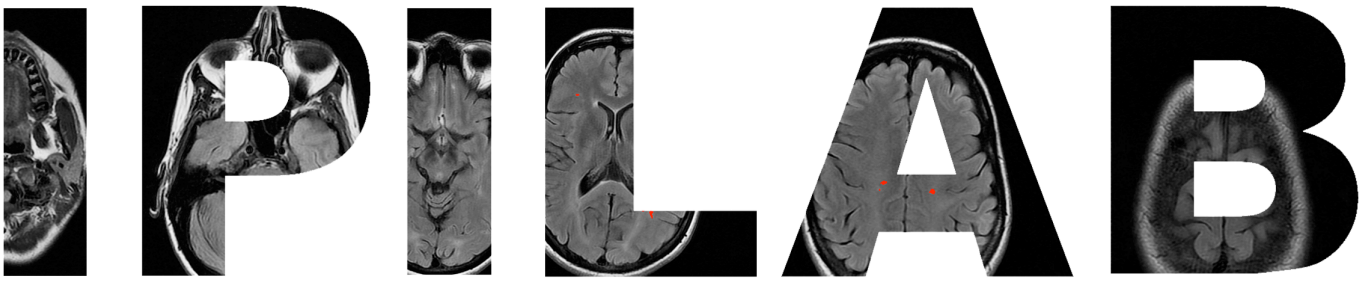

Annual Progress Report
February 2015

DEPARTMENT OF BIOMEDICAL ENGINEERING
VITERBI SCHOOL OF ENGINEERING
UNIVERSITY OF SOUTHERN CALIFORNIA

2015 Annual Report

Image Processing and Informatics Laboratory

Denney Research Center (DRB) 265, 1042 Downey Way, Los Angeles CA 90089-1111. Tel: (213) 821-8395

2014 – 2015 SUMMARY

The Image Processing and Informatics Laboratory (IPILab) has moved to its new and possibly final location near the USC Biomedical Engineering Department in the Denney Research Center (DRB) 265 located on the University Park Campus. The most significant transition is that Dr. Brent Liu, IPILab Director, has accepted a position as full-time teaching professor starting last Fall 2014. Despite this transition, the IPILab continues to thrive with a new direction towards training the new generation of up and coming scientists and researchers interested in Imaging Informatics research. IPILab continues to provide a bridge of collaboration between the two schools - Viterbi School of Engineering and the Keck School of Medicine – as well as hosting visitors interested in the Imaging Informatics research field.

Last year's milestones for past IPILab members include the following:

Two former Provost Fellow PhD students Ruchi Deshpande and Ximing Wang, former T32 trainee Kevin Ma, and PhD student Sneha Verma - all from the BME graduate program - have continued their PhD research. Ruchi advanced to PhD candidacy in April 2015, and was awarded the Alfred E. Mann Biomedical Engineering Fellowship in August 2015. Both she and Kevin will defend at the end of summer 2015. Ximing will follow closely as he plans to advance to PhD candidacy in May 2015. We have three additional MS graduate students from the BME program who are participated in research training activities and plan to enroll in the PhD program. The USC Summer Undergraduate Research Program continues to fund our efforts to recruit and foster bright young undergraduate students searching for future academic research directions and we recruited two undergraduate researchers. This year we also received funding from the Northrop Grumman Enterprise Student Design Project to support undergraduate engineers in IPILab related research projects. In addition, IPILab participated with the Engineering for Health Academy Program in conjunction with Bravo Medical Magnet High School in Los Angeles, CA to train two Senior High School students in Imaging Informatics research for the entire academic school year. IPILab hosted two Visiting Scholars, Hiroshi Arai from the Japan Patent Office and Professor Xue-Jun Zhang from the School of Computer, Electronics and Information at Guangzi University to foster collaborative research for one year. With this list above, the entire academic continuum from High School to Post-Graduate has been represented by the IPILab family.

We have continued in our areas of Medical Imaging Informatics research with a transition to new frontier areas of research: 1) The development of an eFolder System for Multiple Sclerosis Patients; 2) The development of imaging informatics core for large-scale stroke rehab clinical trials (e.g., Interdisciplinary Comprehensive Arm Rehabilitation Evaluations – ICARE); 3) Continued development of data mining of DICOM-RT objects in conventional radiation therapy of Head and Neck cancer patients; 4) An ePR to provide decision support in evaluating does optimization in Stroke Rehabilitation (DOSE); 5) An ePR-based system for Spinal Cord Injury patients for treating pain with Proton Therapy Radiosurgery; and 6) Integrating wearable sensors and imaging data in Wheelchair-bound patients. We attended the RSNA conference in December 2014 with 2 presentations. We are continuing to

transition to new areas in Rehabilitative Science and Physical Therapy since multi-media data is utilized in the research field in addition to patient-related imaging informatics data to form a new Rehab Informatics domain.

In the Table of Contents, this 2015 Annual Report includes materials related to the IPILab, IPILab R & D plans and current results, selected published and in-press peer-reviewed papers during the year, as well as preprints to appear in the *Proceedings of the International Society for Optical Engineering (SPIE) in Medical Imaging*, Orlando, FL, February 22-23, 2015.

Our research has been supported by:

- NIH/NINDS/NICHD U01NS05625 (ICARE)
- NIH/NICHD R01HD065438 (DOSE)
- DOD/Loma Linda University Subcontract No. W81XWH-11-2-0151
- USC Undergraduate Research Award No. 22-1508-1030
- Northrop Grumman Enterprise Student Research Program
- ImageNation, LLC, USA

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STAFF AND COLLABORATORS

Faculty and Administration	
Michael Khoo, PhD Professor and Chairman, Department of Biomedical Engineering (BME)	**Carolee Winstein, PhD** Professor, Biokinesiology and Physical Therapy
Brent J. Liu, PhD Associate Professor of BME Director, IPILab	**Ewa Pietka, PhD, DSc** Professor, Technical University of Silesia, Poland *Visiting Professor of Radiology*
H.K. Huang, DSc, FRCR (Hon.), FAIMBE Professor Emeritus of BME & Radiology	**Jianguo Zhang, PhD** Professor, Shanghai Institute of Technical Physics, The Chinese Academy of Science *Visiting Professor of Radiology*
James Sayre, PhD Professor of Biostatistics and Radiological Science, UCLA *Consultant*	**Edward V. Grant, MD, FACR** Professor and Chairman, Department of Radiology
Maria YY Law, MPhil, BRS, PhD Consultant (Medical Imaging and Radiotherapy) Hong Kong Sanatorium and Hospital *Visiting Associate Professor of Radiology*	**Heinz U. Lemke, Professor** Technical University Berlin
Dr. Jill McNitt-Gray, PhD Professor, Departments of Biological Sciences and BME	**Dr. Philip Requejo, PhD** Adjunct Assistant Professor, BME and Kinesiology
Lilyana Amezcua, MD Assistant Professor of Neurology, Keck Hospital of USC	**Sophia Chun, MD** Chief, SCI at Veterans Health Association
Meng Law, MD Director of Neuroradiology, Keck Hospital of USC	**James Slater, MD** Radiation Medicine, Loma Linda University
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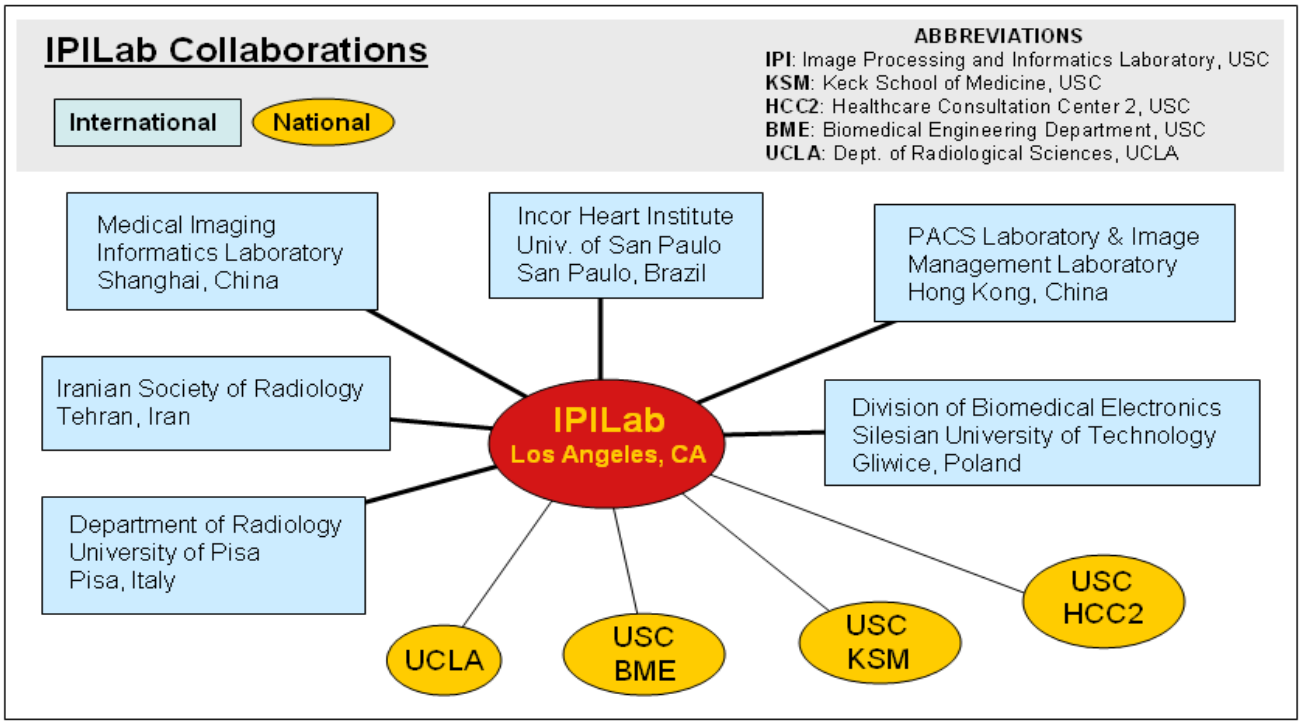
Paymann Moin, MD Radiologist, Advanced Imaging Center, Valencia, CA	**Richard Lee, MD** Radiology Resident
Anh Le, PhD Instructor, UT Southwestern Medical Center	**Jasper Lee, PhD** R&D Manager, SCImage, Los Altos. CA
James Fernandez, MD Radiology Resident, USC	**Hiroshi Arai** Patent Examiner, Japan Patent Office
Graduate Student Assistants	
Kevin Ma, MS (PhD Candidate) **Ruchi Deshpande, MS (PhD Candidate)** **Ximing Wang, MS** **Sneha Verma, MS**	**Jeff Tse** **Mike Kwon** **Joseph Liu**
Undergraduate Research Interns	
Ly Pham	**Nikhil Kotha**

IPILAB ENVIRONMENT AND COLLABORATIONS



IPILAB WEBSITE

University of Southern California

USC Viterbi School of Engineering

Image Processing and Informatics Lab

Keck School of Medicine USC

Home | About | People | Research | Clinical Service | Education | Links | Contacts

About Us

The Image Processing and Informatics Laboratory (IPI) is located at 1042 Downey Way. Denney Research Center (DRB) 264, Los Angeles, CA 90089-1111

Our research facility includes PACS Simulator, Fault-tolerance Server, Data Grid, PACS workstations, CAD servers, and connections to two clinical PACS.

Reseach topics include:

- Computer Aided Detection and Diagnosis
- Data Grid and Image Archival
- Imaging Informatics Technology
- PDA Application in Clinical Environment
- Radiation Therapy Informatics
- Clinical Workflow Model
- CAD - PACS Integration Toolkit
- EPR for a surgical environment
- Multimedia ePR for Rehabilitation
- eFolder for Multiple Sclerosis Decision Support
- Spinal Cord Injury Pain Classification

NEWS AND EVENTS

IPILab has moved to USC Park Campus

October 16th, 2014

We have moved from our previous location in Annenberg Research Park to within the Department of Biomedical Engineering on the USC University Park Campus, in the Denney Research Center Building. Our new location helps to create a more convenient research and learning environment, which encourages more collaborations and sharing of ideas with other research groups in our BME department. We welcome you to visit our new laboratory and offices at:

Denney Research Center (DRB) 264
1042 Downey Way
Los Angeles, CA 90089-1111
Telephone: 213.821.8395

IPILab Update: RSNA 2013

August 20th, 2013

The IPILab have 4 abstracts accepted to RSNA (Radiological Society of North America) 2013.

The list is as follows:

Web-based DICOM-SR Viewer for CAD data of multiple sclerosis lesions in an imaging informatics-based eFolder
Authors: *Brent Liu, Kevin Ma, Jeff Zhang*

An open source, rich-client web application for visualizing DICOM RT data
Authors: *Brent J. Liu, Ruchi R. Deshpande, David Clunie, John DeMarco, Jorge Documet*

Web-based neurological pain classifier tool utilizing Bayesian decision theory for pain classification in spinal cord injury patients.
Authors: *Sneha K. Verma, Sophia Chun, Brent J. Liu*

An imaging informatics-based system with a novel intelligent workflow engine to support rehabilitation clinical trial research
Authors: *Brent Liu, Ximing Wang, Clarisa Martinez, Carolee Winstein*

We would appreciate your interests in our topics.

IPILab Update: RSNA 2011

August 24th, 2011

IPILab have 10 abstracts accepted to RSNA (Radiological Society of North America) 2011, as well as two abstracts from our collaborators.

The list is as follows:

- Extending Imaging Informatics beyond Radiology: A Web-based Multimedia System to Improve Decision Support through Movement Analysis of Elite Athletes [Educational Exhibit]
- Clinical Experiences and Challenges from the Implementation of a Zero Footprint Mobile DICOM WADO Display Solution for Smartphones and Tablets [Poster]

RSNA 2014 POSTERS

USC University of Southern California

RSNA 2014 A Century of Transforming Medicine

Big data in multiple sclerosis analysis: data mining and analysis using a web-based longitudinal study viewer in an imaging informatics-based eFolder system

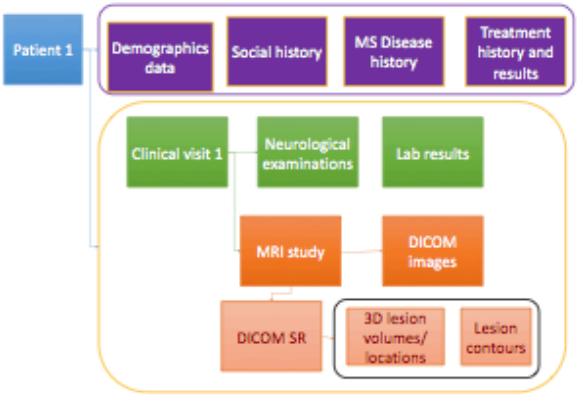
K Ma[1]; X Wang[1]; M Shiroishi[2]; A Lerner[2]; L Amezcua[3]; B Liu[1]

[1]Image Processing and Informatics Lab, Dept. of Biomedical Engineering, Viterbi School of Engineering, USC
[2]Dept. of Radiology, Keck School of Medicine, USC [3]Dept. of Neurology, Keck School of Medicine, USC

Introduction:

- Big data in medical imaging includes both large quantity and complexity of modern patient data: integrating complete patient profiles with imaging data to provide more comprehensive patient care
- The multiple sclerosis eFolder is designed to perform big data analysis in medical imaging by:
  - Integrating patients' social demographic data, neurological exam data, imaging data, and quantitative image analysis data
  - Tracking disease progress in longitudinal MR studies
  - Quantitatively analyze patient's imaging data and relate changes with treatment, patient's age, medical history, etc.
  - Web-based platform allowing large-scale data storage and analysis across multiple sites

MS eFolder Big Data Model

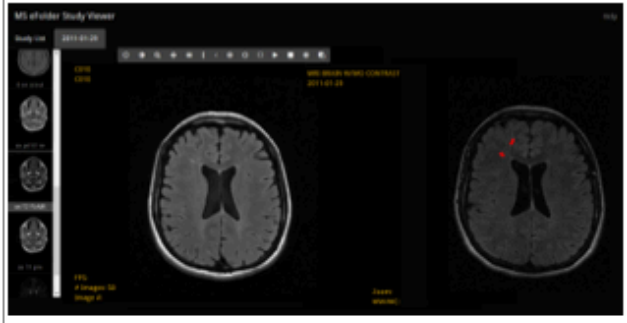


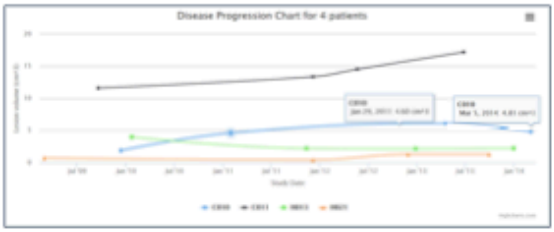
USC University of Southern California

RSNA 2014 A Century of Transforming Medicine

Highlighted Features to Demonstrate:

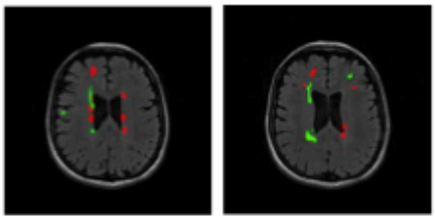
- Enhanced DICOM image viewer with longitudinal study viewing, with visual representations of lesion volume changes over time
- Graphically charting a patient's disease progression
- Perform large-scale data analysis of patients' lesion characteristics based on ethnicity differences
- Complete MS patient profiles with longitudinal studies
- Data mining of MS patients by demographic information, medical history, and quantitative imaging data (i.e. lesion volume, lesion location, white/grey matter volume) in the structured report format

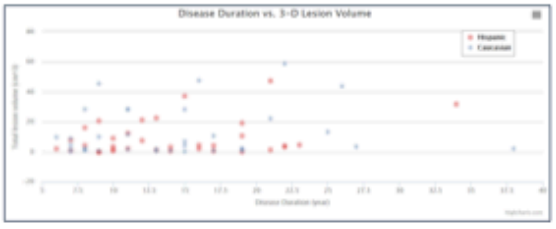




Red: from 2011-01-29 study

Green: from 2014-03-05 study





USC University of Southern California | *Image Processing and Informatics Lab (IPILab)* | RSNA 2014

Moving Towards Big Data Analytics in Radiation Therapy – Dynamic Decision Support through Data Mining

R. Deshpande, MS[1]; J. DeMarco, PhD[2]; B. J. Liu, PhD[1]

1 – Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, CA

2- Department of Radiation Oncology, University of California, Los Angeles, CA

GOAL: Streamline Radiation Therapy Workflow for Simplified, Methodical & Evidence-Based Treatment Planning

Knowledge: Database of retrospective plans	Insights: Relevant decision support recommendations	Diversity: Multi-institutional data to broaden knowledge diversity	Vendor-Neutrality: DICOM standards to enable diversity

WORKFLOW: Comparison of Radiation Therapy Treatment Planning workflow with & without Decision Support

CONVENTIONAL TREATMENT PLANNING

Experience, Judgment, Guidelines

1. Physicians draw upon personal experience only
2. Residents & new physicians are at a loss
3. Guidelines are universal, not patient specific
4. Process is not fully quantified

Clinician sets Dose Optimization Parameters

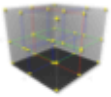
How much dose can healthy tissue tolerate?

