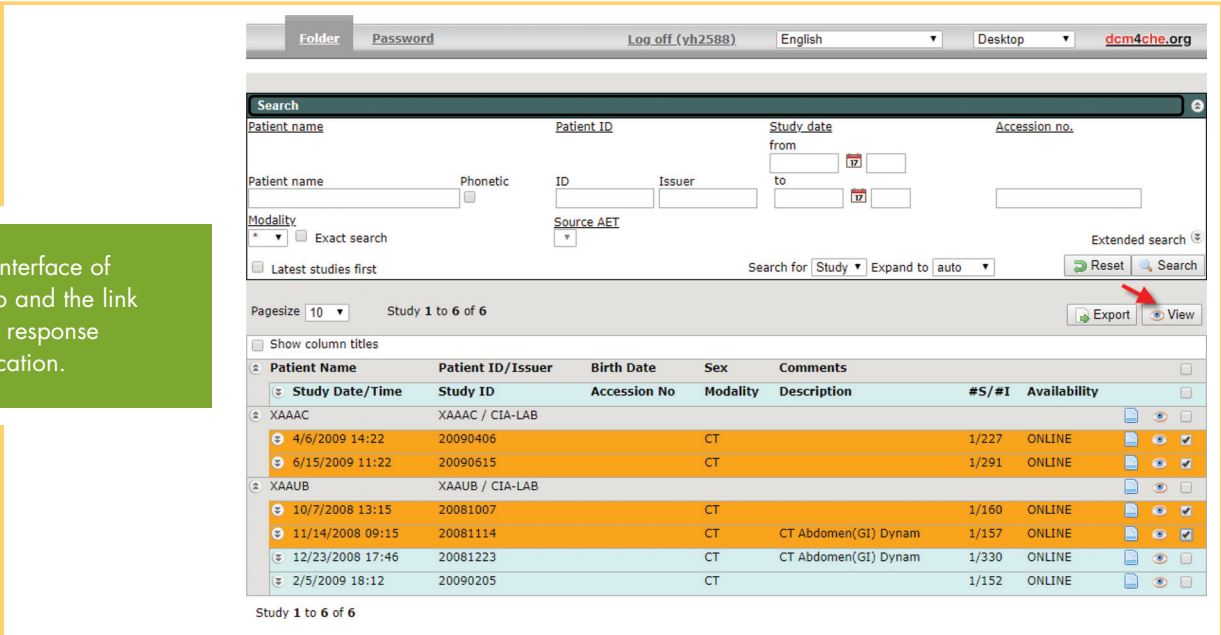
and a system layer. The components in the DICOM archive server are: (A.1) a DCM4CHEE–web user interface, (A.2) a DCM4CHEE-JBoss server application, (A.3) a web-based response-assessment application, and (A.4) a MySQL database for DCM4CHEE. The component in the tumor segmentation and measurement server is a MySQL database for tumor segmentation and measurement results (B.1). We will now describe the details of each component in the web-based response-assessment system.

DCM4CHEE–Web User Interface (A.1). DCM4CHEE is a collection of open-source applications and utilities for managing and archiving DICOM imaging. It was developed in the Java programming language. The DCM4CHEE application uses the DICOM, HL7 services and interfaces to provide storage, retrieval, and workflow of DICOM imaging.

The DCM4CHEE–web user interface (shown in Figure 4) runs entirely in web browsers of client PCs. It can search for patients or studies, browse the archived DICOM information listed in a patient-study-series-image layout, and launch the response-assessment application.

