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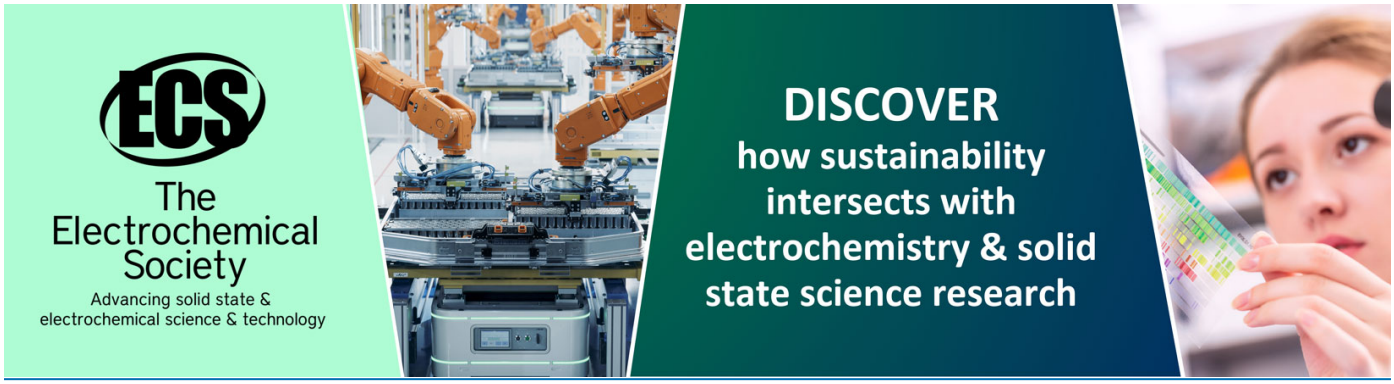

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Development of a Multi-Centre Clinical Trial Data Archiving and Analysis Platform for Functional Imaging

Brandon Driscoll [1], David Jaffray [1,2,3] & Catherine Coolens [1,2,3]

1) Department of Radiation Physics, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, Ontario, M5G 2M9, Canada
2) Department Radiation Oncology, University of Toronto, 150 College St, Toronto, Ontario, M5S 3E2, Canada
3) Techna Institute, University Health Network 124-100 College Street, Toronto, Ontario, M5G 1L5, Canada

Contact Email: Brandon.Driscoll@rmp.uhn.ca

Abstract. Purpose: To provide clinicians & researchers participating in multi-centre clinical trials with a central repository for large volume dynamic imaging data as well as a set of tools for providing end-to-end testing and image analysis standards of practice. Methods: There are three main pieces to the data archiving and analysis system; the PACS server, the data analysis computer(s) and the high-speed networks that connect them. Each clinical trial is anonymized using a customizable anonymizer and is stored on a PACS only accessible by AE title access control. The remote analysis station consists of a single virtual machine per trial running on a powerful PC supporting multiple simultaneous instances. Imaging data management and analysis is performed within ClearCanvas Workstation® using custom designed plug-ins for kinetic modelling (The DCE-Tool®), quality assurance (The DCE-QA Tool) and RECIST. Results: A framework has been set up currently serving seven clinical trials spanning five hospitals with three more trials to be added over the next six months. After initial rapid image transfer (+ 2 MB/s), all data analysis is done server side making it robust and rapid. This has provided the ability to perform computationally expensive operations such as voxel-wise kinetic modelling on very large data archives (+20 GB/50k images/patient) remotely with minimal end-user hardware. Conclusions: This system is currently in its proof of concept stage but has been used successfully to send and analyze data from remote hospitals. Next steps will involve scaling up the system with a more powerful PACS and multiple high powered analysis machines as well as adding real-time review capabilities.

1. Introduction

Quality results from multi-center radiation oncology clinical trials require consistent and robust trial protocols capable of quantifying or eliminating differences across participating institutions. The Quantitative Imaging for Personalized Cancer Medicine (QIPCM) initiative funded by the Ontario Institute for Cancer Research attempts to address these issues through 3 main aims. 1) Establish a stable software platform for image reads/analysis in clinical trials with capabilities for centralized image archival and remote real-time review. 2) Commission a suite of defined imaging procedures and corresponding accreditation tests for use in clinical trials. 3) Establish and operate a subsidized service to implement and support robust, quantitative imaging in clinical trials.

As part of this initiative, the goal of this work was to provide clinicians & researchers participating in multi-center clinical trials with a central repository and cloud-based software tool set for storing/sharing functional imaging data. This platform will facilitate end-to-end testing and image analysis standards of practice as well as a means of performing dynamic contrast enhanced (DCE) QA to enable scanner accreditation.

2. Methods

There are 4 main components to the Clinical Trials involving Functional Imaging (CTFI) data archiving and analysis system: the CTFI Patient Database, the CTFI PACS, the data analysis engine(s) and the high-speed networks that connect them (Figure 1).