Treatment Planning System Computes Final Plan

Beam Intensity Modulation, Final Dose Matrix

PLANNING WITH DECISION SUPPORT

Evidence Based Recommendations



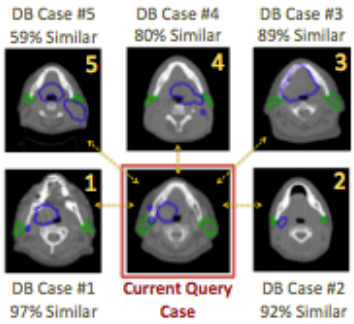
1. Shows what is optimal *and* practically achievable
2. Draws upon practices from multiple institutions & experience from multiple physicians
3. Fully quantified and automated

USC University of Southern California | *Image Processing and Informatics Lab (IPILab)* | RSNA 2014

SYSTEM COMPONENTS

Anatomical Similarity Estimation

Goal: Identify anatomically similar patients from the knowledge base of retrospective cases to use as templates for new patients

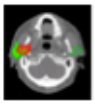


WHAT: Use the spatial relationship between tumor and Organs At Risk to determine similarity

FEATURES: Tumor-OAR Distance, Tumor-OAR Overlap, Tumor location with respect to OARs, Tumor Volume

User-Driven Queries

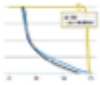
Goal: To identify which similar cases have the best dose characteristics



"Pick similar database cases where Right Parotid Dose < 25 Gy "

WHY: The right parotid is at high risk. Pick cases that achieved the lowest parotid doses to serve as references

"Pick similar database cases where Mean Tumor Dose > 70 Gy "



WHY: Destroying the tumor is of the highest priority. Pick cases that meet the minimum target dose prescription

"Pick database cases for which Similarity > 95 % "

WHY: The user can pick similarity thresholds depending on the similarity score distribution

Data Sharing Infrastructure

Goal: To facilitate multi-institutional collaboration and enhance diversity of the knowledge base

WHAT: Software components that enable simple and secure contribution of treatment planning data from participating sites to the server

FEATURES:

- DICOM RT ensures vendor neutrality
- Browser based DICOM Parser uploads only de-identified fields
- Hassle free HIPAA compliance
- UI facilitates smooth data sharing

SPIE 2015 PRE-PRINTS

Design and Evaluation of an Imaging Informatics System for Analytics-Based Decision Support in Radiation Therapy

Ruchi Deshpande[a], John DeMarco[b], Brent J. Liu[a]
[a]Image Processing and Informatics Laboratory, Department of Biomedical Engineering, University of Southern California, 1042 Downey Way, DRB 265, Los Angeles, CA, USA 90089;
[b]Department of Radiation Oncology, University of California Los Angeles, 200 Medical Plaza Drive, Los Angeles, CA

ABSTRACT

We have developed a comprehensive DICOM RT specific database of retrospective treatment planning data for radiation therapy of head and neck cancer. Further, we have designed and built an imaging informatics module that utilizes this database to perform data mining. The end-goal of this data mining system is to provide radiation therapy decision support for incoming head and neck cancer patients, by identifying best practices from previous patients who had the most similar tumor geometries. Since the performance of such systems often depends on the size and quality of the retrospective database, we have also placed an emphasis on developing infrastructure and strategies to encourage data sharing and participation from multiple institutions. The infrastructure and decision support algorithm have both been tested and evaluated with 51 sets of retrospective treatment planning data of head and neck cancer patients. We will present the overall design and architecture of our system, an overview of our decision support mechanism as well as the results of our evaluation.

Keywords: Decision Support, Radiation Therapy, Radiation Oncology, IMRT, Imaging Informatics, Head and Neck Cancer, DICOM RT

1. INTRODUCTION

The biggest challenge in utilizing Radiation Therapy to treat cancer is targeting the tumor with maximum possible radiation dose, while sparing the surrounding normal Organs At Risk (OARs) as much as possible. This is especially difficult to accomplish when the OARs are small and situated very close to the tumor, as in the case of head and neck cancer. Since it is often not possible to spare the OARs in entirety, it is advisable to limit their dose exposure as much as possible. However, the lowest possible, yet practically achievable dose to vital OARs cannot be computed quantitatively, and so clinicians must rely on experience, evidence-based guidelines and trial-and-error methods to arrive at close approximations during treatment planning. This is where computational data mining techniques can help by determining best practices from previous patients with similar anatomical tumor-OAR configurations, to use as templates for the current patient. Our ultimate objective is to build a decision support system that assists clinicians in identifying good OAR dose end-points for patients, and further, in determining treatment-planning parameters that lead to these optimal dose end-points. In order to accomplish this, we must also build a number of essential system components to support the decision making engine by facilitating data collection and management. The following sections describe our workflow analysis and data model, our system architecture, features of the decision support algorithm and preliminary results of evaluating the algorithm.

1.1 Workflow

Before designing a clinical decision support system, or any other medical imaging informatics system, it is essential to analyze the clinical workflow. The next step is to determine where the new system fits into the clinical workflow, and analyze the effect it will have on normal clinical operations. Figure 1 shows the clinical workflow in Radiation Therapy Treatment Planning [5]. It assumes that the patient has already been enrolled for Radiation Therapy, and depicts the steps that follow. These steps are summarized below:

- CT Simulation and Portal Image: Generation of the CT images that are used for treatment planning.

- ROI Contouring: All relevant ROIs are contoured slice-by-slice on the Treatment Planning System (TPS).
- Initial Parameters: Selection and placement of fields, number and direction of beams, etc.
- Dose Grid Calculation: The Treatment Planning System calculates the dose grid.
- Plan Evaluation: Review of Dose Volume Histograms, Isodose contours, dose homogeneity, etc.
- Plan Approval: The radiation oncologist either approves or rejects the plan based on the evaluation results
- Re-adjustments and fine-tuning: Further adjustments to resolve inadequacies (if any) found in the evaluation.

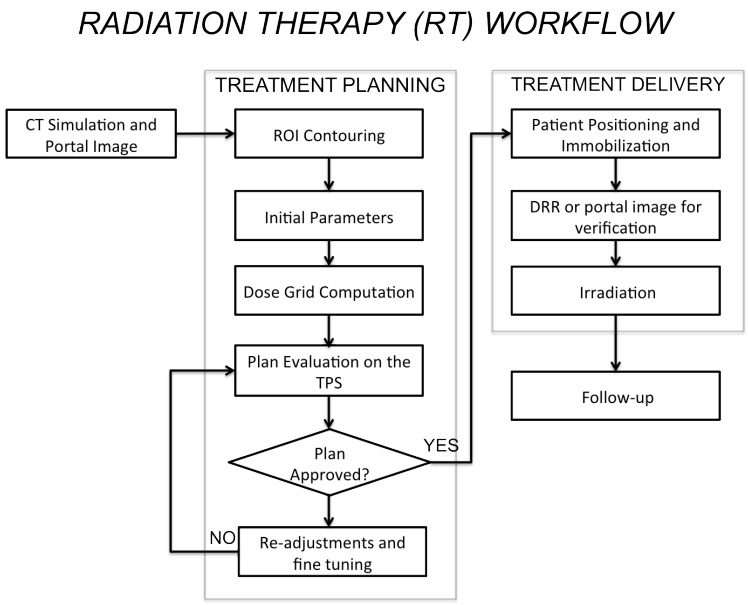


Figure 1. Radiation Therapy Workflow [3]

The decision support system benefits the clinical workflow by potentially reducing the number of iterations of the treatment evaluation loop. Not only can it reduce the number of iterations, but also provides the most optimized evaluation results in very few iterations. This helps to increase workflow efficiency, and to facilitate development of treatment plans that are practical as well as more optimal.

1.2 The Data Model

We have chosen to use the DICOM [4] standard to ensure vendor-neutrality of our system, and as a result our data model is based on the DICOM model of the real world. Good organization and optimal data accessibility are essential in making the machine learning and data analytics tools feasible. A thorough understanding of the structure and the relationship between the principal data elements facilitates proper implementation. The four main types of data objects that the system deals with are: DICOM RT Structure Set, DICOM RT Dose, DICOM RT Plan, DICOM CT Images. Figure 2 shows where each of these objects fit into the data model. The DICOM RT Structure Set object defines the various structures of relevance, or 'Regions Of Interest' (ROIs) such as the radiation target (the tumor) as well as surrounding Organs at Risk (OARs). It also provides the coordinates of the contours that outline these ROIs. The DICOM RT Dose object contains a three-dimensional dose grid, as well as Dose Volume Histogram sequences for all the ROIs defined in the Structure Set object. The DICOM RT Plan object contains technical parameters and details regarding the treatment beams and fields such as shape, number, energy, etc. The CT images are the CT simulation images that are used specifically for treatment planning. The RT objects all fall under a special type of series – the RT series.

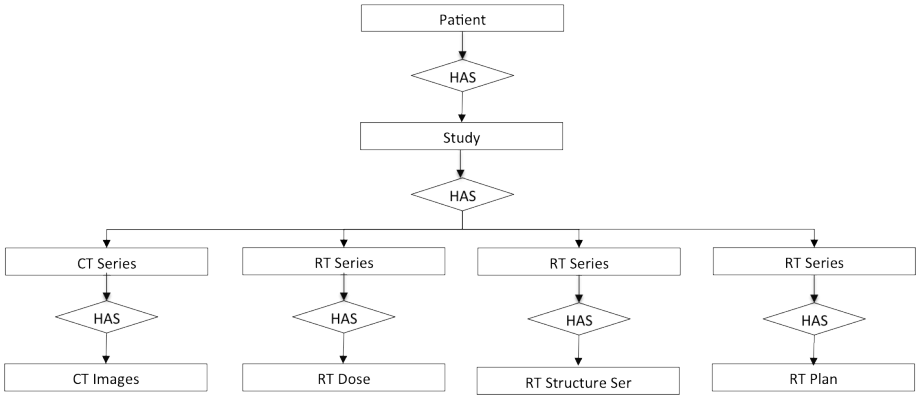


Figure 2. DICOM RT objects in the DICOM data model

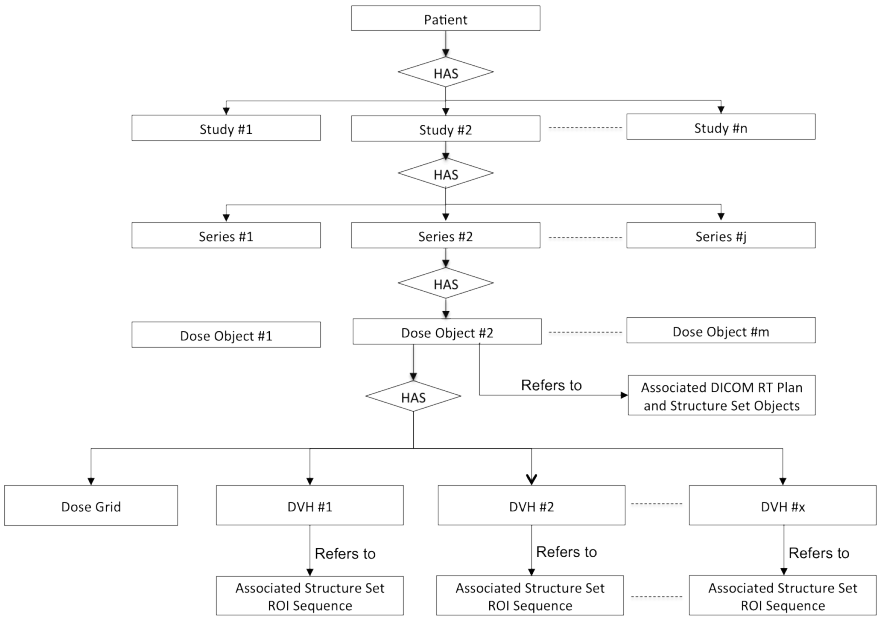


Figure 3. Data Model of the RT Structure Set Object

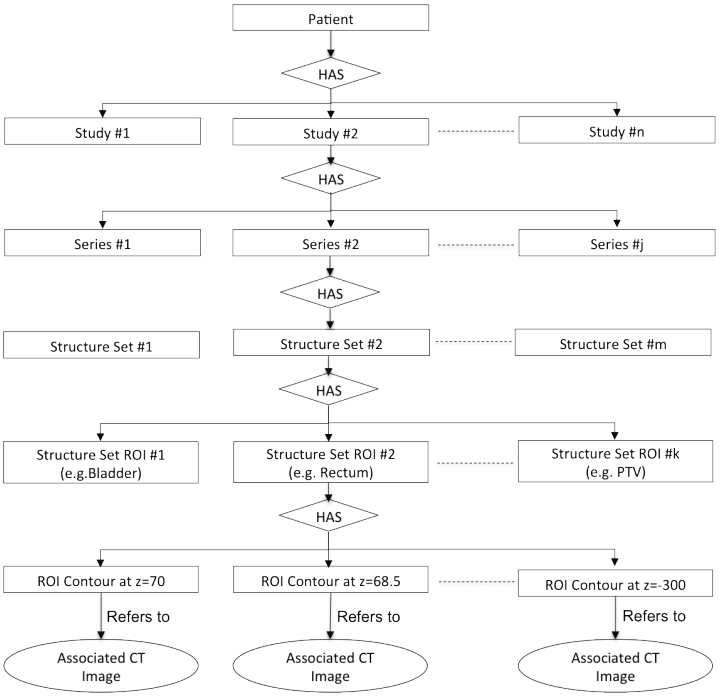


Figure 4. Data Model of the RT Dose Object

2. METHODS

The following sections describe the system architecture and components as well as the decision support algorithm. Proper design and implementation are essential in order to fulfill system goals.

2.1 An Overview of System Architecture

Figure 5 depicts the system architecture and inter-connections between the various components. The main components of the system are described below:

1) The DICOM Parser: The parser is responsible for reception and management of incoming DICOM data. It can operate in one of two modes. The first is server-side parsing, wherein the files are uploaded after anonymization, and then parsed on the server by a python script. The second is client side parsing, where the DICOM files do not leave the client's machine at all, and a JavaScript parser accesses these files through a browser and extracts only certain pre-defined attributes that are known to be anonymous. The parser extracts and then catalogs all the DICOM metadata that it receives into the database.

2) The Database: The database records all relevant metadata associated with various DICOM objects, as well as other data that is derived from the raw DICOM data after processing. Although this derived data is physically contained within the database, it forms a functionally and conceptually specialized subset called the 'knowledge base'. For instance, it contains the overlap volume histogram [1, 2], which is computed from the DICOM RT Dose, RT Structure Set and CT images. Our decision support system uses MySQL, which is an open-source relational database management system.

3) The Feature Extraction Module: This piece is responsible for carrying out computational image processing on the DICOM datasets in order to extract features that can be used by the decision support algorithm. Currently, this is being implemented in MATLAB. A direct connection to MySQL ensures that the results of feature extraction are recorded in the non-DICOM parts of the database in an organized fashion.

4) The Machine Learning module: This module utilizes the features derived by the feature extractor in order to carry out similarity matching between new patients and database patients. This is the heart of the decision support mechanism. This is also being implemented in MATLAB at this point, but we are in the process of porting it to Python scripts that can be integrated directly with the system. The algorithms are performed on the server-side while the results are displayed through the web-based GUI.

5) The Web-based Zero-Footprint Graphical User Interface: The GUI is responsible for presentation and visualization of the results of system analysis, as well as clinical data objects such as CT images, ROI overlays, isodose curves, etc. The GUI is written using HTML and JavaScript.

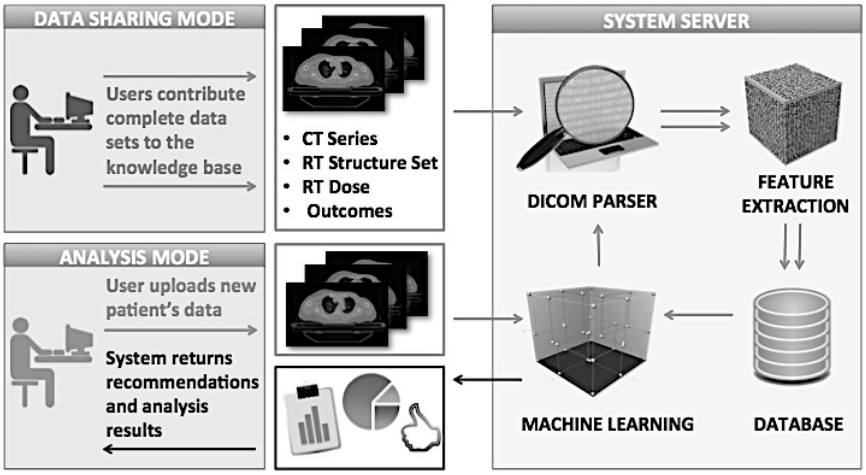


Figure 5. System Component and Architecture diagram

The system may be used in one of two modes as shown in Figure 5. In the data-sharing mode, interested collaborators may contribute treatment planning data to expand the database. On the other hand, the analysis mode allows users to use the system's decision support functionality.

2.2 Client-Side Parser

In order to make the system a collaborative initiative that encourages more participants to contribute data from their institutions, we have enabled the system to work in a local client-side parsing mode. This protocol ensures that the user's DICOM files never leave the client machine. Only those fields that have been pre-selected and verified for anonymity are extracted from the DICOM files that the user selects. This extracted metadata is not identifiable, and thus fulfills HIPAA requirements.

This client-side parser is written in JavaScript. The functions of this toolkit run purely on the client's machine, facilitated by a web browser. The user interface prompts users to select a folder from their local file system. All the DICOM files associated with the treatment data that the user wishes to contribute must be available in this folder. The parser will then associate each data element with an attribute. For e.g. the parser will determine exactly which bytes in the data stream belong to the attribute 'Number of Rows'. Once this mapping is in place, another component of the toolkit will extract data elements for a list of pre-determined attributes, encapsulate this information in a format compatible to the server, and send this encapsulated data to the server.

2.3 The Decision Support Algorithm

The decision support mechanism is based on the principle of identifying anatomically similar database patients to use as reference cases for incoming patients. Anatomical similarity, in this case, refers to the spatial relationship between the tumor and surrounding organs. We have picked specific features that quantify these spatial relationships. By assessing the differences in feature values across various patients, we can derive a similarity ranking for a set of database patients with respect to a new, incoming patient. Some of these features include, but are not limited to – comprehensive distances between OAR voxels and the PTV, overlap between the OARs and the PTV, the directional orientation of the PTV with respect to the OARs, the size of the PTV, etc. These features are calculated for each OAR-ROI pair separately and then combined in a weighted average. After assigning similarity scores to all database patients, we set a similarity threshold to pick a subset of the most similar patients in order to derive practically achievable IMRT dose constraints from them.

3. RESULTS

3.1 Image Sharing Workflow

The implementation of this new client-side DICOM parsing workflow is still in progress. However, we have developed a data sharing workflow that demonstrates how this new protocol can be put to practical use. Currently, the client-side DICOM parser has been fully developed and tested and has been shown to preserve the integrity of the data being extracted. It was tested with a dataset of 10 treatment plans associated with 10 different patients. Each dataset included CT images, DICOM RT Structure Set and DICOM RT Dose. A subject matter expert in Radiation Therapy performed verification of the results. DICOM RT Plan is yet to be tested. Figure 6 shows the workflow of this new data sharing protocol for research applications.

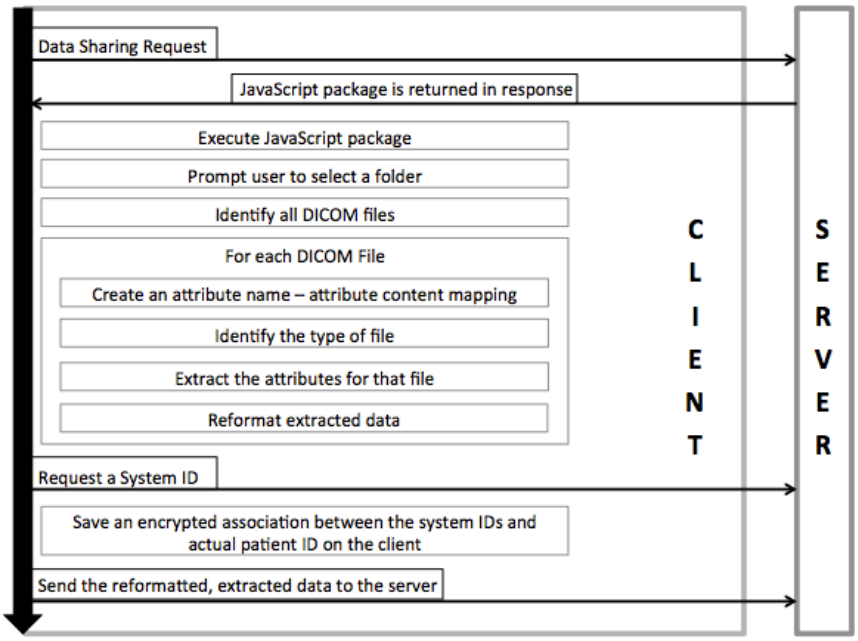


Figure 6. Data Sharing Protocol Workflow in a Cloud-based Environment

(1) The user must first initiate a data sharing protocol with the server. This is a notification to the server that a client wishes to upload data.
(2) The server then returns an acknowledgement and transfers resources back to the client in the form of a JavaScript package that is executed by the client's web browser.
(3) The user is first prompted to select a folder containing all the DICOM files to be processed.
(4) The parser identifies all the DICOM and non-DICOM files stored within sub-folders in the main selected folder. For every DICOM file encountered, the file type is first identified.
(5) Based on the type of file, the parser selects a set of pre-determined attributes to extract since a different set of attributes is associated with each file type.
(6) The values or content for those attributes are extracted and reformatted.
(7) Next, the JavaScript tool sends a request to the server for a new system ID to associate the data with.
(8) This system ID is then stored in a mapping with the true patient ID of the dataset. This mapping is stored in an encrypted format on the client's machine, and can be loaded the next time the user wants to upload follow-up information for the same patient.
(9) The de-identified, reformatted data is then transferred to the server for storage.