DCM4CHEE-JBoss Server Application (A.2). The DCM4CHEE-JBoss server application consists of a collection of open-source applications and utilities that have been developed in the Java programming language for improved performance and portability. It contains the Health Level 7 (HL7) and Digital Imaging Communication in Medicine (DICOM) services and interfaces that are required to provide storage, retrieval, and workflow to a healthcare environment. A DCM4CHEE-JBoss server application is prepackaged and deployed within the JBoss application server. By taking advantage of many JBoss features, such as JMS (Java Message Service), EJB (Enterprise Java Beans), Servlet Engine, etc., and assuming the role of several IHE (Integrating the Healthcare Enterprise) actors for the sake of interoperability, the DCM4CHEE-JBoss server application provides the following services: (1) DICOM Storage, acting as an archive to store DICOM images to standard file systems, with compression if necessary; (2) DICOM Query/Retrieve, querying the archive for DICOM images, and retrieving them; and (3) WADO (Web Access to DICOM Objects) and RID (Retrieve Information for Display), supporting web access to the archived data.

Web-Based Response-Assessment Application (A.3). The web-based response-assessment application is based on WEASIS, a versatile open-source DIOM viewer. The framework of the response-assessment application is explained in detail in Yang et al. (4). The response-assessment application can be easily packaged for portable distribution or web-based distribution. In our system, we use the web-based distribution.

The web-based response-assessment application is hosted by the DCM4CHEE-JBoss in the DICOM archive server, and launched by the DCM4CHEE-Web. It does not persistently retain user information. Thus, the database of DCM4CHEE and the database of tumor segmentation and measurement keep exactly the same user information. In other words, to register a user, the user's information should be saved into both databases. This is a prerequisite for the web-based response-assessment application to be able to retrieve tumor segmentation and measurement results and review tumor contours using the WEASIS viewer.

MySQL Database for DCM4CHEE (A.4). The MySQL database for DCM4CHEE manages all the user information of DCM4CHEE and DICOM information, for example, user credentials, user access rights, and the path of a DICOM image in the DICOM storage.

MySQL Database for Tumor Segmentation and Measurement Results (B.1). The MySQL database storing and managing tumor segmentation and measurement results in a dedicated server with superior data protection and twice-daily data backup, rather than in the DICOM image archive sever with inferior data protection and monthly data backup.

We keep the tumor segmentation database and the DCM4CHEE database independent for the purpose of easy upgrade and backup. Also, the user table of the DCM4CHEE database is used more often than the tumor segmentation database. We thus store the user registration information in two databases. We synchronize the 2 user registration databases by a program so that a change in one registration database will be automatically made to the other registration database.