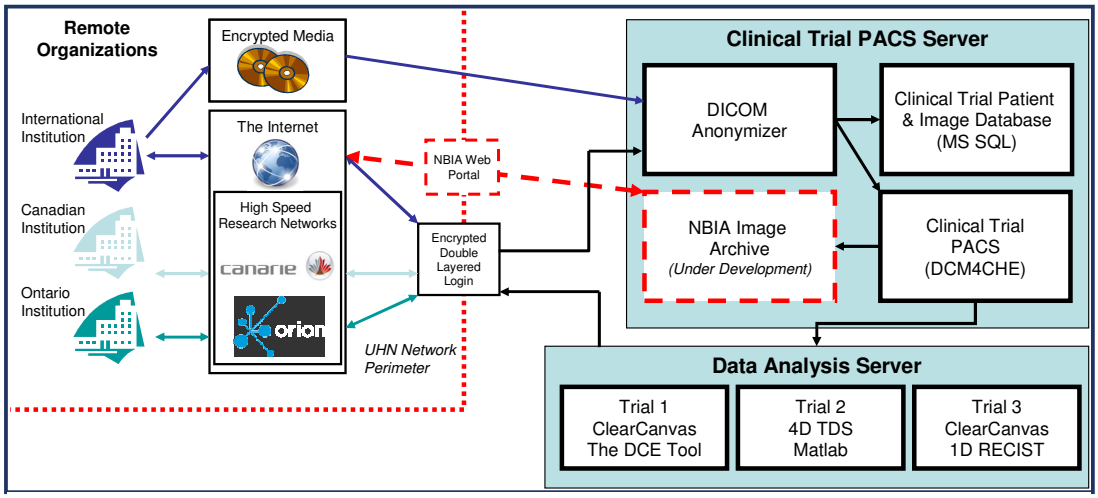

Figure 1: Graphical representation of multicenter clinical trial data management and analysis setup

2.1. Accessing the Network and Transferring Functional Imaging Data

When a clinical trial is registered with the QIPCM initiative, user accounts are generated along with a One Time Pad for remote access. Both the use of the one time pad as well as the users own log in and password are required to access the system. Any computer connected to the internet can gain access to the clinical trial data and management system through a web portal provided they have been assigned the appropriate account information.

Considering the size of image data being transferred the connection between the remote center and the University Health Network (UHN) should be as fast as possible. Many hospitals and research organizations across Ontario are connected to the 100 gigabit per second ORION fibre-optic research network (or CANARIE for the rest of Canada). If the remote PC is connected to one of these organizations, transfer speeds between networks are substantially improved. If the remote PC is not connected to one of the high speed research networks the data can alternatively sent by encrypted hard disk or DVD.

It is important to note that data is only transferred from the remote site to the server once after it is acquired. From then on all data remains within the UHN network and the servers are connected by gigabit connections so transfer between the PACS and analysis PC is very fast.

2.2. Clinical Trial PACS Server

A server has been commissioned which works as a clinical trial data repository. The server currently hosts our data anonymizer, a PACS (picture archiving and communication system) and a Clinical Trial Patient Database running in MS SQL. Figure 2 below outlines how these 3 separate parts interact.

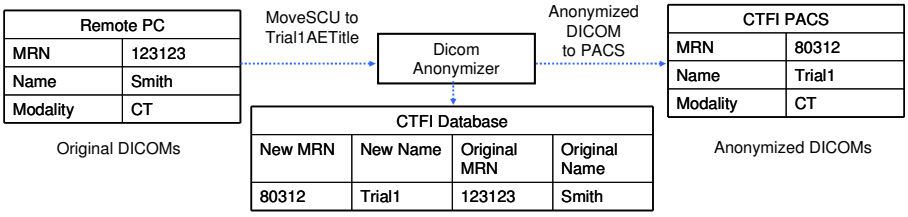

Figure 2: Outline of the CTFI data storage and anonymization pipeline.

2.2.1. Data Anonymization

Since it can never be guaranteed that the data remote sites send to the system will be fully anonymized, the data transfer process includes an anonymizer which receives the original DICOM files and passes them along to the database and the PACS.

A different AE Title is associated with each trial so that different anonymization schemes can be allowed and proper access rights can be enforced. The anonymization works for any modality and has the capability to filter out objects which might contain patient information such as dose reports or other secondary image sets.

2.2.2. Clinical Trial Patient Database

The CTFI database is automatically propagated as DICOM files are received from each clinical trial. The database is designed in MS SQL and queries can be created such that PI's can check the current status of their imaging trial. The patient info that is removed from the DICOM header is stored in a controlled table in the database.

2.2.3. Clinical Trial PACS

The anonymized DICOM data are then forwarded to the Clinical Trial PACS. The PACS runs the DICOM archive and image manager software DCM4Chee (DCM4che.org). The images and study derivatives stored within the PACS are visible only to the appropriate users by AE Title access control.