3.2 Evaluation of the Similarity Matching algorithm

The evaluation of our decision support system can be divided into two parts. The first deals with the accuracy and overall performance of the algorithm. The second part involves assessment of the clinical impact of our system. We are currently focusing on the first part – evaluating the algorithm itself. In order to validate its results, we must test its

performance in identifying dissimilarities between various OAR-PTV spatial configurations. We plan to accomplish this by introducing artificial translational, rotational and scaling errors to the ROI masks for each patient. By testing the relationship between the magnitude of these errors and the output distance features of the algorithm, we can evaluate the algorithm's accuracy in identifying varying degrees of similarity between different ROI constellations.

To begin with, we simulated spherical PTV and OAR masks per study by extracting the three-dimensional centroids of the actual PTVs and ROIs. This was done to remove the effects of ROI shapes in gauging similarity. The PTV was then displaced away from the OAR in all three dimensions, and the effect of this displacement on our algorithm's features was then observed. This process was repeated 30 times per study, with different levels of displacement per iteration.

The three features that we evaluated are listed in Table 1, alongside the multiple correlation coefficients that quantify the relationship between the displacement vectors (input) and the algorithm's distance features that estimate the dissimilarity (output) introduced by these displacement vectors. The 'multiple correlation co-efficient' column in the table provides the mean multiple correlation coefficients across 10 studies, where 30 distortions were introduced per study. The table shows that there is a pretty strong relationship between the strength of artificially introduced distortions and magnitude of the dissimilarity metrics calculated by the algorithm. However, the algorithm must be tested further with scaling and rotational distortions as well.

Table 1. Association between artificially introduced distortions and computationally calculated differences caused by distortions

Artificially introduced translation error relative to the original ROI masks (Input)	**Dissimilarity b/w original and distorted ROI masks measured by the algorithm (Output)**	**Multiple correlation co-efficient (R^2)**
Components of 3D displacement vectors	Difference between distance profiles (OVH)	0.981
Magnitude of displacement vectors and the x-y projection of their direction angles	Difference between the azimuth angles of the vectors connecting ROI centroids	0.977
z-Component and magnitude of the displacement vector	Difference between the elevation angles of the vectors connecting ROI centroids	0.903

4. DISCUSSION

In summary, we have developed a system that mobilizes data from extensive treatment planning databases, cancer registries, etc.; derives knowledge from this data; and uses it to help clinicians make better informed decisions. In order to ensure compatibility and vendor neutrality, we have chosen to work with DICOM data, especially since most TPS vendors provide the ability to export planning data to DICOM RT. In addition, DICOM provides an organized and effective data model that we have used to build our database schema. We have also developed a data sharing protocol that may encourage more clinicians to contribute data, and may even be incorporated into future registries and research databases. The decision support algorithm itself is under continual testing and improvement. We have conducted informal and subjective analyses of the system's performance, and have found it's potential clinical impact to be very promising. So far, it has succeeded in identifying a number of cases where using the system could yield inputs that might lead to better dose end-points. This stage of our evaluation is currently being planned and designed.

5. CONCLUSION

We have presented the concept of a decision support system for treatment planning of head and neck cancer cases in radiation therapy. We have also outlined the system architecture, described its various components and how they fit together. The outline of our system evaluation was discussed, and preliminary results were touched upon.

REFERENCES

[1] Kazhdan M., Simari P., McNutt T., Wu B., et al., "A Shape Relationship Descriptor for Radiation Therapy Planning", MICCAI 2009; 5762:100-108

[2] Wu B., Ricchetti F., Sanguineti G., Kazhdan M., et al., "Patient geometry-driven information retrieval for IMRT treatment plan quality control", Med Phys. 2009;36(12):5497-505
[3] Deshpande R., Zhou, A., Zhang, J., et al., "Role of an imaging informatics-based DICOM-RT cancer registry in evaluating treatment parameters of IMRT for prostate cancer", Proceedings of SPIE Vol. 8674, 86740O (2013)
[4] Digital Imaging and Communications in Medicine (DICOM) Part 3. Information object definitions. PS3.3-2009
[5] Law M. Y. Y., Liu B. J., "Informatics in Radiology – DICOM RT and Its Utilization in Radiation Therapy", RadioGraphics 2009; 29:655-667

An Imaging Informatics-Based System to Support Animal Studies For Treating Pain in Spinal Cord Injury Utilizing Proton Beam Radiotherapy

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Abstract

In previous years we demonstrated an imaging informatics system designed to support multi-institutional research focused on the utilization of proton therapy for treating spinal cord injury (SCI)-related pain. This year we will demonstrate an update on the system with new modules added to perform image processing on evaluation data using protein-staining methods to observe effects of proton therapy. The overarching goal of the research is to determine the effectiveness of using the proton beam for treating SCI-related neuropathic pain as an alternative to invasive surgical lesioning. The research is a joint collaboration between three major institutes, University of Southern California (data collection/integration and image analysis), Spinal Cord Institute VA Healthcare System, Long Beach (patient subject recruitment), and Loma Linda University and Medical Center (human and preclinical animal studies). The system that we are presenting is one its kind which is capable of integrating a large range of data types, including text data, imaging data, DICOM objects from proton therapy treatment and pathological data. For multi-institutional studies, keeping data secure and integrated is very crucial. Different kinds of data within the study workflow are generated at different stages and different groups of people who process and analyze them in order to see hidden patterns within healthcare data from a broader perspective. The uniqueness of our system relies on the fact that it is platform independent and web-based which makes it very useful in such a large-scale study.

Introduction

Many US combat personnel have sustained nervous tissue trauma during service, which results in neuropathic pain. Neuropathic pain is a significant factor affecting level of function and quality of life. Managing neuropathic pain is challenging problem, as neuropathic syndromes tends to be severe and often refractory to pharmacologic management. There are various studies in which significant effect of drugs could be demonstrated. However, these effects are rated, as partial and a substantial fraction of spinal cord injury (SCI) patients do not benefit from it. The main objective of this clinical study is to determine the effectiveness of using Proton Beam radiotherapy for treating spinal cord injury (SCI) related neuropathic pain as an alternative to invasive surgical lesioning. In select patients, synapse lesioning can provide significant pain control. In previous papers, we presented an imaging informatics-based system, which utilizes DICOM objects for treating pain in SCI patients. This is the first system of its kind that supports integration and standardization of imaging informatics data in DICOM format; clinical evaluation forms outcomes data and treatment planning data from the Treatment planning station (TPS) utilized to administer the proton therapy in DICOM-RT format. It also supports evaluation of SCI subjects for recruitment into the clinical study, which includes the development, and integration of digital forms and tools for automatic evaluation and classification of SCI pain. Overall this system integrates four modules which are Module 1: Pain classifier, Module 2: Web based imaging viewer, Module 3: Proton Therapy treatment data and Module 4: Pathological Image Analysis Tool. In this paper we are presenting the fourth module for the system, which is designed to meet the need for image analysis of pathological images, which are generated during the protein, staining process. This research is a joint collaboration with University of Southern California (USC), Spinal Cord Institute VA Healthcare System, Long Beach, and Loma Linda University. In the following sections we will discuss various stages involved in this study and the system architecture. Also, we will describe various independent modules (Pain classifier, WADO viewer), which are developed to support different stages of this study. We will also discuss the DICOM module for integrating DICOM and DICOM-RT-ION data.

Methods

Background on spinal cord injury related neuropathic pain:

Pain continues to be a significant problem in people with SCI. Despite this there is little consensus regarding the nature, terminology and definitions of the various types of pain that occurs following SCI. This has led to large variation in the reported incidence and prevalence of pain following spinal cord injury. Treatment studies have been hampered by inconsistent and inaccurate identification of pain types. Recently, a group of researchers presented their effort to classify

pain in a systematic way, which is shown in figure 1. The classification, organizes SCI pain hierarchically into three tiers:

- **The first tier** includes the types of nociceptive pain, neuropathic pain, and other and unknown pain.
- **The second tier** includes for the neuropathic and nociceptive categories various subtypes of pain identifies in previous SCI classification.
- **The third tier** is used to specify the primary pain source at the organ level as well as pathology, of either is known. For the "other" pain category, this tier is used to specify distinct reorganized pain entities or syndromes, which do not fulfill the criteria for nociceptive or neuropathic pain.

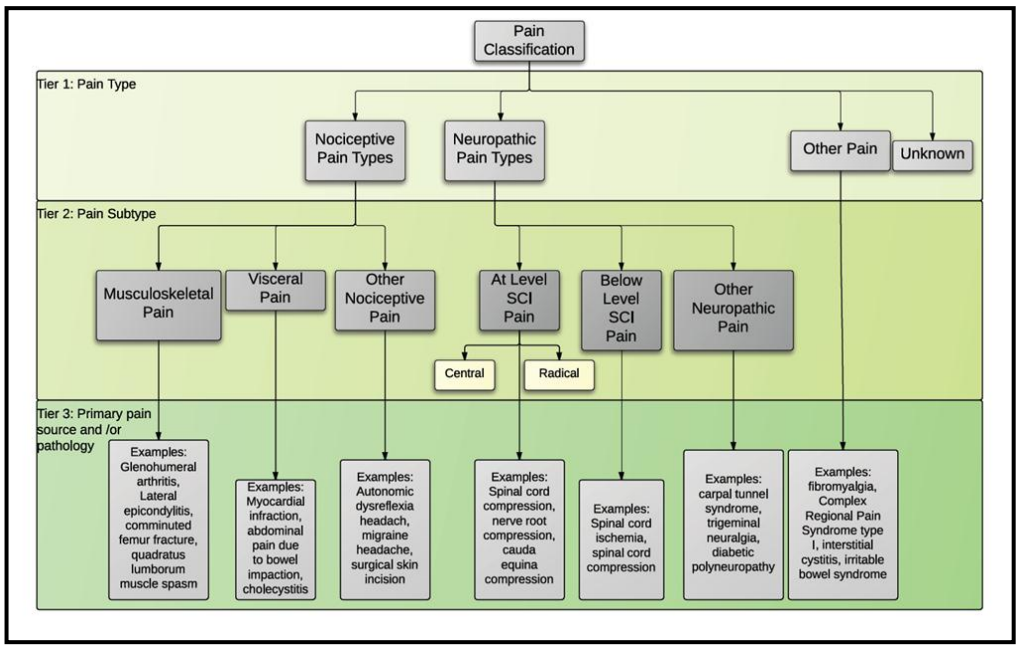

Figure 1: Pain Classification

Pain Management:

Management of chronic pain syndromes following SCI proves very difficult and unfortunately is often only partially effective. As already mentioned, when treating chronic pain, it is essential to comprehensively evaluate the types of pain and psychosocial factors contributing with emphasis on functional capabilities, behavioral responses to pain, adjustment to disability and degree of motivation. This is of great importance when selecting an appropriate combination of pharmacological, physical, and psychological and other treatment approaches. Treatable underlying pathology, such as local nerve root compression or post-traumatic syringomyelia (with expanding syrinx formation) must be excluded.

Neuropathic pain responds poorly to most available treatments including opioids. The drugs that have been demonstrated to be most effective are the anticonvulsants and tricyclic antidepressants. Anticonvulsants work by dampening abnormal neuronal activity in peripheral nerves and the central nervous system. Tricyclic antidepressants are thought to work by increasing the available amounts of the inhibitory transmitters serotonin and noradrenaline. Several surgical approaches (cordotomy, segmental cordectomy, deep brain stimulation) have been reported to provide some pain control, at least initially, although the long-term results in treating SCI-related neuropathic pain have been disappointing. Lesioning of dorsal root entry zone is generally recognized as the most effective surgical treatment for SCI related neuropathic pain. Therefore, a radio-surgical procedure targeting the synapses located in the dorsal root entry zone will a very good option for treating neuropathic pain.

Overview of clinical workflow: Below are the key stages of this clinical study, as shown in figure 2,

- **Patient recruitment at VA Long Beach**
  - ❖ Patient Initial Interview: This first stage is when patient meets the physician for the first time. Physician collects information related to injury (history, pain descriptions etc).
  - ❖ Pain classification: Pain information is used to classify cases with specific pain (neuropathic in this case).

- **Pain Treatment at Loma Linda University**
  - ❖ Consultation: Once the patient's pain is identified as neuropathic pain, the physician will meet with the patients in order to consult about the treatment plan.
  - ❖ Treatment planning: According to the patient needs, a treatment plan is designed for proton beam therapy. At this stage different DICOM objects will be captured which are described in the next section.
  - ❖ Treatment delivery: Treatment will be delivered at this stage and treatment record will be generated.
- **Follow up / Treatment evaluation:** At this stage the improvement in patient condition will be accessed using potential imaging biomarkers.

Also there are two additional stages, which are:

- **Preclinical Animal Study:** Treatment is actually tested on animal first.
- **Preclinical Animal Study evaluation:** Effects of treatment are analyzed to find out if the desired effect if obtained.

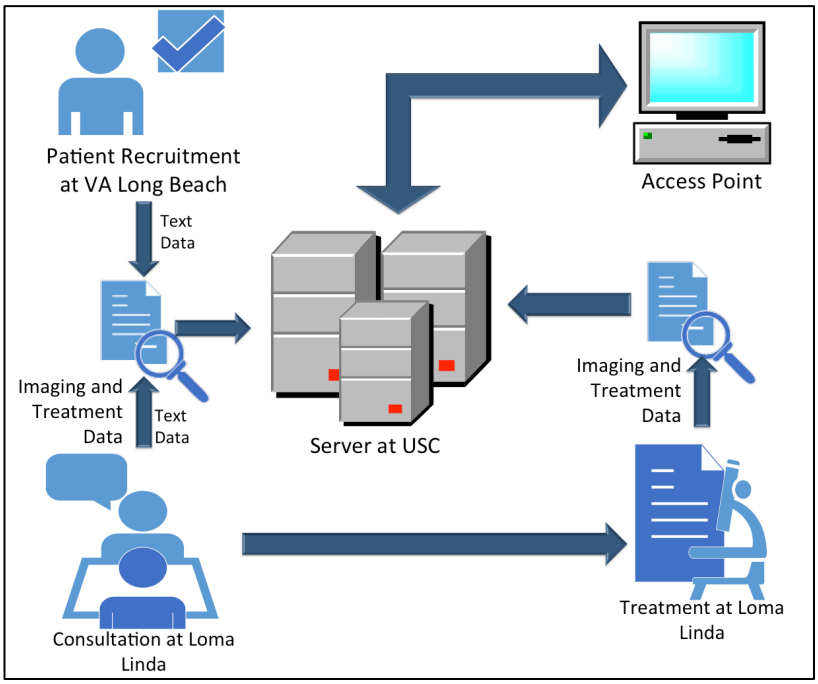

Figure 2: Clinical Study Overview

Data Elements and Data Flow: For efficient data mining algorithms and a computer support system to work, proper organization and accessibility of data is essential. Data from proton therapy is contained in various DICOM-RT objects as well as other data objects as described below:

- **SCI Pain Related Data**: SCI pain data is a holding place for all information regarding pain type. It contains location of pain, group's details, intensity of pain and all different kind of information that get generated during pain classification for patient recruitment and treatment evaluation phase.
- **RT Structure Set**: To carry out radiotherapy treatment planning, the target tissue and organs at risk (OAR) are defined. This process of segmentation of tomographic images or drawings contours of target tumor and OARs leads to a set of structure, which are defined by DICOM RT structure set object.
- **RT Dose**: Treatment planning systems calculate the radiation dose distribution as a matrix of points associated doses. These dose grid files are supported in the DICOM RT dose object. Definitions also exist in the DICOM RT dose specifications to store relationship between dose and structure through dose volume histograms and dose region of interest (ROI) statics.

- **RT Image**: The RT image objet addresses the requirement for image transfer found in general radiotherapy applications performed on conventional simulators, virtual simulations, and portal imaging devices. Such images may either be acquired directly from the device or digitized using a film digitizer.
- **RT ION Plan**: The RT Ion plan addresses the requirement for transfer of treatment plans generated by manual entry, a virtual simulation system, or a treatment planning system before or during a course of proton therapy treatment. Such plans may contain fractionation information, and define proton beams.
- **RT ION Beams treatment record**: The RT ion beams treatment record addresses the requirement for transfer of treatment session reports generated by a treatment verification system during a course of proton beam treatment, with optional cumulative summary information. It may also be used for transfer of treatment information during delivery

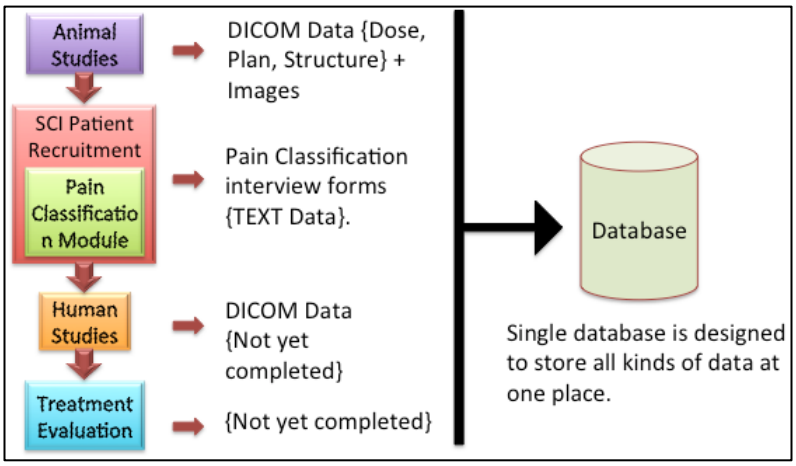

Figure 3: Data Model

- **Protein Staining Imaging:** Protein staining is a process, which is used to detect effects of proton therapy in animal tissues. During this process imaging data is generated in JPEG format, which is analyzed by the expert. In order to automate this process, we develop a system, which is able to integrate this data as well as process it using decision support system.

System Architecture:
Based on various stages of clinical study, as shown in figure 1 and different data elements, we designed an informatics-based system as shown in figure 4. Key components for the system include:

- **Input Data** - It consists of different forms of data, which are either generated or collected at various stages in the workflow. It consists of following:

  - **Recruitment Data** – This data comprises of pain classification object. It contains information for pain sites such as dermatome level, anatomical region, joint related information, ASIA level etc. It also consists text data that indicates of anyone pain location is associated with any other pain location. If there is a relation between multiple pain locations than it also gives details about how they are related.

  - **Initial Form Data** – This consists of the text based form data that is collected during patient recruitment, treatment and follow up.

  - **CT, RT & RT-ION Objects** – This consists of CT images and DICOM objects such as RT structure set, RT Dose, RT Image, RT ION Plan, RT ION Beams treatment record. All are described in Data model section above.

- **Treatment Records** – These are the records collected from the patient charts.

