CAD in clinical trials: Current role and architectural requirements


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Abstract

Computer-aided diagnosis (CAD) technology is becoming an important tool to assess treatment response in clinical trials. However, CAD software alone is not sufficient to conduct an imaging-based clinical trial. There are a number of architectural requirements such as image receive (from multiple field sites), a database for storing quantitative measures, and data mining and reporting capabilities. In this paper we describe the architectural requirements to incorporate CAD into clinical trials and illustrate their functionality in therapeutic trials for emphysema.

Keywords: Computer-aided diagnosis; Clinical trials; Emphysema

1. Introduction

Computer-aided diagnosis (CAD) technology is being developed for detection, quantitation and change assessment and has potential applications in therapeutic assessment. Computer-aided diagnosis systems have focused on lesion detection applications in mammography, colonography and lung nodule detection [1–5]. Systems have shown promising experimental results, and some commercial systems are now available. There have also been significant efforts to develop and test lesion size measurement tools [6–8]. These remain active areas of CAD research to improve detection performance and to validate systems for response assessment. This research is vital if CAD detection systems are to become an integral part of oncology clinical trials, for although they have great potential they are not yet considered essential.

However, in the domain of diffuse lung disease, and in particular emphysema, CAD is now playing a central role in clinical trials of new therapies. Emphysema results in the destruction of lung parenchyma. Lung compliance increases and, because of the loss of radial traction on the conducting airways, the airways collapse prematurely during expiration, causing airflow obstruction and the inability to breathe. Emphysema is a major cause of morbidity and mortality for an estimated 60 million patients world-wide. CT imaging can effectively depict emphysema severity (see Fig. 1), and it can be quantitated by density mask [9,10]. The density mask measure is the percentage of voxels below a particular Hounsfield Unit (HU) threshold, which corresponds to air-containing holes in the parenchyma. Thus, CAD software that can segment the lung anatomy and derive quantitative measures such as density mask scores can allow us to assess the severity of emphysema. This information can be used to identify patients that are candidates for treatment and to assess the response of patients post-treatment.

However, CAD software alone is not sufficient to conduct an imaging-based clinical trial. There are a number of architectural requirements such as image receive (from multiple field sites), a database for storing quantitative measures, and data mining and reporting capabilities. In this paper we will describe the architectural requirements to incorporate CAD into clinical trials and illustrate their functionality in therapeutic trials for emphysema.

2. Methods

The key functional components for CAD in clinical trials are: DICOM image receiver; CAD system for quantitation; CAD review workstation; statistical analysis workstation; and web server for reporting of results. These components are linked through a database management system as shown in Fig. 2. We will illustrate the functionality and interaction between these components in emphysema treatment trials.
Fig. 1. Lung CT image showing regions of bullous emphysema destruction, predominantly in the lower lobes (arrows), with computer-determined involvement percentages.

2.1. Emphysema treatment trials

Currently there are limited treatment options available for patients suffering with emphysema. For advanced stages of the disease a lung transplant or lung volume reduction surgery can be considered. The latter technique can only be applied in cases with heterogeneous emphysema, i.e., when one lobe of the lung is emphysematous and the adjacent lobe less severely effected. The more diseased lobe is surgically removed in the hope of creating additional space in the chest cavity to allow the adjacent (healthier) lung to expand. However, both techniques are highly invasive and carry significant risk of complication.

New minimally invasive therapeutic options for emphysema are now currently being tested in clinical trials. One such example is the endobronchial valve for emphysema palliation trial (VENT) conducted by Emphasys Medical Inc. (Redwood City, CA) [11]. A one-way valve (Emphasys Zephyr® Endobronchial Valve) is inserted bronchoscopically into the airway feeding the most severely diseased lobe. This valve only allows air to escape from the lobe, thereby inducing lobar volume reduction and achieving a result similar to lung volume reduction surgery without a major surgery, therefore posing less risk to the patient [12–16]. CAD technology has been central to this trial. A CAD system is being used to segment the lung into its component lobes and to assess the severity of emphysema in each lobe. This enables determination of emphysema heterogeneity (eligibility of the patient for treatment) and the most severely affected lobe into which the valve should be placed.

2.2. Image management

Image transfer and storage capabilities are an essential component of the clinical trials infrastructure. The VENT involves patient data collection at 57 clinical sites in the United States and Europe. These images are transferred by DICOM push or by mail on CD (if network transfer rates are limited). A CAD infrastructure also requires image storage with redundancy for fault-tolerance. In this case we use a pair of mirrored data servers.
each with RAID 5. Grid-based approaches are also being developed for image transfer and fault-tolerance [17].

Imaging protocols in clinical trials usually contain multiple series. For example, the VENT protocol involves thick and thin-section CT imaging at two suspended breathold levels: total lung capacity (TLC) and residual volume (RV). These series must be consistently labelled so that they can be organized within the database prior to CAD processing. The labelling is determined at the core laboratory by review of the images and DICOM fields. Image quality control and protocol adherence at clinical sites are vital for reproducible quantitation. For each imaging study received at the core lab, study quality is checked for adherence to protocol and a numerical grade is given. This score and comments are included in an email to the site to provide ongoing feedback and maintain image quality. The scores also provide important monitoring information for sponsors on overall image quality in the trial.