Workflow

Figure 5 shows a sequence diagram of the workflow that users use to login to the system and views selected DICOM images.
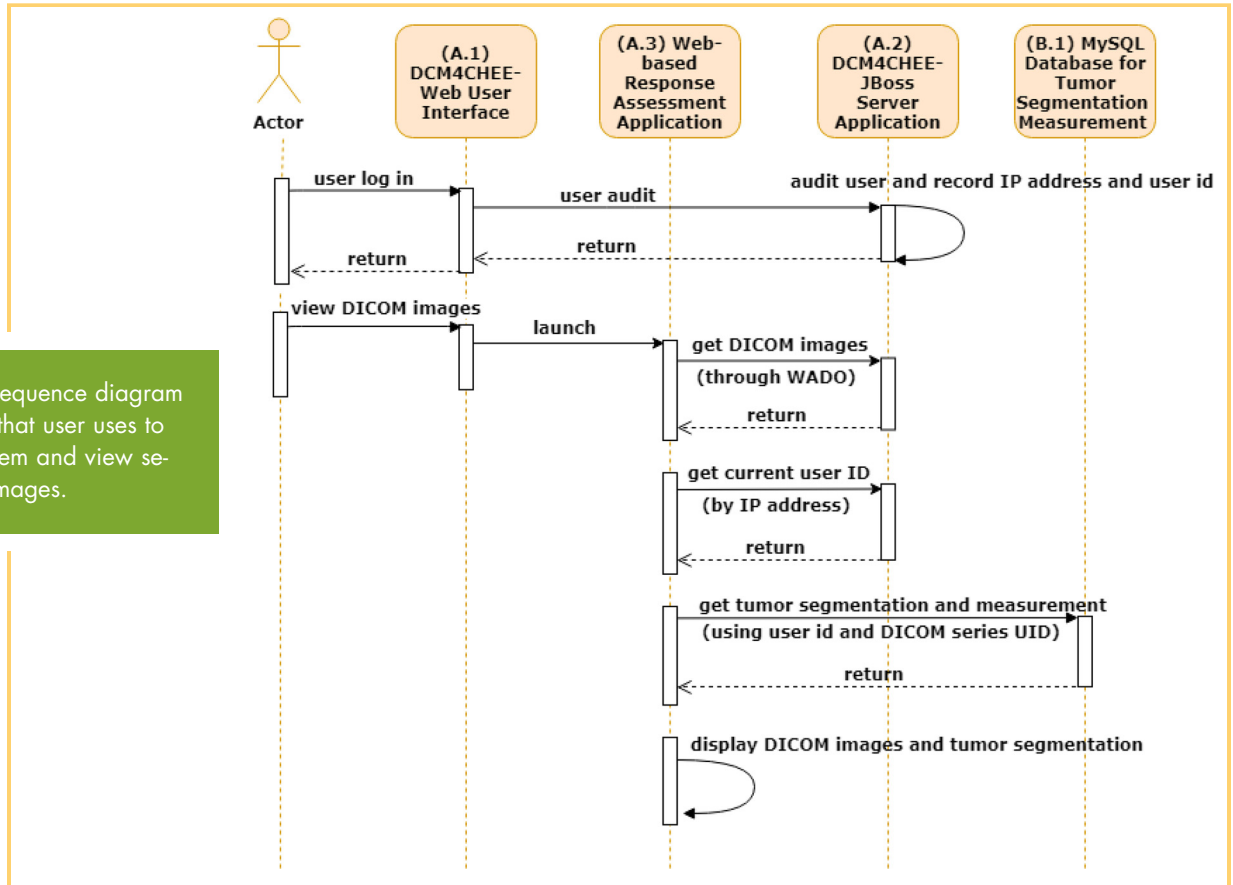
Figure 5. The sequence diagram of the workflow that user uses to log in to the system and view selected DICOM images.

When a user logs in to the system in a web browser, the DCM4CHEE-JBoss server application records the IP address of the user's PC and the user's credentials in the MySQL database for DCM4CHEE, as shown in the upper part of Figure 5. Once approved by the DCM4CHEE-JBoss server application, the user will see the DCM4CHEE–web user interface shown in Figure 4. Then the user may choose DICOM images of patients, studies, or series and click the link (highlighted in Figure 4) to web-based response-assessment application to view them.

The web-based response-assessment application can retrieve DICOM images archived by DCM4CHEE, because the DCM4CHEE-JBoss server application supports web access of DICOM images. A middle ware, called a WEASIS-PACS-connector, streamlines the process of retrieving DICOM images. When the user requests viewing the selected DICOM images, using the DICOM Query service of DCM4CHEE-JBoss, the middle ware collects the necessary information to launch the web-based response-assessment application.

After the response-assessment application is launched, it gets the DICOM image archived by DCM4CHEE, through the WADO Service of DCM4CHEE-JBoss. Next, the response-assessment application gets a user ID from the client PC's IP address from the DCM4CHEE-JBoss server application, as both user ID and client PC's IP address have been recorded by the DCM4CHEE-JBoss server application. Later, using user id and DICOM series UIDs of DICOM images, the response-assessment application gets tumor segmentation and measurement from the MySQL database for tumor segmentation and measurement results. Last, the response-assessment application displays DICOM images and their associated tumor segmentation.

Finally, the response-assessment application shows the selected DICOM images. The user can use response-assessment applications to segment tumors immediately. Only response-assessment applications and the database of tumor segmentation and measurement results are involved in the process of tumor segmentation, which was detailed in our previous paper (4).