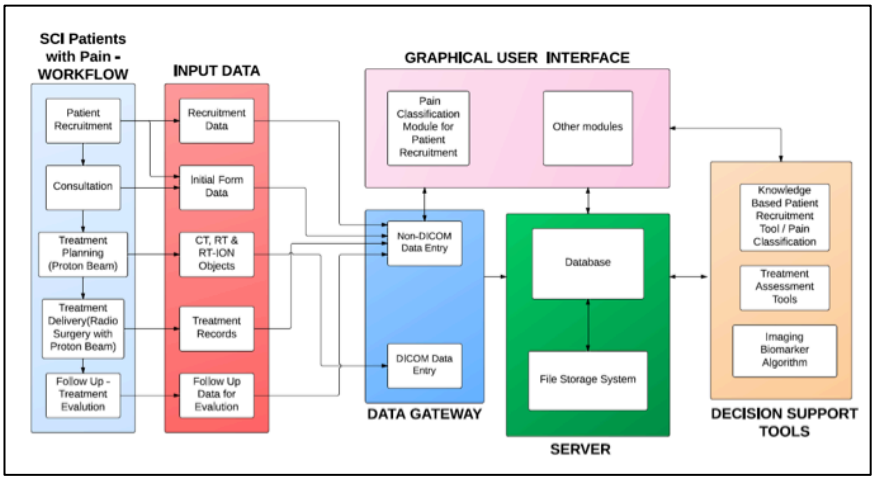

Figure 4: System Architecture

- **Data Gateway**- The data gateway is responsible to get DICOM and non-DICOM data, which is collected or generated at various stages of the work, flow, and store it properly inside the system database. Data gateway has two small modules as described below:

  - **DICOM Module** – The DICOM module allows the system to receive DICOM RT and DICOM RT ION objects from PACS or any TPS that can export DICOM Objects. This allows the data to be uploaded to the system through an upload web interface. Upon receiving the DICOM object the DICOM receiver transfers it to the server and triggers the DICOM extractor to update the database and obtain the knowledge information. Query/ Retrieve Tool, which will be available in future, will be able to provide user the ability to query and retrieve DICOM studies from PACS, TPS, or any DICOM storage node to the Server.

  - **Non-DICOM Module** – The non-DICOM module has two components: Text processing module and DICOM RT converter. The former is designed to handle clinical data in a non-DICOM format (text, Excel spreadsheet etc) and the later to convert data, which are defined in DICOM standard to DICOM objects.

- **Server** – The server provides computational power to other components of the system such as decision support tool, web interface and data gateway. All data, DICOM and non-DICOM, is stored and accessed using the central database. This database design is according to the DICOM data model, which is explained in previous section. The design of the database plays a major role as it affects the response time of the entire system as a whole. Also various data objects that are collected has to be stored in the file system using this data base, therefore it is necessary that all form of data is taken into consideration before designing and implementing it. File storage is a major physical memory holder, which contains entire data at one place.

- **Graphical User Interface** - This is the front end of the system, which allows users (patients, physicians and researchers) to interact with the system. Right now the system has a pain classifier developed and is under testing process. In the future, various modules for treatment assessment will also be available.

- **Decision Support Tools** - There are various decision support tools that can be built upon the knowledge that is contained in the server regarding patient history, pain information, treatment planning and outcomes. Our focus here is to collect all the information, and determine some efficient data-mining algorithm to train the system so that it can pull out information, which can later help in evaluation of the treatment. Also once it's working it can be used to improve the effectiveness of the treatment. Also for this project the decision support tools are very use full in the patient recruitment process. We have developed one such tool, for pain classification, which is explained in the next section.

Pathological Image Analysis Module:

Animal studies were done as the phase 1 to select the most appropriate proton dose which can be used on human tissue before giving the treatment to human subjects. Mini-pigs were used in this study because of their anatomic and physiologic similarity to humans, which makes them the species of choice for verifying dose and treatment techniques. Verification studies included imaging, treatment planning and proton beam delivery using planning data. In order to study the effects of proton beam on animal tissue, pathological tests were performed after the animals were euthanized after 12 months or the time when a significant treatment effect is statistically confirmed. Two types of methods are used in this case: Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and Glial fibrillary acidic protein (GFAP). The output of these methods is in the form of JPEG, which is a well-known standard for images. Figure 5 shows the example of the images (TUNEL and GFAP). TUNEL assay has been designed to detect apoptotic cells that undergo extensive DNA degradation during the late stages of apoptosis.

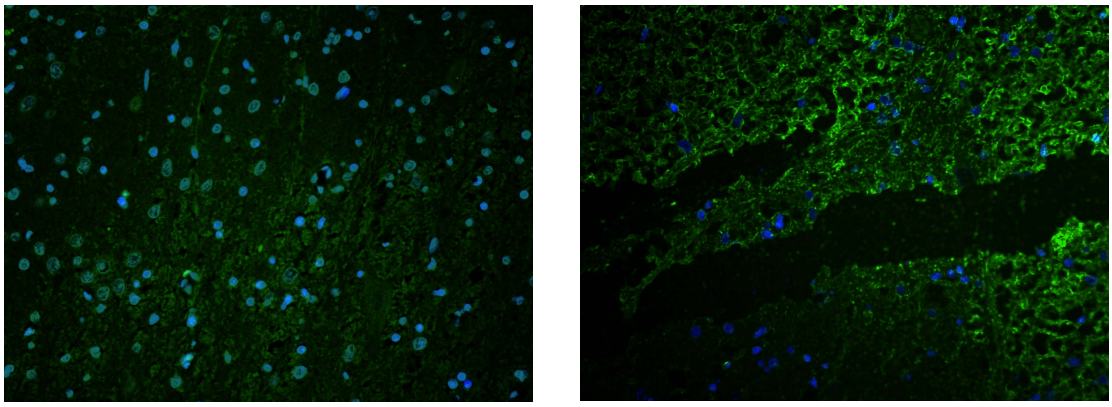

Figure 5: TUNEL & GFAP Image example

Pathological Image Analysis Module Workflow:
As seen in figure 5, the sample image contains bright green and blue spots. Green represents TUNEL Positive and Blue represent the cell nucleus. The output of the image analysis can be expressed as percentage of TUNEL positive per total nucleus or TUNEL positive per area. Also there are staining variations between different batches of specimen.

A prototype of this module was developed using MATLAB and utilizes color intensity based segmentation to contour the green and blue regions of the images as seen in figure 6.

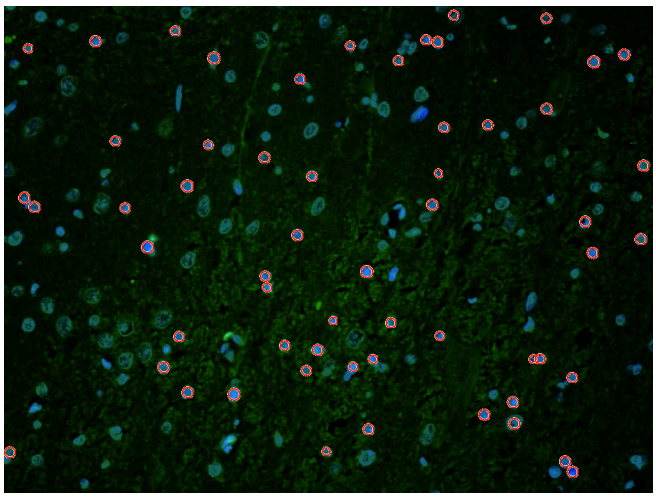

Figure 6: Segmented image

Results

A web-based informatics system is designed and developed which is capable of integrating information from various phases of a large research project. The design of this system is such that it allows the development of all modules independently using various technologies including machine learning algorithms and DICOM data objects. Current system is able to integrate information and run machine-learning algorithms on the data collected via various modules, which includes patient recruitment data, DICOM data and protein staining data.

Figure 7 shows the interactive web based tool for pain classification, which is based on the three layers of knowledge, which were discussed in previous sections. The patients can enter pain information by marking on the human figure and also fill out pain related questions on the same page. Figure 7 shows how pain classification information is available once the patient answers all questions. It shows the probability of pain being a neuropathic versus other pain type. The current system is able to integrate information and run machine-learning algorithms on the data collected via various modules which includes patient recruitment data (demographics, pain history, pain location etc) collected using the pain classifier and DICOM data which are uploaded into the system using the DICOM up loader module. The interface for imaging data reviewer and DICOM object viewer is shown in Figure 8 & 9. Figure 10 shows the prototype of the above described pathological image analysis module.

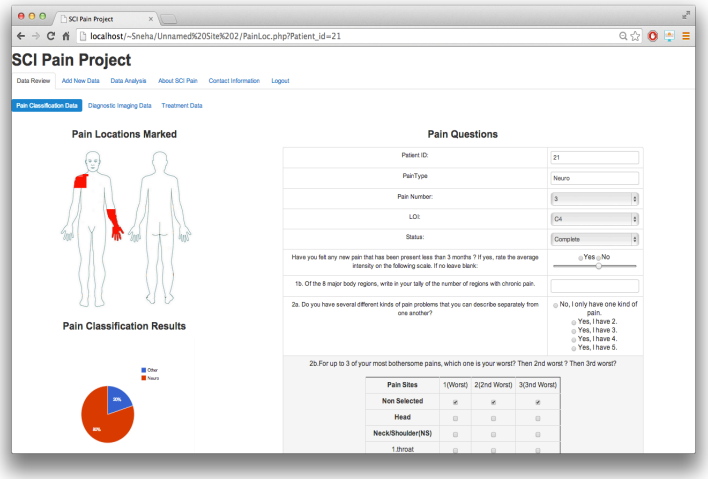

Figure 7: Pain Classification Module Interface (Input)

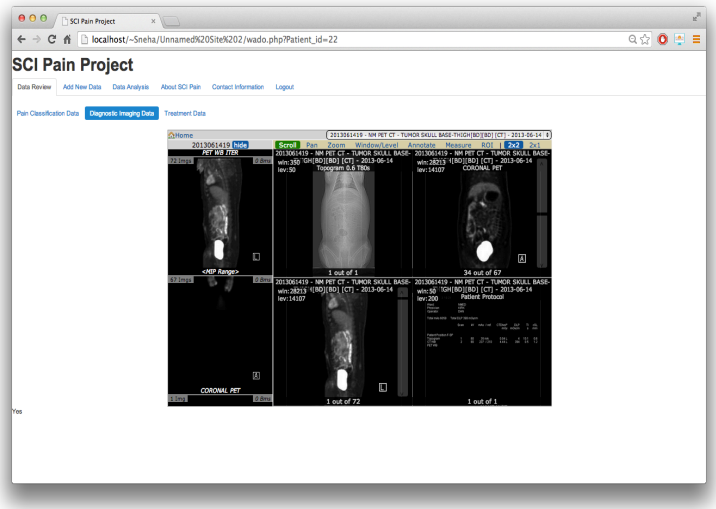

Figure 8: Imaging Data Viewer Module Interface

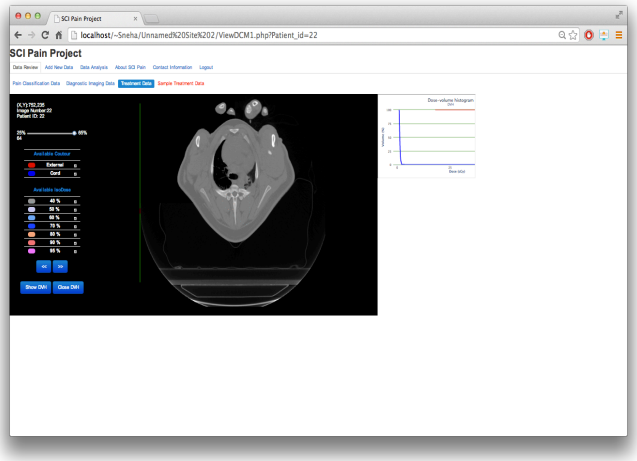

Figure 9: Treatment Data Reviewer Module Interface

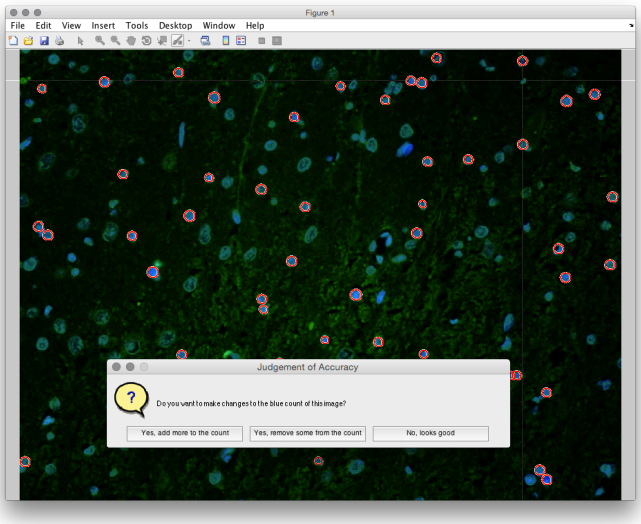

Figure 10: Pathological Image Analysis module

Conclusions & Future work

This is the first system of its kind that integrates preclinical data, from animal studies and research related human studies, on one web-based platform with standardized DICOM data objects. It supports integration and standardization of imaging informatics data in DICOM format; clinical evaluation forms outcomes data and treatment planning data from the Treatment planning station (TPS) utilized to administer the radiation dose in DICOM-RT format. In addition, it supports evaluation of SCI subjects for recruitment into the clinical study, which includes the development, and integration of digital forms and tools for automatic subject evaluation and classification of SCI pain as well as a rules-based decision tree. An additional pathological data analysis package was developed and integrated into the system, which allows protein-staining slides of preclinical animal studies to be included into the system. The system is one a kind, which not only stores different kinds of data in a centralized system and allows different users to access it, but it also allows to see hidden patterns which are discovered using various data mining techniques and to ensure data integrity and confidentiality.

References

[1] Siddall PJ, Taylor DA, Cousins MJ, Classification of pain following spinal cord injury. Spinal Cord (1997) 35, 69-75

[2] Bryce TN, Biering-Soreson F, Finnerup NB, et al International Spinal Cord Injury Pain Classification: Part I. Background and Description. Spinal Cord(2012) 50, 413-417

[3] Middleton J, Siddall P, Managing Pain for adults with spinal cord injury. Rural Spinal Cord Injury Project, June 2002 Revised 2004

[4] Zhang A, Gertych A, Liu BJ, Automatic Bone Age Assessment for Young Children from Newborn to 7-Year-Old Using Carpal Bones, Computerized Medical Imaging and Graphics, 31:4-5, pp. 311-321, 299-310, 2007.

[5] Zhang A, Sayre J, Vachon L, Liu BJ, Huang HK, Cross-racial Discrepancies of Growth Patterns in Bone Age Assessment using the Greulich and Pyle Atlas, Radiology, V. 290, No. 1, pp. 228-235, 2009.

[6] Fernandez, J., Deshpande, R., Wang, X., Liu, B., Brazaitis, M., Munter, F., Liu, M., "Evaluation of a stand-alone computer-aided detection system for acute intra-cranial hemorrhage in emergency environments" in Medical Imaging 2011: Advanced PACS-based Imaging Informatics and Therapeutic Applications, edited by William W. Boonn, Brent J. Liu, Proceedings of SPIE Vol. 7967 (SPIE, Bellingham, WA 2011) 79670H.

Characterizing stroke lesions using digital templates and computer-aided lesion quantification tools in a web-based imaging informatics system for a large-scale stroke rehabilitation clinical trial

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ABSTRACT

Previously, we presented an Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) imaging informatics system that supports a large-scale phase III stroke rehabilitation trial. The ePR system is capable of displaying anonymized patient imaging studies and reports, and the system is accessible to multiple clinical trial sites and users across the United States via the web. However, the prior multicenter stroke rehabilitation trials lack any significant neuroimaging analysis infrastructure. In stroke related clinical trials, identification of the stroke lesion characteristics can be meaningful as recent research shows that lesion characteristics are related to stroke scale and functional recovery after stroke. To facilitate the stroke clinical trials, we hope to gain insight into specific lesion characteristics, such as vascular territory, for patients enrolled into large stroke rehabilitation trials. To enhance the system's capability for data analysis and data reporting, we have integrated new features with the system: a digital brain template display, a computer-aided lesion quantification tool and a digital case report form. The digital brain templates are compiled from published vascular territory templates at each of 5 angles of incidence. These templates were updated to include territories in the brainstem using a vascular territory atlas and the Medical Image Processing, Analysis and Visualization (MIPAV) tool. The digital templates are displayed for side-by-side comparisons and transparent template overlay onto patients' images in the image viewer. The computer aided lesion quantification tool quantifies planimetric lesion volume from user-defined contour. The digital case report form stores user input into a database, then displays contents in the interface to allow for reviewing, editing, and new inputs. In sum, the newly integrated system features provide the user with readily-accessible web-based tools to identify the vascular territory involved, estimate 3D lesion volume, and store these results in a web-based digital format.

Keywords: electronic Patient Record (ePR), Clinical Service, Digital brain templates

1. INTRODUCTION

Stroke is among the top causes of death in the world. Stroke is also the leading cause of significant disability in the world. Approximately, 65% of stroke survivors experience long-term functional limitations and predominantly motor impairments.[1] Recovery of the functionality is important as the difficulty in using the arm can significantly reduce qualify of the life. Physical therapies are one of the major treatments for the recovery after the stroke. To improve the efficacy of current physical rehabilitation treatment, an NIH-supported phase III clinical trial, interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) project, aims to evaluate a new physical therapy treatment method. In this clinical trial, imaging data are utilized to investigate the correlation between recovery and the lesion size and location. In SPIE 2012, we presented an imaging informatics-based electronic patient record (ePR) system to

support the trial[2]. The ePR system is capable of anonymizing, displaying patient imaging studies and reports, and facilitating multi-site collaboration by sharing images within seven clinical sites across the United States. In the past 2 years, 360 patients have been enrolled and over 1100 imaging studies have been uploaded to the system.

However, prior multicenter stroke rehabilitation trials lack any significant neuroimaging analysis infrastructure. This is mostly due to the challenges in handling big data, including data sharing, searching, transferring, analyzing and visualization. Moreover, challenges also include developing a uniform method to analyze scans of varying modality (MRI vs. CT), acquisition settings (different MRI at each clinical site), quality, and time point after stroke.

In stroke related clinical trials, identification of the stroke lesion characteristics can be meaningful as recent research shows that lesion characteristics are related to stroke scale and functional recovery after stroke. To facilitate the stroke clinical trials, we hope to gain insight into specific lesion characteristics, such as vascular territory, for patients enrolled into large stroke rehabilitation trials. To enhance the system's capability for data analysis and data reporting, we have added three new features: a digital brain template display, a computer-aided lesion quantification tool and a digital case report form. The new, integrated system features provide the user with readily-accessible web-based tools to calculate planimetric lesion volume, mark lesion location relative to brain anatomy, and store these results in a web-based digital format.

2. METHODS

The existing solution for ICARE clinical trial is a web-developed system with tools supporting imaging and informatics data. The system is developed in PHP, apache server and MySQL database management system. The system has integrated an uploader with an anonymizer, which de-identify private information and transmit the imaging data through a secure internet connection. The DICOM header is parsed and sorted for storage in a centralized database. The existing system has integrated an annotation tool to markup images, a region-of interest (ROI) extraction tool for manually draw ROI, and a 2-Dimensional measurement tool. The zero-footprint DICOM web viewing application facilitates the tele-consultation. Access though PC, laptops and iPad are supported, and facilitates clinicians by entering data directly via iPad.

Based on the existing system, we developed the three new tools and integrate them with the WADO viewer. The tools are developed based on HTML 5 and JavaScript.

2.1 Digital Brain Templates

Recent studies have shown potential correlations in patients with stroke. In order to accurately localize the ischemic lesions on CT and MRI, the knowledge of vascular supply is also required. MRI allows neurologists to identify anatomic structures precisely, but their arterial supply is not depicted clearly. Therefore, a standardized arterial supply mapping atlas will help clinicians to improve the investigation of the clinicoanatomic correlations with stroke.