2.3. Data Analysis Computers

A separate high powered server is used as an access point to the local network. Within this data analysis engine, multiple virtual machines exist (1 per clinical trial). Each virtual machine currently runs a Clear Canvas Workstation and will serve two main purposes; encrypted data transfer from the remote PC to the CTFI server and analysis of the images using one of the custom analysis tools. Two main functional imaging analysis tools were developed for the Clear Canvas platform; one for kinetic modeling (The DCE-Tool®, www.theDCETool.com, section 2.3.1) and one for RECIST (Response Evaluation Criteria in Solid Tumors) (Section 2.3.2). This setup provides the ability to remotely perform computationally expensive operations on very large data archives with minimal end-user hardware. The analysis framework also provides the ability to export the study derivatives back to the Clinical Trial PACS. Other customized tools can also be installed on the clinical trial virtual machine including 4D Functional Image Analysis tools such as 4D TDS [1] or 3D image registration tools.

2.3.1. The DCE Tool

The DCE Tool, within the ClearCanvas framework, is a software plug-in for developing and sharing research results using DCE-CT/MR and PET perfusion studies. Although DCE-CT,MR and PET perfusion studies can provide a direct and quantitative assessment of tumor blood flow, the analysis of these studies are computationally demanding and time consuming.

Some of the important features of the DCE Tool include CT, MR & PET Support, a 4D Time Browser, 2D and 3D ROI Support, MR Intensity to Contrast conversion and a range of different kinetic models including Tofts[2], ATH[3] and Thorwarth[4]. The software is capable of performing

standard 2D/3D ROI analysis or Voxel-Wise analysis and the results can be exported to Microsoft Excel/CSV.

2.3.2. 1D RECIST

1D RECIST is a very common trial endpoint to measure tumour progression[5]. It is not computationally expensive but it is important to have a centralized analysis point for trial results. For this reason the 1D RECIST plug-in was created for ClearCanvas. This tool supports RECIST 1.1 and has automatic long and short axis calculation from a traced ROI. The software can track individual patient response through time via import/export of results and is currently being extended for clinical use.

2.4. Procedures for Tests and Trials: QA and Accreditation of DCE-CT

In order to develop a set of QA procedures for the use of DCE-CT in multi-center clinical trials a previously designed flow phantom[6], was fully validated and then utilized to design a set of standard operating procedures and QA metrics. The developed QA protocol was then applied at three institutions that were part of clinical trial involving DCE-CT and results were compared[7].

An additional ClearCanvas plug-in was designed to support this process in the form of the DCE QA Tool. This tool is capable of performing static and dynamic QA analysis by performing a curve comparison to varied truth protocols in terms of total mass as well as goodness of fit (R^2). These results can be exported to Microsoft Excel for comparison between scanners and protocols.

3. Results

A framework has been set up and currently serves 12 clinical trials spanning 5 hospitals with more trials to be added over the upcoming months. The image store currently holds over 725,000 individual tomographic slices (> 4300 3D volumes) from over 124 functional imaging studies. After initial rapid image transfer, (> 2 MB/s over ORION), all data analysis is done server-side, making it robust and rapid. This has provided the ability to perform computationally expensive operations such as voxel-wise kinetic modeling on very large data archives (+20 GB/50k images/patient) remotely with minimal end-user hardware. This centralized data analysis and storage model also greatly simplifies the addition of new trials and remote sites as very minimal set up is required for the end user.

4. Discussion

The Multi-Centre Clinical Trial Data Analysis and Archival system is fully operational and supporting a number of internal and external trials. The database is constantly growing and the infrastructure needed to support the trials is being upgraded over the next 2 months. At the end of that process the database will have robust backup solutions in place and storage space sufficient to hold 16 million images. Over the next two years the system will also move towards web based viewer platform which is currently in development. This server side rendered viewer will control access to the PACS thus removing the need for one time pads and remote desktop connections.

By having a centralized analysis point using a standardized tool, variations in results can be minimized while allowing multiple observer studies to use the same image files under the same conditions which will increase the reliability of the results[8].

It is important to recognize the work that has been done by the National Cancer Institute (NCI) in attempting to facilitate the archiving and sharing of biomedical imaging through the creation of the National Biomedical Image Archive (NBIA). In order to interact with the many organizations around the world that have begun to use the NBIA standard for sharing and storing images, we are in the process of setting up our own NBIA image repository on the Clinical Trial PACS computer in parallel with our existing setup.

Finally, though the most progress has been made in developing SOPs for DCE-CT QA work has been ongoing on PET and DCE-MR QA protocol development. The phantom has now been validated for DCE-MR using the 3.0 T MR system[9] at the Princess Margaret Cancer Center and the next steps will be to design a robust QA protocol for this modality. A preliminary PET/CT QA protocol has also

been developed using the NEMA IEC Body Set phantom based on the general guidelines of the NCI Centers of Quantitative Imaging Excellence PET/CT protocol[10]. This adapted protocol is being utilized to accredit the multiple institutions in a multi-center Melanoma trial involving FAZA imaging.

5. Conclusions

The Multi-Centre Clinical Trial Data Archiving and Analysis Platform is currently in the process of moving from the proof of concept stage to a production system. It has been used successfully to send and analyze data from remote hospitals as well as to support a number of internal high volume functional imaging trials. Next steps will involve scaling up the system with a more powerful PACS and multiple high powered analysis machines as well as adding real-time review capabilities.

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