To support these requirements a database management system is essential. Our data model is based on the DICOM hierarchy that is augmented as follows. The Image table contains a file path to the location of the actual DICOM files (images) on the data server. There are additional table associated with the Series table that contain fields for labelling specific series and storing image quality scores and comments.

2.3. CAD analysis

CAD techniques are used to provide automated image segmentation and quantitation. For the VENT lobar lung segmentation is required. A model-based approach for automatic segmentation of the lung parenchyma in CT has been previously published [18,19]. To subdivide the lungs into lobes a semi-automated approach has been developed. On thick-section images the major and minor inter-lobar fissures are drawn manually on the axial images (see Fig. 3c). This is done manually since the fissural surfaces are thin and difficult to detect due to partial volume averaging (see Fig. 3b). After the fissures are contoured, an automated region growing technique is applied to extract the lobes as separate regions of interest (ROIs). On thin-section images the fissures are more visible, as shown in Fig. 3a, and techniques are being developed that use gradient and 3D continuity to automatically detect the fissural surface [20]. However, in the VENT thick-section imaging is being used to provide the primary measure of emphysema because density mask measurements were originally validated against pathology specimens using 10 mm thick slices [9].

The ability to edit segmentation results is vital since “automated” CAD systems are often inaccurate for clinical trials patients with disease patterns different to those on which the sys-

Fig. 3. Semi-automated lobar segmentation for a CT scan acquired at residual volume (RV). (a) Thin-section CT showing inter-lobar fissures (arrows). (b) Corresponding thick-section image (from same scan) with partial volume averaging leading to low contrast of the fissures. (c) Approximate manually drawn fissures on thick-section. (d) Automated segmentation of left upper, left lower, right middle and right lower lobes (right upper lobe is not visible on this slice).
tem was developed (trained). For example, emphysema distorts the architecture of the lungs and their fissural surfaces meaning that automated systems often fail and must be edited. For this to be practical in clinical trials, the automated algorithm is run and then initially edited by a laboratory technician. The segmentation is then approved by a radiologist.

Following segmentation the system then computes the density mask (DM) as the percentage of pixels within each lobe that are below $-910$ HU (a threshold determined by Ref. [9]). Based on this score, a patient is eligible for treatment if they have heterogeneous emphysema, i.e., different scores in adjacent lobes. The CAD system can then also determine the target lobe as the most severely diseased, i.e., highest DM score.

To support these operations the database contains tables for storing segmentation results as ROIs [21], quantitative data and user information. The data model also allows a radiologist to sign-off on a case at which point it becomes locked in the database. The necessary tables are associated with an image series, i.e., with rows in the Series table.

2.4. Statistical analysis and reporting

Results for an individual patient are reported in Portable Document Format (PDF) via the web (see Fig. 4). Clinical sites have password-protected access to reports for their patients. This web-based report shows status information for a given patient (whether images have been received and analysed) as well as density mask scores and lobar targeting information. These forms are generated on the fly by querying the database, meaning that the moment a radiologist approves a case at the core lab the report is available online at the clinical site.

The database can also be mined to perform quality control (QC) checks and to perform statistical analyses related to the trial. For the VENT we expect that change in lobar volume will be an indicator of the success of the treatment. Therefore as part of the QC procedures CT-derived lung volumes are compared against total lung capacity obtained from pulmonary function tests (body plethysmography).

3. Results

A large number of clinical trial subjects have been analysed within the CAD infrastructure. For example, in the VENT 1264 patients were screened using quantitative CAD. As part of the QC for these subjects, their TLC CT volume was found to have a high correlation ($r = 0.89$) with pulmonary function tests.

Fig. 5 shows the potential of CAD to evaluate lobar volume reduction in emphysema treatment trials. It shows 3D renderings...
of segmented right lung lobes before and after a lobar volume reduction treatment. The images indicate reduction of the right upper lobe volume and expansion of the right lower lobe post-treatment.

4. Discussion

This work represents a major advance for CAD in terms of treatment decision support and response assessment. Physicians are now making treatment decisions in a minimally invasive procedure based directly on output from a CAD system.

Quantitation of lung disease on CT is an active area of research [22,1,3] and in particular for emphysema [10]. A number of systems are under development for automated lobar segmentation on thin-section CT image data [23–25]. However, reliable lobar segmentation remains a challenge because of anatomically incomplete fissures, anatomic variability of the minor fissure and because of irregularities in the fissural plane due to diseases such as emphysema. Moreover, these techniques are only applicable to thin-section imaging. Therefore, to achieve reliable lobar segmentation using thick-section CT images we employed the semi-automated approach described above. To our knowledge, the VENT represents the largest number of cases on which quantitative lobar lung analysis has been performed in a clinical trial.

A key to acceptance and wide-spread application of CAD technology is in strong validation studies and an emphasis on standardization and QC. The density mask measure has been validated against pathology [9], and analyses for QC purposes have been central to VENT as described in Section 3.

For CAD to be usable in clinical trials a number of components are required beyond the CAD system itself. In this paper we have described the key components and an architecture in which they are linked through a database management system. We have described an application of the architecture in an emphysema trial where CAD played a new and pivotal role in treatment planning. The architectural requirements are similar for clinical trials involving other diseases and organ systems, and we have also applied this infrastructure in the oncology domain [26,27].

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References