In our study, the digital brain template is compiled from published vascular territory templates at each of 5 angles of incidence [3]. These templates were updated to include territories in the brainstem using a vascular territory atlas [4] and the Medical Image Processing, Analysis and Visualization (MIPAV) tool[5]. The templates include a system of 12 axial sections of the hemispheres, brodmann area, and the area of anterior, middle, posterior cerebral arteries.

The templates were converted to PNG format with a transparent background, and uploaded to the system. As shown in figure 1, the digital templates are displayed for side-by-side comparisons. The right side shows the atlas with thumbnails. By selecting one of the templates from the template library on the right side, the system automatically overlay the transparent template onto the images. Selecting another template will result in replacing the current template with the other template onto the images. The user is also able to remove the templates and start over by clicking "Clear Template" button on top of the right side template library.

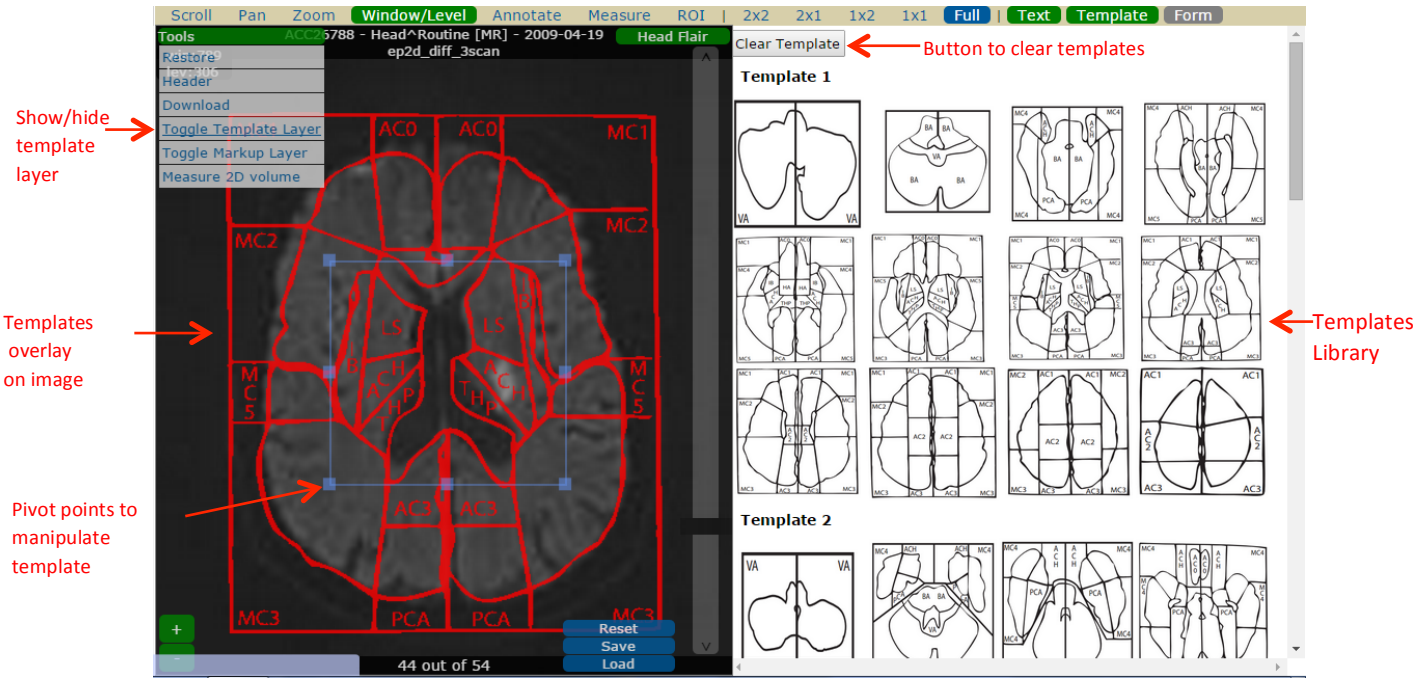

Figure 1. Vascular territory template feature – this subject has a stroke in the left anterior choroidal artery territory, denoted ACH on the template (Templates adapted from Damasio et al. [2])

On the left side, the figure 1 demonstrates a template with the brain. The template is marked up in red curves and broke up to separate districts. Each area is marked with an annotation. In figure 1, this subject has a stroke in the left anterior choroidal artery territory, denoted ACH on the template. Surrounding the center of the template, there are eight blue pivot points on the template image, which allows the user to drag, rotation, and resize the templates. By the manipulation of the image, the user is able to choose the corresponding template and match the template with the brain image. After the user chosen the appropriate the template, the system also allows user hide the templates layer for normal view of the image and show the template overlay on the image. This design aims to facilitate the user to compare the image with and without templates.

2.2 Planimetric Lesion Quantification Tool

In addition to the lesion location, the lesion volume is another principal characteristic. The size of the lesion may also correlate with the stroke severity and the recovery progress afterwards. To facilitate the quantification of the lesion volume, a computer-aided lesion quantification tool is developed. The tool is developed based FabricJS[6] and HTML 5. As demonstrated in figure 2, the tool allows user to draw a contour randomly. When the drawing is finished, the starting point and the end point of the curve connect automatically and the area circled by the curve is filled with a semitransparent mask. The planimetric volume of the filled area is computed based on the masked pixels and spacing information in the DICOM header. If the user circles multiple lesions on the image, the tool will compute the total volume of the lesions.

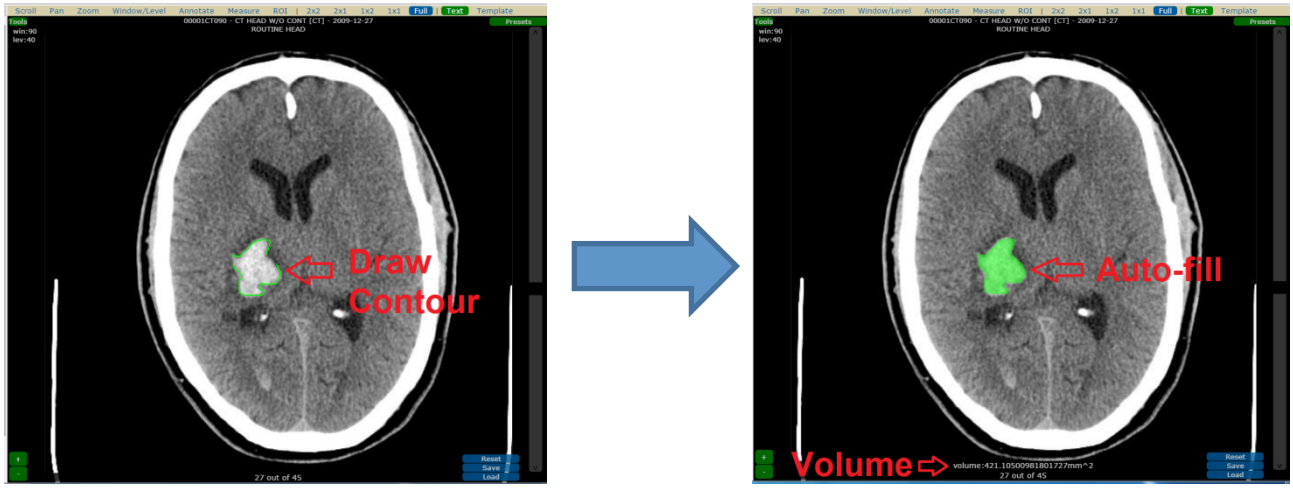

Figure 2. Planimetric Volume Quantification Tool. The tool is equipped with a free-drawing tool and will fill the contour drawn by the user. Planimetric volume is computed based on the filled pixels and the spacing information from the DICOM header. The left image shows the step one: draw a contour. The right image shows the step two: the system automatically fills the area in the contour and shows the computed volume at the bottom of the image.

2.3 Side-by-Side Case Report Form

To facilitate the data collection and the reading result of the characteristics of the lesion, the system also integrates with a side-by-side case report digital form. Compared to traditional method, the side by side design delivers an intuitive view of both images and case report form and hence offers convenience to users. Some information that can be retrieved from DICOM header is automatically loaded to the case report form.

The figure 3 demonstrates the application of three tools jointly. After the user chose the proper template, defining the contour of the lesion, calculated the volume of the lesion, the system is able to show the side-by-side case report form on the same screen. Therefore the imaging analysis results can be recorded through the case report form.

The digital case report form sends user's data into the database, then displays contents in the interface to allow editing and new inputs. Each user is able to see if any other user has reviewed the image, but not allowed to see or modify other's reading result. The integrated web-based system was also optimized using feedback from stroke and rehabilitation physicians.

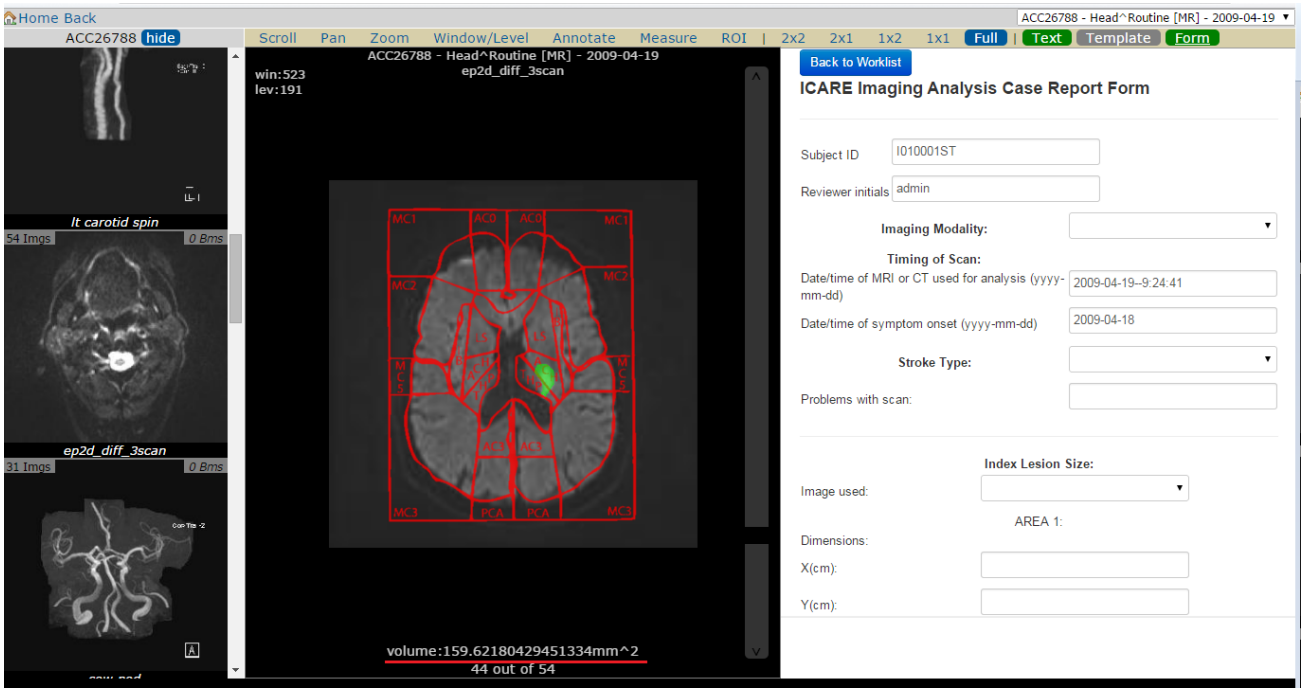

Figure 3. Side-by-side Case Report Form. This figure demonstrates the integration of three new tools. After the user chose the proper template, defining the contour of the lesion, calculated the volume of the lesion, the system is able to show the side-by-side case report form on the same screen. Therefore the imaging analysis results can be recorded through the case report form.

3. RESULTS

Based on the existing ICARE clinical trial informatics system, we have developed three new features. Each feature has been evaluated by users to perform data viewing, data input, and lesion characteristics analysis. The system has collected over 1100 studies from over 360 participants. The system has been validated and is being used by the ICARE clinical trial for imaging analysis currently. In ICARE clinical trial, each study will be evaluated by two neurologists and the results will be compared. The user's feedback is also being collected for future improvements.

4. DISCUSSION and FUTURE WORK

Although some stroke rehabilitation clinical trials have been supported by ePR systems, most of the trials lack a neuroimaging analysis infrastructure. To support neuroimaging analysis, this paper presents web-based stroke study evaluation tools in our multi-site clinical trial ePR system. The vascular territory brain template and planimetric lesion volume quantification tools are readily-accessible for users to perform stroke study evaluations and aid in the workflow of the clinical trial. The vascular territory template atlas provides a tool to facilitate the identification of the lesion location from the arterial supply perspective, not only the anatomical perspective. The other advantage of the tool is that it allows personnel with no prior training in neuroimaging to correctly identify the affected vascular territory. The lesion quantification tool provides a convenience and accurate tool to estimate the lesion volume. Compared to 3D lesion detection tool, which may differ significant from different readers, the planimetric volume is more accurate and repeatable. The side-by-side case report form also provides a convenient way for users to collect reading results. In addition to ICARE clinical trial, these features can also be adapted to meet the requirements of other clinical trials with similar needs.

In the neuroimaging research field, there are already a variety of advanced analysis software. However, the big neuroimaging analysis family is still lack of powerful web-based analysis software. Compared to the stand-alone

analysis software, web-based system are more powerful in data sharing, collaboration and tele-consultation. The web-based characteristic also reduces the requirements of client's devices, and can be easily integrated with a cloud-based computing system, which offers powerful computational capability for data analysis. Another advantage is that user is able to see the analysis result directly from the web-browser without downloading and storing the data in the local machine. Although there are already several web-based system emerged in last several years, these systems are mostly focus on visualization tools, e.g. visualization of the surface. The web-based analysis tools are not available with most of the web-based system. Therefore, by presenting the three features, this paper aims to continue on the web-based neuroimaging analysis tool in future and expand the concept to general neuroimaging clinical trials.

Acknowledgement This work is supported by NIH/NICHD R01HD065438

5. REFERENCE

[1] Cheol E. Han, Michael A. Arbib, Nicolas Schweighofer, Stroke Rehabilitation Reaches a Threshold, Plos Computational Biology

[2] Ximing Wang ; Jorge Documet ; Kathleen A. Garrison ; Carolee J. Winstein ; Brent Liu; A multimedia comprehensive informatics system with decision support tools for a multi-site collaboration research of stroke rehabilitation. Proc. SPIE 8319, Medical Imaging 2012: Advanced PACS-based Imaging Informatics and Therapeutic Applications, 83190U (February 23, 2012); doi:10.1117/12.910971.

[3] Hanna Damasio, MD, Antonio Damasio, MD, PhD. Lesion Analysis in Neuropsychology. Oxford University Press. 1989.

[4] Laurent Tatu, MD, Thierry Moulin, MD, Julien Bogousslavsky, MD and Henri Duvernoy, MD. Arterial territories of the human brain: cerebral hemispheres, Neurology June 1998 vol. 50 no. 6 1699-1708

[5] Medical Image Processing, Analysis, and Visualization Application. http://mipav.cit.nih.gov/

[6] FabricJS library. http://fabricjs.com/

Big data in multiple sclerosis: development of a web-based longitudinal study viewer in an imaging informatics-based eFolder system for complex data analysis and management

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ABSTRACT

In the past, we have developed and displayed a multiple sclerosis eFolder system for patient data storage, image viewing, and automatic lesion quantification results stored in DICOM-SR format. The web-based system aims to be integrated in DICOM-compliant clinical and research environments to aid clinicians in patient treatments and disease tracking. This year, we have further developed the eFolder system to handle big data analysis and data mining in today's medical imaging field. The database has been updated to allow data mining and data look-up from DICOM-SR lesion analysis contents. Longitudinal studies are tracked, and any changes in lesion volumes and brain parenchyma volumes are calculated and shown on the web-based user interface as graphical representations. Longitudinal lesion characteristic changes are compared with patients' disease history, including treatments, symptom progressions, and any other changes in the disease profile. The image viewer is updated such that imaging studies can be viewed side-by-side to allow visual comparisons. We aim to use the web-based medical imaging informatics eFolder system to demonstrate big data analysis in medical imaging, and use the analysis results to predict MS disease trends and patterns in Hispanic and Caucasian populations in our pilot study. The discovery of disease patterns among the two ethnicities is a big data analysis result that will help lead to personalized patient care and treatment planning.

Keywords: multiple sclerosis, big data, data mining, DICOM

1. INTRODUCTION

This manuscript presents new advancements in a disease-centric patient record and data management system for Multiple Sclerosis patients. The eFolder project has been redefined to fit current goals of "big data" in medical imaging and imaging informatics research. The manuscript explains the methodology of storing and managing large amounts of patient data, creating unique and specialized data analysis techniques and results, and will present preliminary results, analysis, and future works for the eFolder to better fit in the clinical and research needs of big data analysis.

1.1. Multiple Sclerosis research

Multiple Sclerosis (MS) is an autoimmune neurological disease that affects approximately 2.5 million people worldwide, and proximately 200 new patients are diagnosed with MS each week in the United States. The body's own immune system attacked the central nervous system, causing damages and scar tissues (called lesions) in brain parenchyma, spinal cord, and optic nerves[1]. There is no known cure for MS, and thus treatments for MS include disease management, reducing number and severity of attacks, and improve patients' ability to function in daily lives[2, 3]. Therefore, longitudinal disease tracking of patients become key in MS treatment.

Magnetic Resonance Imaging (MRI) is a commonly-used tool in diagnosing and monitoring MS by visually displaying lesions[4]. In longitudinal tracking, existing individual MS lesions need to be identified and quantified for monitoring patients' responses to treatments as well as disease progress. To solve these challenges, an imaging-informatics based eFolder has been designed to store and display MS patient data with MR images and MS lesion quantification results. The benefits of the eFolder include integrated patient data repository, an automatic lesion detection and quantification system to allow disease tracking on MR, and a data mining tool for both clinical and research purposes.

1.2. The MS eFolder project

The MS eFolder is a disease-centric, imaging informatics based electronic system that allows management of patient data, imaging data, and post-processing data. The purpose is to integrate patient's neurological examinations, demographic data, and disease history with patient's radiological images to help track a patient's disease profile and disease progression. The MS eFolder system has three main design components: database, graphical user interface, and a computer-aided detection (CAD) system that can quantify lesion volume and number of lesions. The CAD system is used to detect disease changes on the imaging level, including changes in quantity and size of 3-dimensional lesions and changes in brain parenchyma ratio, and correlate MS lesion characteristics (size, number, location) with patient's demographic data for research purposes.

1.2.1. eFolder Database

The eFolder database stores text data such as patient history, MR image locations, and lesion quantification results. Database schema has been developed in MySQL The database structure is built such that one single patient has a unique data entry regarding demographics and social data, has a list of all MR studies regarding to MS, and a list of all post processing results available for that patient. The data therefore is patient-centric and allows quick access to a patient's historical data. Patient demographic data is collected and designed via physicians' survey forms. The imaging database follows the DICOM structure to store metadata from headers. The CAD results database stores quantified lesion statistics on both study and image level. The purpose of the database design is to allow patient lookup and query/retrieve of images based on disease profiles and MS lesion characteristics.

1.2.2. Computer-aided Lesion Detection (CAD) and quantification system

The MS CAD algorithm is designed to output lesion volumes, lesion locations, and total lesion load. The detailed algorithm design splits up into three parts: preprocessing, lesion voxel identification by probability thresholding, and lesion quantification. The algorithm has been prototyped in MATLAB and has been refined to increase post-processing efficiency by reducing processing time.

The CAD algorithm is designed on 3-D MRI brain images. It uses T1 and FLAIR (Fluid attenuated inversion recovery) axial sequences. The algorithm converts the series of MR images into a three-dimensional matrix for 3-D lesion analysis. Lesion voxel classification is based on Statistical Parametric Mapping (SPM) brain image analysis toolkit for MATLAB[4]. Grey matter and white matter are first segmented, and an expectation minimization algorithm for k multidimensional Gaussian mixture[5] is applied to the brain images. The estimation results are used to determine the likelihood of a lesion voxel based on whether the voxel intensity is outside the predetermined normal range. The normal range is current set at within 3 standard deviations of normal FLAIR intensities.