DISCUSSION

We have developed a web-based imaging system to support the development and validation of quantitative imaging biomarkers for improved assessment of (solid) tumor responses to therapies, particularly novel targeted therapy and immunotherapy. The web-based response-assessment application of this system is based on the open-source DICOM image viewer WEASIS. To manage DICOM images, the response-assessment imaging system incorporates DCM4CHEE, an open-source DICOM image archive. The system consists of 2 interdependent servers with a Linux operating system: 1 hosts the DICOM image archive and web-based response-assessment application and the other hosts image biomarkers, for instance, tumor segmentation and unidimensional and volumetric measurement results. Users can log in to the web-based response-assessment imaging system using a web browser, and browse data on patients or on studies, and remotely access DICOM images and tumor segmentation on them.

The web-based response-assessment has many advantages over the previous portable response-assessment system: (1) archiving the DICOM images in a server rather than on a local hard disk of the client's PC, the system promotes the management of

DICOM images, for example, access control and storage of the DICOM images increase and (2) the system facilitates the distributing, updating, and upgrading of the response-assessment application by configuring the application to be web-based and to be hosted in a server.

As mentioned earlier, our objective is to develop an advanced imaging platform to accelerate the development and validation of novel quantitative imaging biomarkers for tumor response assessment by providing efficient tumor measurement tools. Our research system to assess tumor response is built based on an open-source, the WEASIS, platform. It is a PACS-like workstation that has basic image-viewing and manipulation functions. We customized it specifically for the assessment of advanced quantitative imaging biomarkers by (1) developing an industrial standard, novel relational database structure to store segmented tumor contours and measurements (4); (2) integrating our homegrown advanced tumor segmentation and editing tools so that tumor contours can be delineated more accurately and efficiently; (3) providing lesion tracking tools to reduce human error in tumor measurements at multiple scan time-points; and (4) making the system more user-friendly across multiple platforms and various screen sizes, and more accessible from different locations. Most importantly, our system is designed with an extendable architecture, so that other image-based quantitative tasks (eg, body fat quantification) can be easily added to the system.

We are aware that there exist many open-source and commercially available tools that provide similar functionality for lesion segmentation and/or lesion tracking. For example, there are 3D Slicer (11), ePAD (12), ITK-SNAP (13), OsiriX MD (14), and ClearCanvas (15). 3D Slicer is an open-source software platform and widely used by researchers worldwide for medical image processing (eg, lesion segmentation) and 3-dimensional visualization. However, 3D Slicer is not developed specifically for tumor response assessment, and thus, when using it for this purpose, it will not be as efficient as ours. For example, the 3D Slicer does not provide any lesion tracking tools that would be important when measuring lesions on longitudinal scan time points. ePAD is a web-based image viewer and annotator for quantitative image analysis. The system uses Annotation and Image Markup (AIM) file for tumor segmentation and measurement results and stores these files in an AIM Annotation Database. The AIM Annotation Database is an XML database that is known to be inefficient and unreliable for storing and maintaining large volumes of data. As to commercially available systems, such as OsiriX MD and ClearCanvas, the significant advantage of our system over them lies in its great capability to be extended. For example, we can add radiomic feature extraction methods easily to our system, whereas a commercial system has a hard time doing so.

Our response-assessment system has shown value in its ability to efficiently obtain/measure tumor size, particularly tumor volume, at serial scan time points in clinical trial settings to help monitor changes in total tumor burden—a potentially better imaging biomarker of response.

We will integrate our custom-developed radiomics features into our response-assessment system, so that it can be used to explore tumor imaging phenotypes for therapy response predictions and patient stratification for future clinical trials. We also plan to extend this system for exploring the data of DICOM images and tumor segmentation results, such as using artificial intelligence to automatically identify target lesions on baseline scans and new lesions on follow-up scans.

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