The results from the voxel classification algorithm is then clustered and quantified based on DICOM values, and the final output includes individual lesion volumes in 3D, lesion locations in coordinate space, and total lesion load for the study.

1.3. IHE Post-processing workflow with MS eFolder

Previously, we presented a workflow profile and simulation for MS eFolder within a clinical environment. The workflow is designed based on the Integrating the Healthcare Enterprise (IHE) post-processing workflow profile[6,7]. Figure 1 shows how the MS eFolder is hit in the clinical workflow.

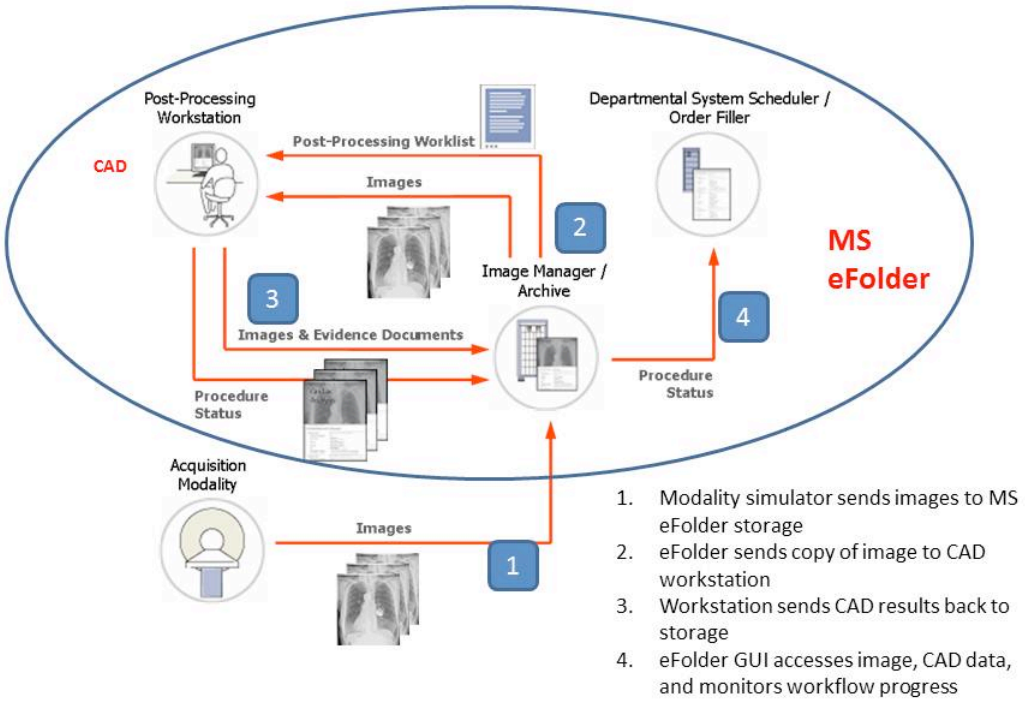

Figure 1. MS eFolder workflow diagram with IHE postprocessing profile. The blue circle indicates all of the components included in the eFolder. The steps 1 through 4 indicates the order of workflow of the demonstration.

The workflow for MS eFolder integration is defined in four steps:

1. MR images are sent from modality simulator to the eFolder server for archiving
2. The eFolder server sends a copy of the images to the CAD Workstation for postprocessing analysis
3. The CAD Workstation sends the completed CAD report back to eFolder server for archiving
4. At the completion of each of the previous steps, a status tracking tool inside eFolder displays alerts of the study progress to the user

The workflow was demonstrated successfully in the laboratory environment, complete with DICOM-SR object display.

1.4. Big Data in Medical Imaging and Imaging Informatics

"Big data" is a new term that describes collection and analysis of large amount and variety of data8. The idea and application of big data is frequently referred to in business analytics, system integration, machine learning, simulation, and visualization9. The characteristics of big data involves volume, variety, velocity, and complexity of data collected. The advantages of analyzing big data is to make data quickly and easily

available to users, as well as offering unique and innovative data analysis tools that may observe trends in research subjects. Results from big data analysis can help draw conclusions of complex problems and help improve a system's performance.

The idea of big data has recently started to apply to the field of medical imaging and imaging informatics. Medical imaging data fits the idea of big data in the four key characteristics mentioned above: a typical radiology clinic generates very large amount of data per year, and the amount of data only increases as enterprise healthcare solutions are on the rise, and more and more data is generated on the daily basis (volume and velocity). For a hospital or clinic, data includes images, videos, waveform, text data, reports, and so on (variety). For each patient, his or her health record in a hospital also includes variety of data, which needs to be integrated to perform advanced analysis (complexity). Figure 2 shows an example of complexity of a MS patient's data, and how eFolder's data model is designed to accommodate the different types of data.

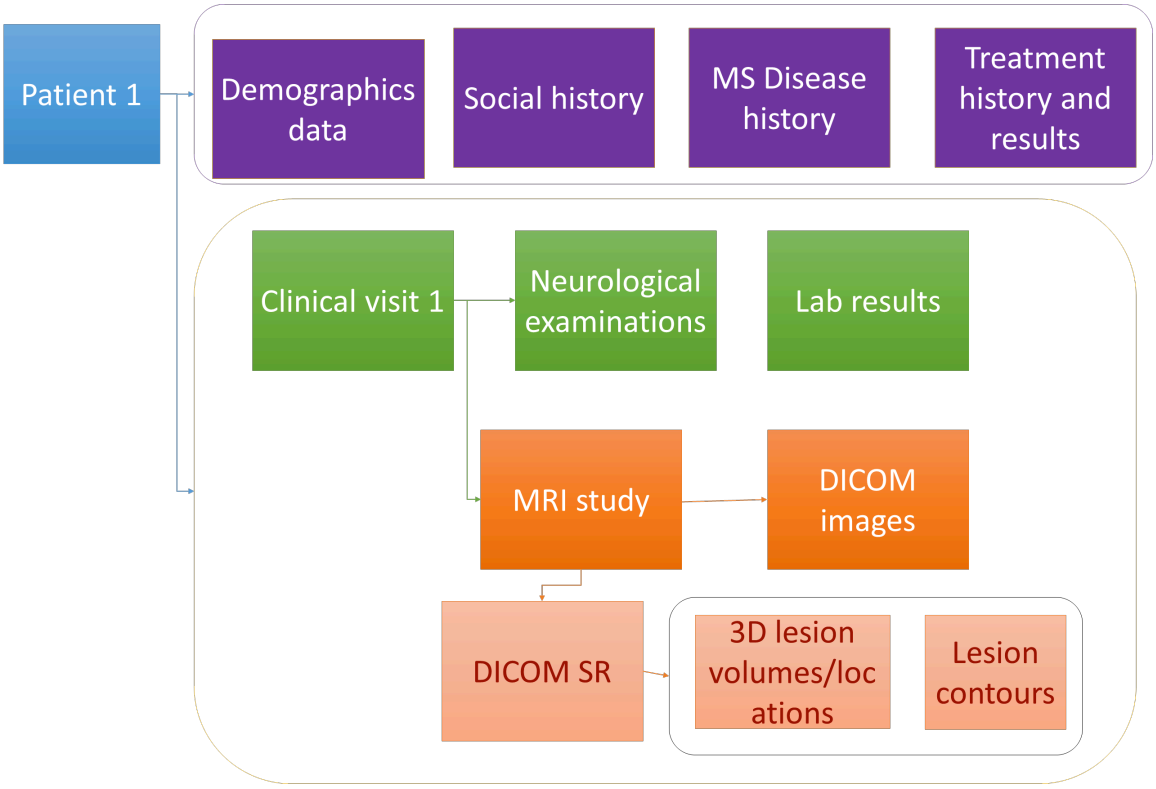

Figure 2. MS eFolder data model that showcases complexity of one patient's data. Each patient, in addition may have multiple clinical visits and scans that further expands the data model. The number of patients, and the number of studies each patient has, highlights the need for big data analysis in medical imaging informatics.

For this paper, we present methodology of how the eFolder incorporates these characteristics in an imaging informatics solution for patient data management and analysis.

2. METHODS

In this section, we will explain additional toolkits that further highlight MS eFolder's capabilities of handling big data analysis from two perspectives: perform longitudinal analysis on MS patients, and perform large-scale data mining using eFolder's database and viewer.

2.1. Data collection

Image and patient data used in the MS eFolder setup is the same as existing eFolder data that has been collected over 3 years. A total of 72 patients are collected: 36 Hispanic and 36 Caucasian patients. The patients of two groups are matched by gender, age (within 5 years), disease duration (within 5 years), and disease type (all are relapse-remitting). All brain MR studies are collected at University of Southern California Academic Medical Center and Los Angeles County Hospital. MR images are in DICOM format and anonymized. All studies contain noncontrast T1 and FLAIR axial slices as required by the MS CAD algorithm. In addition, 4 patients have been selected with longitudinal studies. These patients (randomly selected) have had yearly MRI scans completed at USC-LAC hospitals. Four imaging studies for each patient, taken from years 2009 to 2014, are collected to test the longitudinal study viewer.

2.1.1. CAD data

The CAD algorithm has been performed on all 72 studies and additional longitudinal studies. In addition, lesion contours by neuroradiologists at USC have been collected to act as gold standard for lesion detection. The contours were done manually by two neuroradiologists on Fuji Synapse 3D post-processing client in the clinical environment. Currently the manual contours are used in this project, as the CAD algorithm is still being refined for more consistent accuracy in its results. Figure 3 shows the MATLAB results of a sample data.

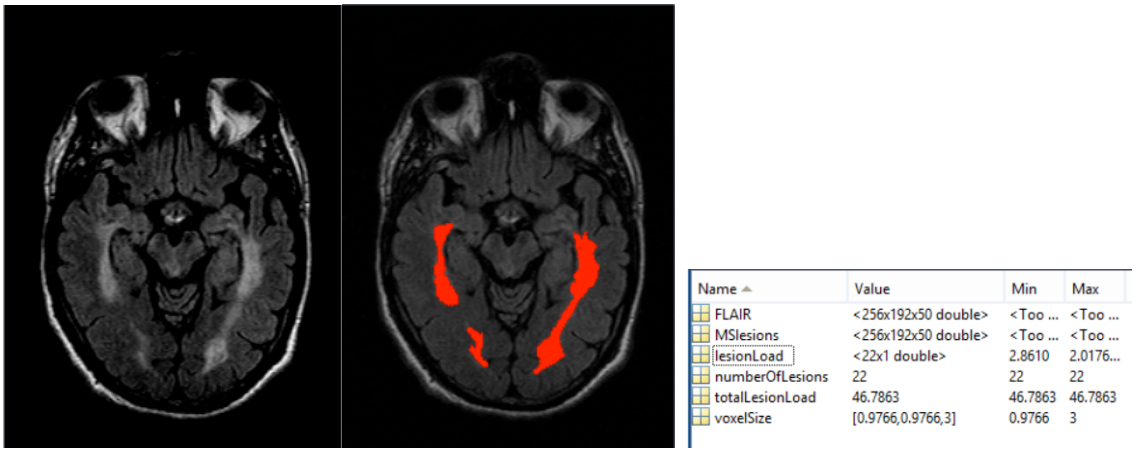

Figure 3. Raw MATLAB output of MS CAD. Left: original FLAIR axial image. Middle: lesion contour overlaid on the FLAIR image. Right: MATLAB outputs. lesionLoad includes individual lesion volumes, numberOfLesions indicates that there are 22 unique lesion bodies in this study, and totalLesionLoad is the sum of all lesion volumes.

2.1.2. Brain Normalization and Lesion Location identification

In order to identify each individual lesions in the same patient in separate longitudinal studies, the studies have to be normalized to a template brain to map the lesions based on their locations. To accomplish this, the brain warping technique using MATLAB's Statistic Parametric Mapping toolkit is again used. SPM's voxel-based morphometry methodology[10,11] is able to warp the subject brain into a template brain with refinement in the subcortical structures. The templated used in this algorithm is the ICBM 152 Nonlinear Atlases version 2009[12,13], which includes labeling of 152 different subcortical structures that is needed for lesion location identification. Once warp parameters for one particular study are obtained through brain warping, the warp parameters will be applied to warp the lesion space from the same study to warp and match the lesion space to the template space. Same lesions across longitudinal studies are identified by their locations in the template space, and those lesion changes can be visually and quantitatively tracked in order to monitor patient's progress. Figure 4 shows a sample workflow of the brain normalization process.

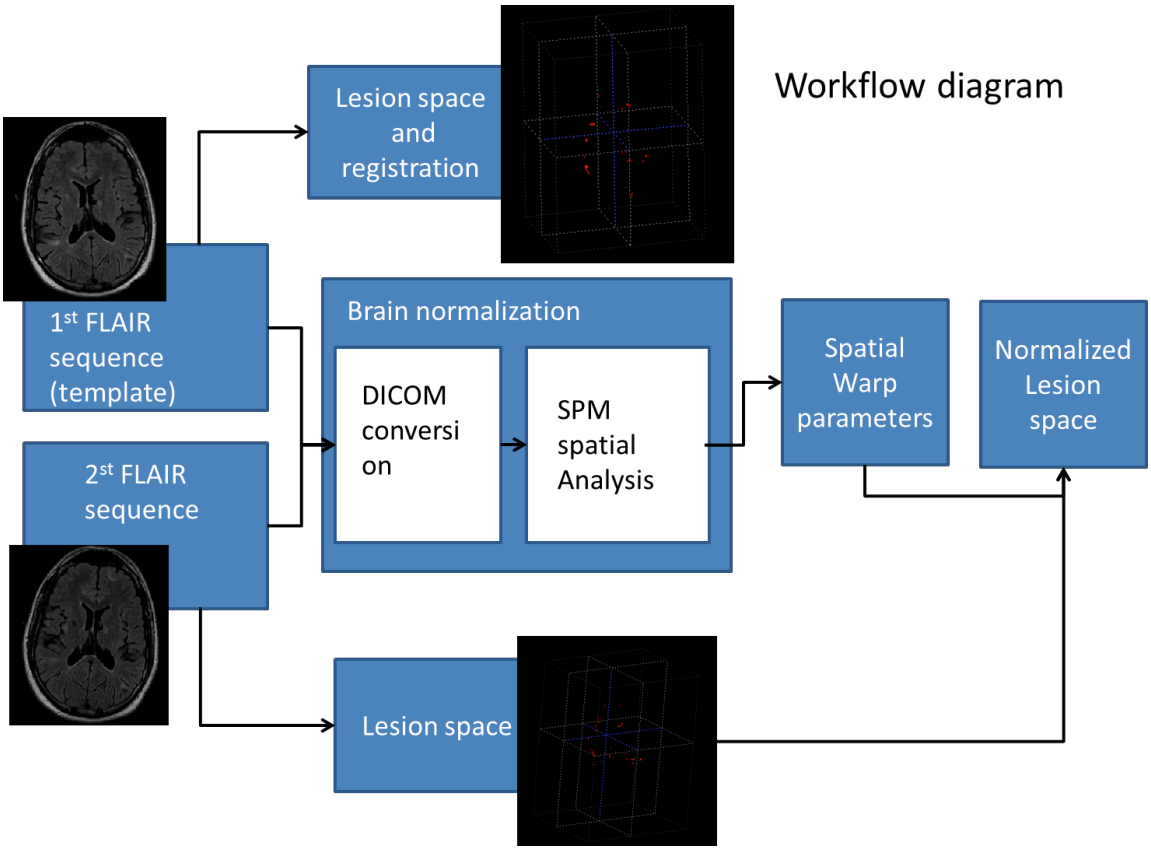

Figure 4. Workflow diagram of brain warping to achieve lesion tracking. The subject's images are first warped by SPM's voxel-based morphology to ICBM template brain, then the warp parameters are used to war the lesion space into the same template space. Lesions then can be tracked by identifying lesion clusters occupying the same coordinates.

2.2. Longitudinal Study and Image Viewer

The eFolder's web-based GUI has been redesigned to include a DICOM image viewer that is designed specifically for viewing longitudinal studies and perform side-by-side image and lesion comparisons to disease progress. Figure 5 shows the current development of the image viewer

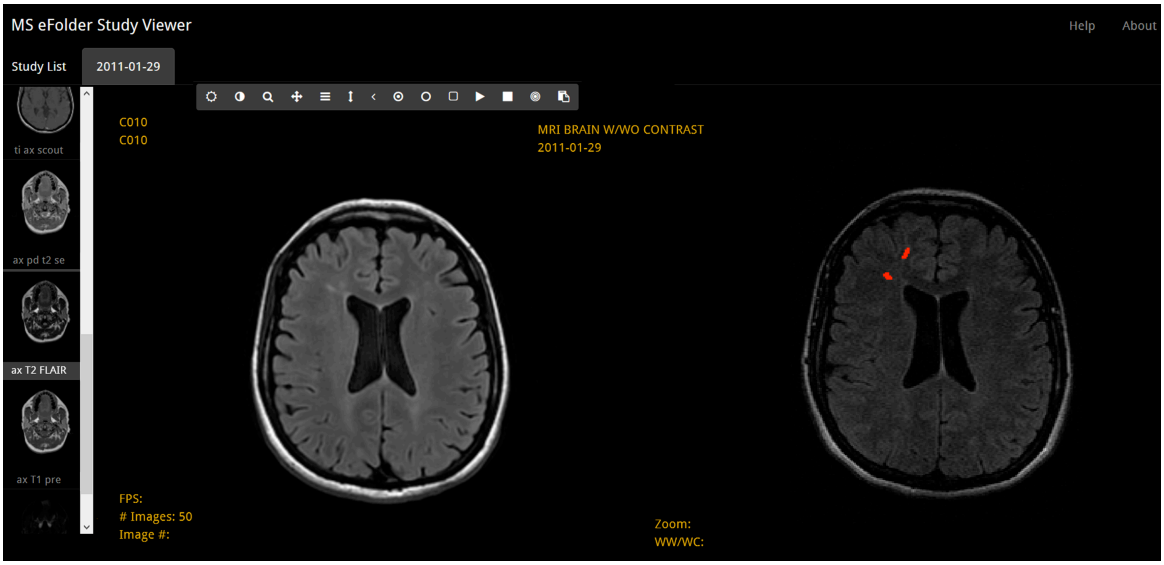

Figure 5. Web-based DICOM image viewer for MS eFolder. The left image is the original DICOM image, and the right image is the DICOM-SC with highlighted lesion contours.

The methodology of the DICOM study viewer is based on the open souce CornerStone JavaScript library[14], while also incorporates JQuery, HTML, and HTML5. For the eFolder system, the viewer is integrated to query and retrieve study information with PHP from eFolder MySQL database.

Additionally, there are several design features to view images from longitudinal studies:

1. DICOM-SC and DICOM-SR objects are displayed alongside images from the study. This feature can be toggled on and off.
2. User can query and retrieve all of the studies of a particular patient, as shown in Figure 6.
3. Users are able to use the second (right) viewing window to display other studies of the same subject via a drop-down menu, for direct comparison between the studies.

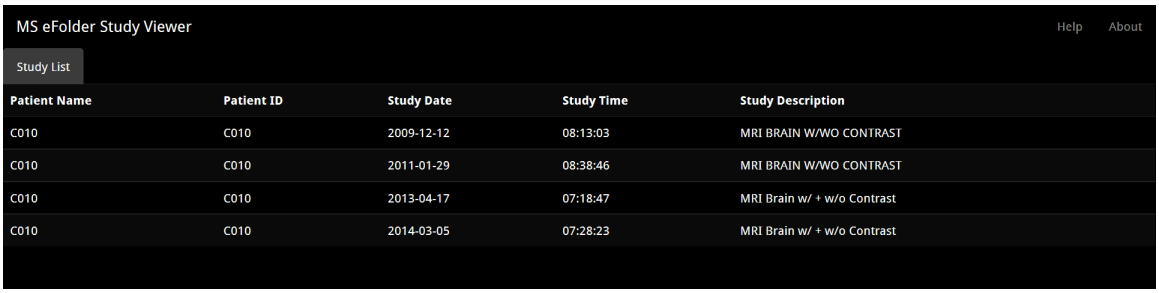

Figure 6. Sample page of the DICOM viewer querying and retrieving all of the studies for the patient 'C010'

The open-source nature of the viewer also allows future implementations of features, several of which are currently in development. These features include:

1. Dynamic lesion contour overlay and display of lesion volume by mouseover of the lesion
2. Enhancing the contour overlay to allow lesion contours from older/newer longitudinal studies, thus creating a direct visual comparison of the lesion volume changes
3. Display of lesion contour objects in 3D
4. Allow query/retrieve based on lesion quantification results.

Figure 7 shows an example of lesion contour overlay for longitudinal studies.

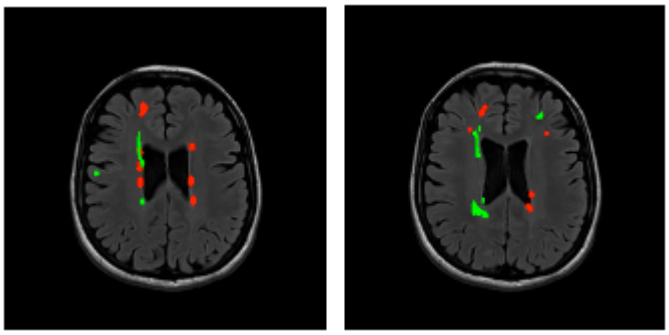

Figure 7. Sample lesion contour overlays on two FLAIR axial slices of the same patient. The red-colored lesion contour is from the 2011 study, and the green lesion contour is the segmentation result from the 2014 study.

2.3. Big data analysis of MS eFolder via data mining tools

For big data analysis, creating unique and complex data analysis from existing data is key. A data analysis toolkit for eFolder has been developed to display analysis results based on user-defined parameters. The web-based toolkit utilizes JQuery and HTML5 libraries provided by open-source toolkit HighCharts[15], and is integrated with PHP and MySQL to access information from the eFolder database. Figure 8 is a sample plotting tool that shows lesion volumes of Hispanic and Caucasian patients versus the number of years that they have been diagnosed to having MS. Figure 9 shows the lesion volume tracking results of the 4 longitudinal studies.

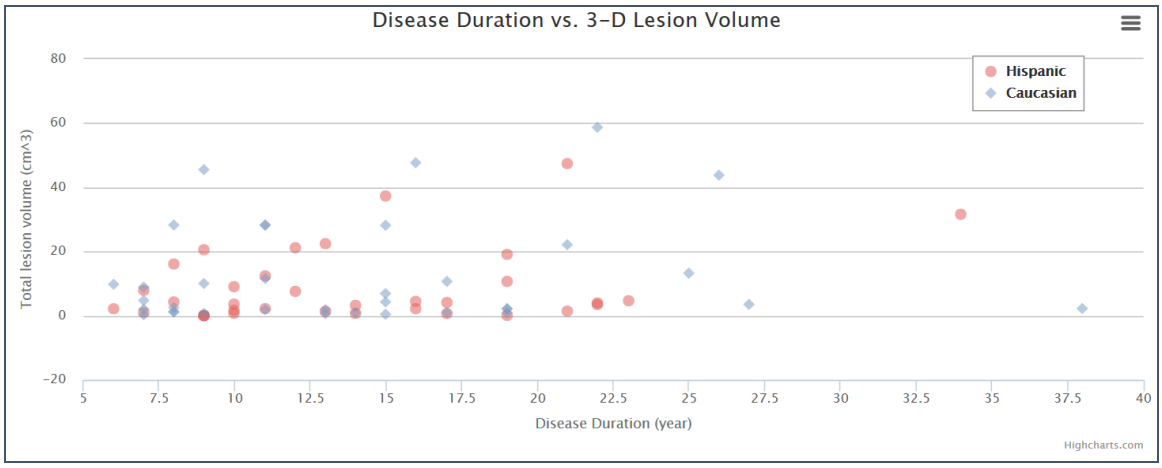

Figure 8. Scatter plot of disease duration vs. 3-D lesion volume for Hispanic and Caucasian MS patients

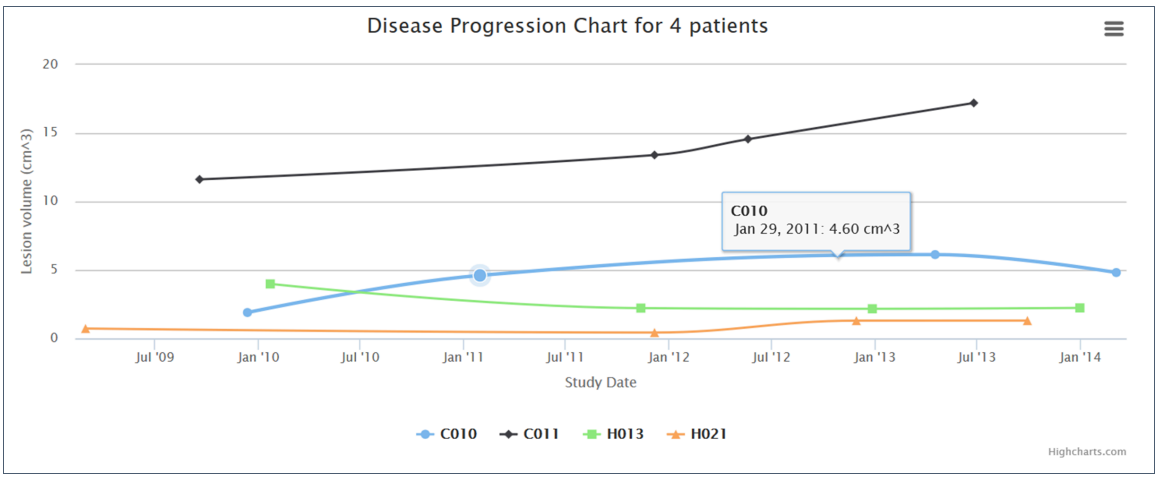

Figure 9. Lesion volume tracking of the 4 patients over 4 studies per patient, with an example of mouse-over that shows statistics of that particular study.

3. RESULTS AND DISCUSSIONS

The data analysis features have been implemented, and the preliminary results have shown that the added toolkits have provided new information and data analysis for users. Brain warping and normalization for identifying lesion location is ongoing, and results are not available at the time of this writing. The quantity of data collected is not qualified to be of "big data", but the complexity of data collected is representative of the type of data collected for electronic patient records, and the eFolder system design can be expanded to accommodate larger amount of data.

For complex data analysis, preliminary results on comparing lesion volume versus disease duration was shown in Figure 8. While the preliminary results on difference between Hispanic and Caucasian patients are inconclusive, the data analysis tool is available for further data analysis with different parameters (gender, age of onset, lesion changes and locations, etc.) Further investigation is currently ongoing to observe trends in large groups of populations.

For longitudinal analysis, the changes in lesion volumes present a more interesting data analysis. Two of the four patients experience a decrease in overall lesion volume. There can be several factors resulting in the analysis, and further analysis and data, including treatment history, lifestyle changes, etc. may help define a more comprehensive outcome analysis. The longitudinal data analysis toolkit can help in future MS-related research with richer and broader available data.

4. CONCLUSION

We have presented the MS eFolder system that utilizes the idea of big data storage and analysis in medical imaging and imaging informatics. The additional toolkits in longitudinal data storage, viewing, and analysis are designed to model the volume and complexity of data that is typical for today's comprehensive electronic health records. The longitudinal image viewer allows user to view a patient's complete history and health records, and able to draw analysis from longitudinal lesion changes and relate that to patient's disease history. The data mining tools allow users to query the database and display analysis results based on customized search criteria, which is useful for research as well as treatment planning in the clinical environment. Future work include system testing and evaluation in the clinical environment, additional features and toolkits for data analysis, and more data collection in quantity and complexity.

REFERENCE

[1] National Multiple Sclerosis Society http://www.nationalmssociety.org/about-multiple-sclerosis/index.aspx
[2] S Ringold, C Lynn, R Glass "Multiple Sclerosis" JAMA. 2005;293(4):514
[3] D Hafler "Multiple Sclerosis" J. Clin. Invest. 2004, 113(6):788-794
[4] Statistical Parametric Mapping http://www.fil.ion.ucl.ac.uk/spm/
[5] P Tsui "Fast EM_GM" http://www.mathworks.us/matlabcentral/fileexchange/9659 downloaded from MATLAB Central
[6] K Ma "Integration of Imaging Informatics-based Multiple Sclerosis eFolder System for multi-site clinical trials utilizing IHE Workflow Profiles", Proc. SPIE 8674, Medical Imaging 2013: Advanced PACS-based Imaging Informatics and Therapeutic Applications, 86740A (March 29, 2013); doi:10.1117/12.2008266;
[7] IHE Post-processing Workflow http://wiki.ihe.net/index.php?title=Post-Processing_Workflow
[8] "What is Big Data?" by University Alliance at Villanova University http://www.villanovau.com/resources/bi/what-is-big-data/#.VOUo6JjF_Vo
[9] J Manylka et al. "Big data: The next frontier for innovation, competition, and productivity." McKinsey&Company, May 2011. http://www.mckinsey.com/insights/business_technology/big_data_the_next_frontier_for_innovation
[10] Ashburner, J., Friston, K.J. "Unified Segmentation." NeuroImage 26.3 (2005): 839-51. Web.
[11] Ashburner, J., Friston, K.J.. "Voxel-Based Morphometry—The Methods." *NeuroImage* 11.6 (2000): 805-21. Web.
[12] DL Collins, AP Zijdenbos, WFC Baaré and AC Evans, ANIMAL+INSECT: Improved Cortical Structure Segmentation,IPMI Lecture Notes in Computer Science, 1999, Volume 1613/1999, 210–223, DOI: http://dx.doi.org/10.1007/3-540-48714-X_16
[13] VS Fonov, AC Evans, RC McKinstry, CR Almli and DL Collins, Unbiased nonlinear average age-appropriate brain templates from birth to adulthood, NeuroImage, Volume 47, Supplement 1, July 2009, Page S102 Organization for Human Brain Mapping 2009 Annual Meeting, DOI: http://dx.doi.org/10.1016/S1053-8119(09)70884-5
[14] C Hafey. "Javalibrary to display interactive medical images including but not limited to DICOM" https://github.com/chafey/cornerstone
[15] HighCharts AS http://www.highcharts.com/

SELECTED PEER REVIEW REPRINTS

Interoperability standards for medical device integration in the OR and issues relating to international approval procedures

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Content

1. The Digital Operating Room

The advances in medical technology, specifically information technology (IT), in the last quarter of the 20th Century have produced extraordinary changes in the way medicine, and in particular surgery, is practiced. These advances have not been without certain drawbacks and shortcomings including escalating healthcare costs and the challenge to handle the complexity of these technologies.

It has been challenging to cost-justify many of the new technological and system advances, associated interventional procedures and the corresponding redesign of healthcare infrastructures, for example, for the Operating Room (OR). The development and dissemination of these technologies have become central issues in the debate over healthcare reform and healthcare finance.

In particular, a number of major technical and organizational challenges are being faced in the attempt to improve the safety and effectiveness of connectivity/interoperability for the diverse array of medical devices and information technology that proliferates in the OR environments today. These have been clearly identified in recent years, for example by J. M. Goldman, MD, (Director, CIMIT Program on Interoperability, and Medical Device “Plug-and-Play” Interoperability Program), as challenges in their MD PnP Program [1]:

- Proprietary medical device systems; long capital equipment cycles (12 years!)
- Limited comprehensive, vetted user requirements (clinically/safety based)
- Absence of proven standards matched to clinical requirements
- Tendency to silo standards that would limit interoperability across continuum of care
- Limited funding for development
- Limited recognition of complexity of challenges in IT-BME convergence and lack of system integrators to build the middleware
- Legal (liability) concerns
- Regulatory pathway questions

In the current MD PnP Program [2] it is interesting to note, that user requirements in the program are established by means of explicit clinical scenarios – i.e. workflow analysis of clinical scenarios at a level of detail needed to create the basis of interoperability solutions and to derive engineering requirements.

In the context of international approval procedures and, relating to the challenge of "Regulatory Pathway" transparency and reduced complexity, the MD PnP Program is leading a working group of companies, academics, and hospitals that are developing a prototype regulatory submission to help refine the FDA clearance process (see FDA workshop content [5]).

To move beyond conceptual demonstrations of new interventional systems and towards the systematic assessment and employment in interventional settings, an understanding of the expected maturity levels of the Digital Operating Room (DOR) at present and in the foreseeable future is helpful [3].

Figure 1 provides an estimated timetable for the past, present and future developments of the DOR over a 25 year period including

- its development up to the present time as well as its continued development and implementation
- the political, economic, and industrial issues that may be encountered [3].

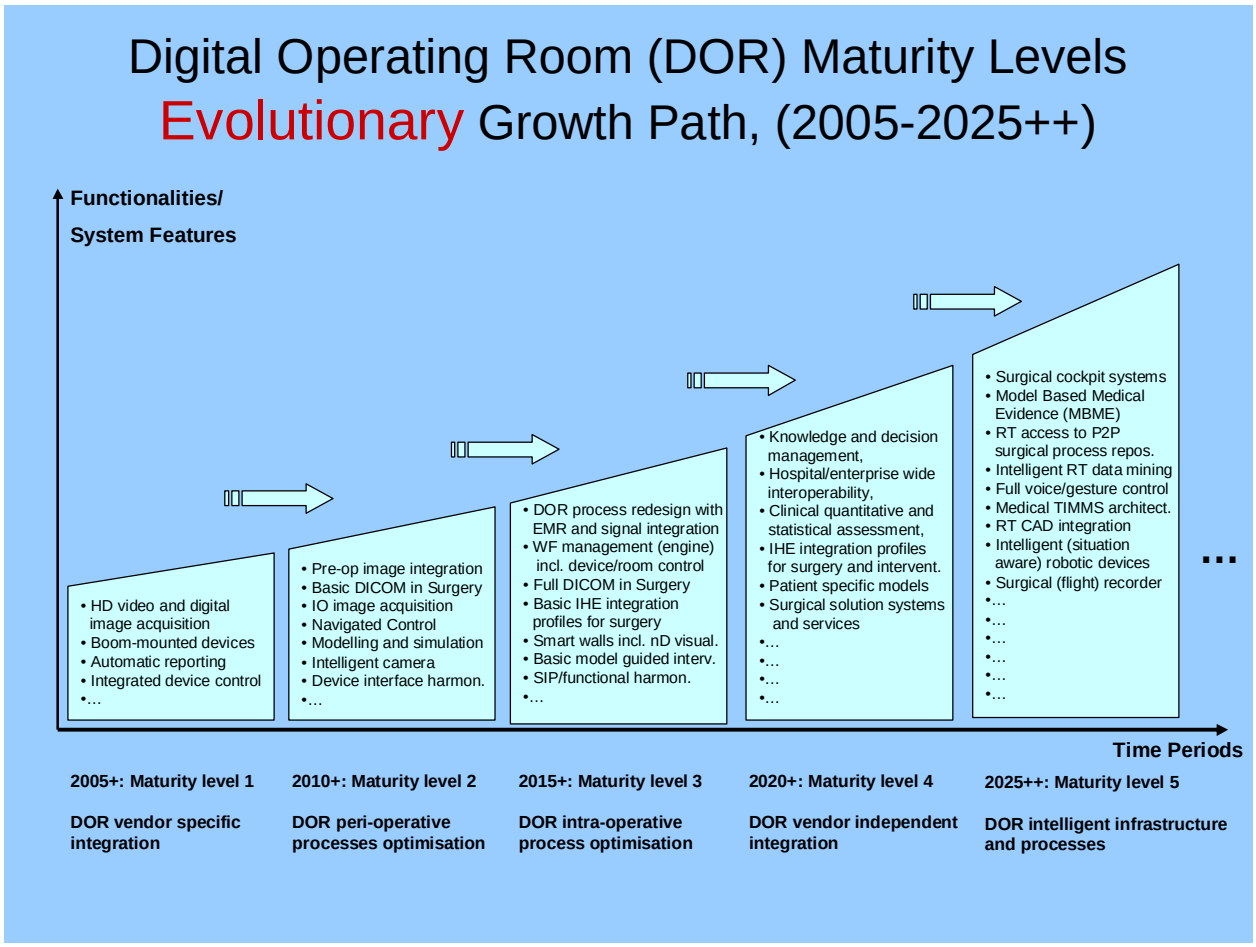

Fig. 1. DOR Maturity levels

Four main areas of technology development for the DOR can be identified:

1. Devices, including signal detection and recording, robotics, guidance systems, simulation technologies, which allow precision in the delivery of personalized operative healthcare;
2. IT Infrastructure, including DICOM, IHE, EMR, Therapy Imaging and Model Management System (TIMMS) infrastructure for the storage, integration, processing and transmission of patient specific data;
3. Functionalities, including specific interventional processes, patient specific modelling, optimization of surgical workflow, TIMMS engines and,

4. Visualization, including the processing, transmission, display and storage of radiographic images, video, and physiologic signals (e.g. a type of surgical PACS).

Each of these areas is following its own characteristic development, validation and approval cycle and methods. In [3], five stages of maturity for the various technical areas have been identified in the development of the Digital Operating Room for the first quarter of the Twenty-First Century:

2005+: Maturity level 1
The first stage of development (maturity level 1) may be characterized by the vendor specific integration of technologies. The critical feature of this stage is considered to be the development of integrated device control. Additional technologies include HD video and digital image acquisition and processing, boom-mounted devices, automatic reporting.

2010+: Maturity level 2
The second stage of development (maturity level 2) may be characterized by peri-operative processes optimisation. The two critical feature of this stage are considered to be the development of pre-operative image integration and navigated control. Additional technologies include basic DICOM in surgery, intra-operative image acquisition, modelling and simulation; and intelligent cameras.

2015+: Maturity level 3
The third stage of development (maturity level 3) may be characterized by intra-operative process optimization. The two critical features of this stage are considered to be the development of a workflow management (TIMMS) engine and full DICOM in surgery. Additional technologies include DOR process redesign with EMR and signal integration, basic IHE integration profiles for surgery, Smart walls including n-dimensional visualization, and basic model guided intervention.

2020+: Maturity level 4
The fourth stage of development (maturity level 4) may be characterized by vendor independent integration of technologies. The critical features of this stage are considered to be the development of hospital/enterprise wide interoperability and patient-specific models. Additional technologies include knowledge and decision management, clinical quantitative and statistical assessment, and IHE integration profiles for surgery, pathology and interventional procedures generally.

2025+: Maturity level 5
The fifth stage of development (maturity level 5) may be characterized by intelligent infrastructure and processes. The critical feature of this stage is considered to be the development of surgical cockpit systems and Medical TIMMS architecture. Additional technologies include real-time access to peer-to-peer surgical process repositories, intelligent real-time data mining, full voice/gesture control, real-time CAD integration, and intelligent (situation aware) robotic devices.

A glimpse of what may be ahead in the OR and predicted in [3] is provided by an interesting example of a surgical workflow management system which includes a Surgical Procedure Manager (SPM) already in clinical use at the International Development Reference Centre (IRDC) in Leipzig [12].

First experiences with this system show that this type of knowledge-based system in the OR can improve efficiency of the interventional processes. It may, however, induce the surgeon to rely excessively on the “intelligence” of the machine to provide the “right” information on patient and processes **at the right place, at the right time and to the right person** in the OR.

Trust in this form of “intelligence” and in the right record keeping and subsequent management of interventional process information for patient outcome evaluation, are new dimensions of concern when machine intelligence moves into therapeutic activities within the context of a digital OR.

Important aspects of these dramatically evolving ICT based methodologies and tools are new requirements for:

1. **DOR IT architectures** providing the right basis for enabling a higher quality of therapeutic interventions by means of interoperability features, for example, real time integration of information in patient-related data structures and therapeutic processes through computer assisted workflow, knowledge and decision management (see also section 2 below).
2. **Standards** which take account of the specific requirements for surgical/interventional workflows, devices and systems. Examples are DICOM in Surgery and IHE Surgery (see also section 3 below).
3. Methods and tools for supporting **approval procedures** on an international level, for example, device/systems classification, clinical and non-clinical testing for safety, high confidence

medical device software and systems through appropriate modeling and simulation, etc. (see also section 4 below).

Fig. 2. ENT surgical workstation supported by a surgical procedure manager (Surgical Deck, OR1)

2. DOR IT architectures for interoperability

Architectural features, for example, as part of an intelligent infrastructure of an OR have only recently become a focus in discussions relating to interventional settings [1,4]. Such an IT reference architecture may be referred to as a Therapy Imaging and Model Management System (TIMMS) [4].

A TIMMS-like architecture and its application for achieving image and model guided therapy has been the subject of discussions in the DICOM and IHE standard activities. An implementation of a prototype based on open standards of the modular TIMMS-like architecture is in progress at the Innovation Centre Computer Assisted Surgery (ICCAS) in Leipzig, Germany. TIMMS is a comprehensive medical-surgical communication and assist system (Fig. 3), which is composed of interconnected computer hardware and software components (such as engines, repositories and an IT infrastructure).

There are seven TIMMS engines, which may be defined as software modules which can be executed on an appropriate computing machine in order to provide interventional functionalities. These engines relate to imaging and biosensor data acquisition, modeling, simulation, workflow and knowledge and decision management, visualization, intervention and validation. Some of these engines are already present and used in modern OR systems.

The Kernel for workflow and knowledge and decision management provides the strategic intelligence for therapeutic planning and workflow execution. Often this module (or parts thereof) is integrated into some of the other engines, as the need may have demanded. This important computing kernel (or “brain”) of the system may use different forms of logic, different database structuring, agents and other forms of artificial intelligence, depending on the specific applications of the performed procedure.

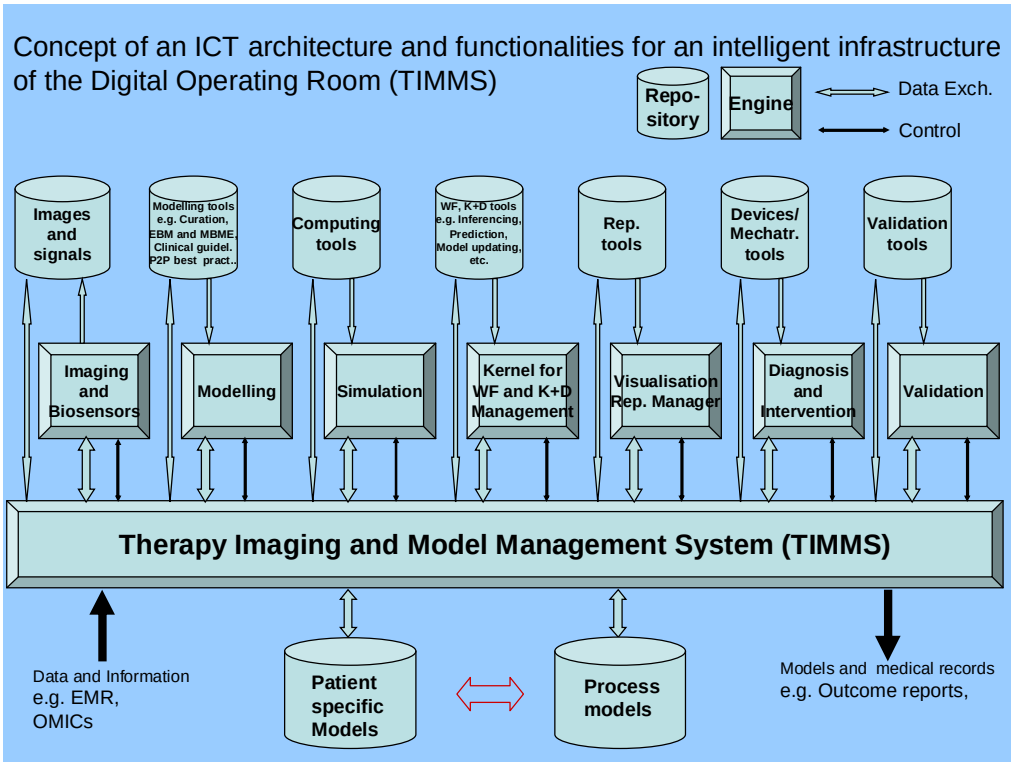

Fig. 3. TIMMS: an informatics platform/structure for model-guided therapy including the engine and repositories for machine intelligence (marked with ellipsoids)

In a full realization, a TIMMS may provide the following features and functions throughout the course of a medical and surgical treatment:

1. Standardized interfaces for communication and mechatronics, thereby creating a unified environment for the input and output of data (including the representative on and display of information and images, as well as the electromechanical control of surgical and navigational devices)
2. Creation and maintenance of a Patient-Specific Model (PSM), thereby providing a multi-scalar, comprehensive, precise, personalized representation of the patient
3. Creation and maintenance of a system for Process Modeling (PM) of all aspects of the surgical workflow, to ensure efficiency, learning and safety throughout operative procedures
4. Real-time knowledge management and decision support system thereby promoting optimized diagnostic, prognostic and therapeutic decisions throughout the treatment workflow
5. Validation and approval procedures, thereby providing quality assurance, patient safety, system security and processing of medical evidence towards securing better patient outcome.

Features 1, 2, 3 and 4 are the prerequisite of an intelligent infrastructure of an OR. A full realization of these functions is still a long way away. In practice, however, some small subsets of patient models, process models and/or real time knowledge management have been implemented and clinically tested. Feature 5 can begin to be properly addressed when features 1-4 have reached a tangible stage of implementation from which one can derive appropriate requirements for safety testing and feature/(usage) classification for devices and systems approval.

Feature 2 is subject to standard activities in working groups in DICOM and IHE in surgery. Feature 5 is of major concern in a number of regulation agencies such as FDA, PMDA, CEN and DIN. FDA and PMDA will be discussed further in section 4 below.

One of the architectures proposed in OR:NET [14] is somewhat different in appearance with respect to the TIMMS architecture but conceptually contains an equivalent base structure (see Fig 4).

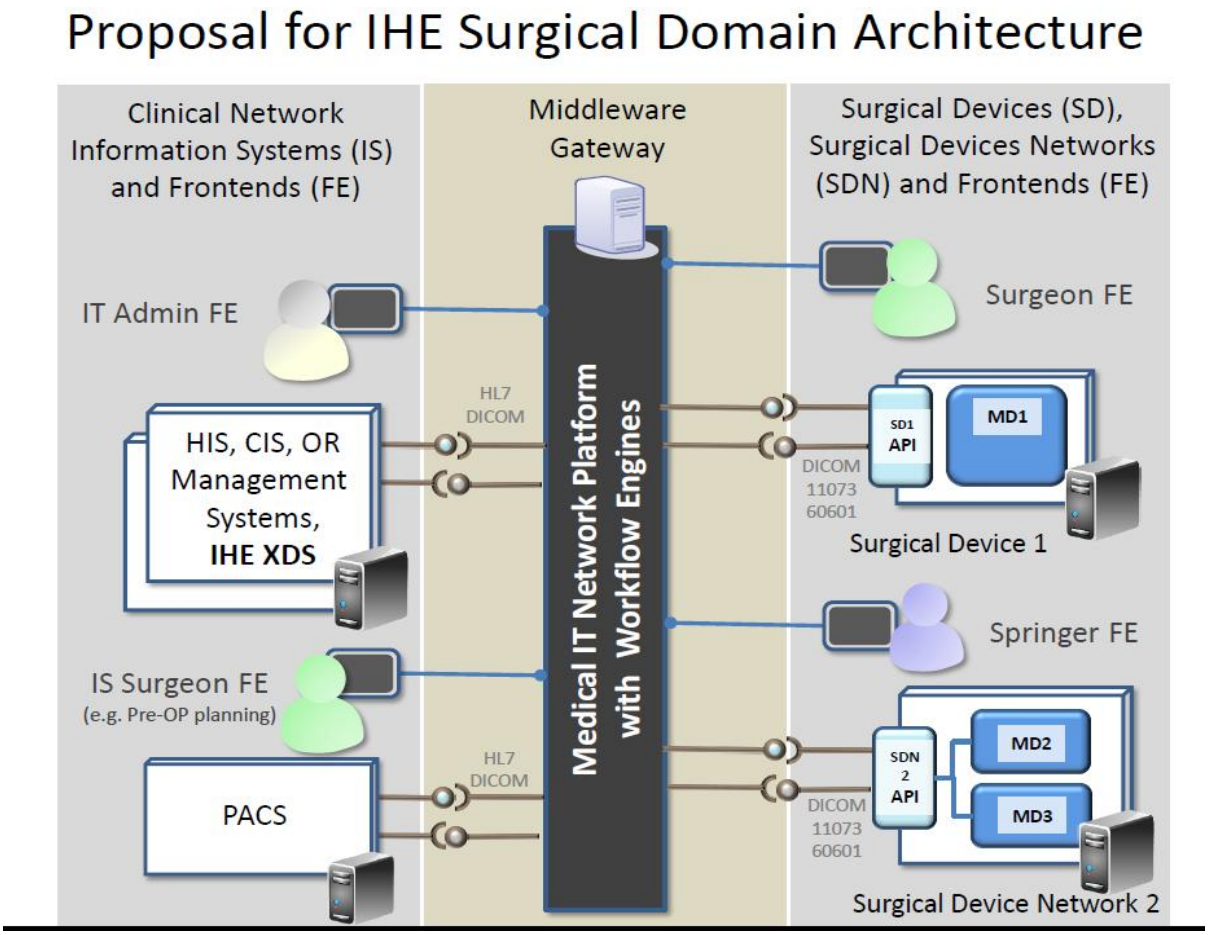

Fig. 4. Proposal for IHE surgical domain architecture (Source: Jörg-Uwe Meyer, MT2IT GmbH & Co)

3. DOR standards

Since 2003/2004 it was recognised [17,18], that the realisation of the "OR of the Future" or DOR, will be a comprehensive undertaking, requiring among others, the development of standards for achieving interoperability of medical devices and systems in the OR. Since then, DICOM and IHE have been considered, in principle, as enablers for fulfilling these requirements.

3.1 DICOM in Surgery

DICOM in Surgery, i.e. the DICOM Working Group 24 was founded in 2005 with the aim to develop DICOM objects and services related to Image Guided Surgery (IGS) and related interventions. Its initial roadmap included:

- Select and define a user community of IGS disciplines in WG24. Initially five surgical disciplines (Neuro, ENT, orthopedics, cardiovascular, thoracoabdominal) and interventional radiology have been selected. Anesthesia is included as long as surgery is affected.
- Compile a representative set of surgical workflows (with a suitable high level of granularity and appropriate workflow modeling standards and surgical ontologies) as a work reference for the scope of WG24. Initially, 3-5 workflows, characteristic for each discipline, should be recorded with sufficient level of detail.
- Derive potential DICOM services from these surgical workflows and identify appropriate use cases.
- Design an information model based on electronic medical record (EMR) and related work on patient modeling to identify IOD (Information Object Definition) extensions for DICOM.
- Take account of the special image communication (1D - 5D) requirements for surgery and mechatronic devices. A close cooperation with other Working Groups should be pursued.
- Connect to integration profiles specified in existing IHE domains.

In close cooperation with industry a number of DICOM supplements have been realised in recent years.

Supplement 132- Surface Segmentation

This IOD can be used to encode tissue segmentation, functional segmentation, and artifact identification for quantification or visualization.

Supplement 131- Implant Template

This supplement describes storage, query and retrieval of implant templates (generally non-patient-specific) as they are used in implantation planning.

Supplement 134 - Implantation Plan

The aim of this supplement is to communicate Implantation Planning information from the planning workstation to the operating room.

Supplement 154 - Optical Surface Scanner

This supplement introduces a modality for optical surface scanners. This allows the user the storage and retrieval of scanned surfaces to and from a PACS.

Some IGS and DOR related problems are currently under discussion in WG 24 that could lead to work items.

- A Universal Reference Coordinate Standard which helps to freely transfer spatial information between involved devices and systems pre- and intraoperatively.
- A standardized way to communicate patient identity to participating devices in the OR.

WG 24 is open for discussion for other potential work items, in particular those which may be indentified, for example, in projects such as OR.NET and MD PnP.

3.2 IHE Surgery

IHE Surgery was founded in 2012 as a provisional IHE domain [15] after la long preparatory phase by the sponsoring organisations, the International Foundation of CARS and the International Society for Computer Aided Surgery. The scope and rationality of the domain include:

- The IHE Surgery domain addresses the problems of interoperability, information sharing, and model sharing to improve the quality of care in surgery and related interventional therapies. It focuses on the needs for Image and Model Guided Therapy (IMGT) Systems.
- The solutions for the interoperability problems in the field of surgery and related interventional therapies are not yet on the level of the solutions presented in the IHE profiles of other IHE domains. Since surgery is one of the core units in a clinical setting, it is therefore important that it is represented as an IHE Domain.

Some of the needs in the context of the DOR that are currently being addressed are:

- Distribution of implant templates for surgeons, applications, and surgical devices.
- Distribution of implantation plan through the preoperative, intraoperative, and postoperative phase.
- Creating, storing, and retrieving of surface segmentations.
- Creating, storing, and retrieving of surface scanner objects.
- Intra- and Inter- Institutional distribution of surgical process models.
- Intra- and Inter- Institutional distribution of digital patient models.

Of particular interest for IHE Surgery are the potential integration profiles or clinical story boards from the clinical domains of ENT, laparoscopic, spinal surgery and anesthesia currently being investigated for the OR.NET Demonstrators and which are expected to be implemented in the last phase of the OR.NET project.

This would support the recommendation expressed in [13], which envisage a strong role of IHE Surgery for transcribing OR.NET use cases (after they have been prioritized and consolidated) into IHE use cases / Integration Profiles (IP) in a move towards a closer cooperation between OR.NET and IHE Surgery, generally.

4. International approval issues

A critical question for the development of IT architectures and standards which support interoperability in the OR, relate to the issues they raise in risk assessment and the appropriate classification by the international approval processes for medical devices and systems.

In the following, the current situation of approval procedures in the USA and Japan will be briefly outlined (*in a follow-up publication they will be compared to regulatory developments in Europe).* Most of these observations are based on presentation and discussions in the course of a CARS 2014 DICOM in Surgery and IHE Surgery Workshop on "DICOM Supplements and IHE Integration Profiles, Implementation and Approval Issues" which took place in Fukuoka, Japan on June 28, 2014.

4.1 FDA (USA)

It appears that the FDA is taking an active role in the discussion relating to interoperability and corresponding issues in approval regulations by also being a member of the MD PnP project [1].

Support for MD PnP program work has come from DoD/TATRC, NSF, NIST, CIMIT, and NIH/NIBIB, which awarded a $10M Quantum grant in October 2010 to develop a healthcare intranet based on integrated medical device systems.

An important part of the key MD PnP Program projects is [2] "Defining a safe regulatory pathway for patient - centric networked medical devices." This being carried out in close partnership with the FDA, progress so far includes a co-sponsored workshop held by FDA in January 2010 on medical device interoperability, followed by a working group of companies, academics, and hospitals that have developed and submitted a pre IDE (Investigational Device Exemption) regulatory submission to help refine the FDA clearance process.

Some of the questions posed by representatives from FDA include [5]:

Clinical issues

What clinical scenarios could make use of medical device interoperability?
Are there clinical scenarios that would not be appropriate?

Engineering issues

How should medical device interoperability be defined in terms of architecture, components, interfaces, functional requirements and performance requirements

Risk issues

What are the risks associated with medical device interoperability and systems of systems composing medical devices? Use of risk models for interoperable systems.

Management issues

Who are the responsible parties and what is their role in design, building, maintenance, improvement as well as development and dissemination of standards and best practices.

It is interesting to note, that the FDA is responding positively to 510(k) application which include in their device description compliance to IHE, DICOM and HL7. For an example see [6] which refers to a recent PACS approval procedure by a major manufacturer who included in its device description:

"Centricity PACS is a standards-based, customizable, and scalable solution supporting several of the Integrating the Healthcare Enterprise (IHE) profiles, Digital Imaging and Communications in Medicine (DICOM), and the Health Level Seven (HL7) protocol standards for managing digital medical images and patient data. Centricity PACS supports radiographic imaging-as in clinical radiography, cardiology, dentistry, and mammography and non-radiologic imaging, including video support".

Also in the area of PACS components or devices it can be observed that compliance to IHE integration profiles is thought to be a significant advantage in FDA approval procedures. For example, Three Palm Software, LLC stated in their application [7]:

"The enterprise workflow of the workstation (WorkstationOneTM Breast Imaging Workstation)

follows IHE integration profiles, specifically, MAMMO (Mammography Image Profile) and RWP (Reporting Workflow Profile)".

Another example of FDA approval applications with IHE integration profiles is in the area of digital radiography software tools for Quality Assessment (QA), in particular "Standardized Dose Reporting for QA" [8]. The Alliance for Radiation Safety in Pediatric Imaging recommends the IHE Radiation Exposure Monitoring (REM) profiles and DICOM Structured Reports (SR) to be applied in this context.

For the purpose of approval, medical devices and systems, such as given above need to be grouped into one of three FDA regulatory classes: Class I, II or III, depending upon the degree of regulation necessary to provide reasonable assurance of their safety and effectiveness.

The three device classes are currently defined as follows [9]:

Class I: Devices are subject to a comprehensive set of regulatory authorities called general controls that are applicable to all classes of devices.

Class II: Devices for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance.

Class III: Devices for which general controls, by themselves, are insufficient and for which there is insufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device. Class III devices typically require premarket approval.

Most medical devices can be classified by finding the matching description of the device in Title 21 of the Code of Federal Regulations (CFR), Parts 862-892. FDA has classified and described over 1,700 distinct types of devices and organized them in the CFR into medical specialty "panels" such as Cardiovascular devices or Ear, Nose, and Throat devices. The devices most relevant for the OR can be found in Part 878 entitled General and Plastic Surgery, Part 876 entitled Gastroenterology-Urology Devices and in Part 892 entitled Radiology.

There exists an extremely comprehensive set of guidelines on how to apply for FDA Premarket Approval (PMA) or premarket notification (often referred to as a 510(k). This is particular the case also when there is software contained in medical devices [10].

An approval application is usually supported by a list of standards which the medical device/system has been shown in tests to be in compliance with. Most of the well known national and international standard bodies are explicitly recognized by the FDA. This list does not include IHE (as IHE is not a standardization organization) but examples of FDA approval application demonstrate that IHE compliance is being used in the device descriptions as a marker for quality. How the importance of compliance with IHE integration profiles is being rated in the approval process, however, is not made clear by the FDA guidelines for Industry as well as their own Food and Drug Administration Staff.

A very special situation exists for an approval application for an IDE, relating to clinical trial approval by foreign companies. In this case, the sponsor of the clinical trial is responsible for submitting the IDE application to the FDA (§812.40) and obtaining Institutional Review Board (IRB) approval before the study can begin. Foreign companies wanting to conduct a clinical study in the U.S. MUST have a U.S. sponsor (§812.18).

4.2 PMDA (Japan)

The Pharmaceuticals and Medical Devices Agency (PMDA) is the FDA equivalent agency for approval procedures for medical and surgical devices and systems in Japan. In principle, it can be observed, that the medical device approval procedure is harmonized with those of other advanced countries.

Figure 5 shows the classification used by PMDA, in principle derived from activities of the GHTF (Global Harmonization Task Force) (USA, EU, Australia, Canada, and Japan). It is (almost) in line with respect to the FDA classification, except that an extra Class IV has been added for highly risky devices. For Class II devices, third-party certifiers *(in EU terminology: notified bodies)* are approved by the Minister of Health, Labor and Welfare (MHLW). The approval criteria, however, are defined by MHLW. It is expected that after November 26, 2014 third-party certifiers will also be permitted to review and approve Class III devices.

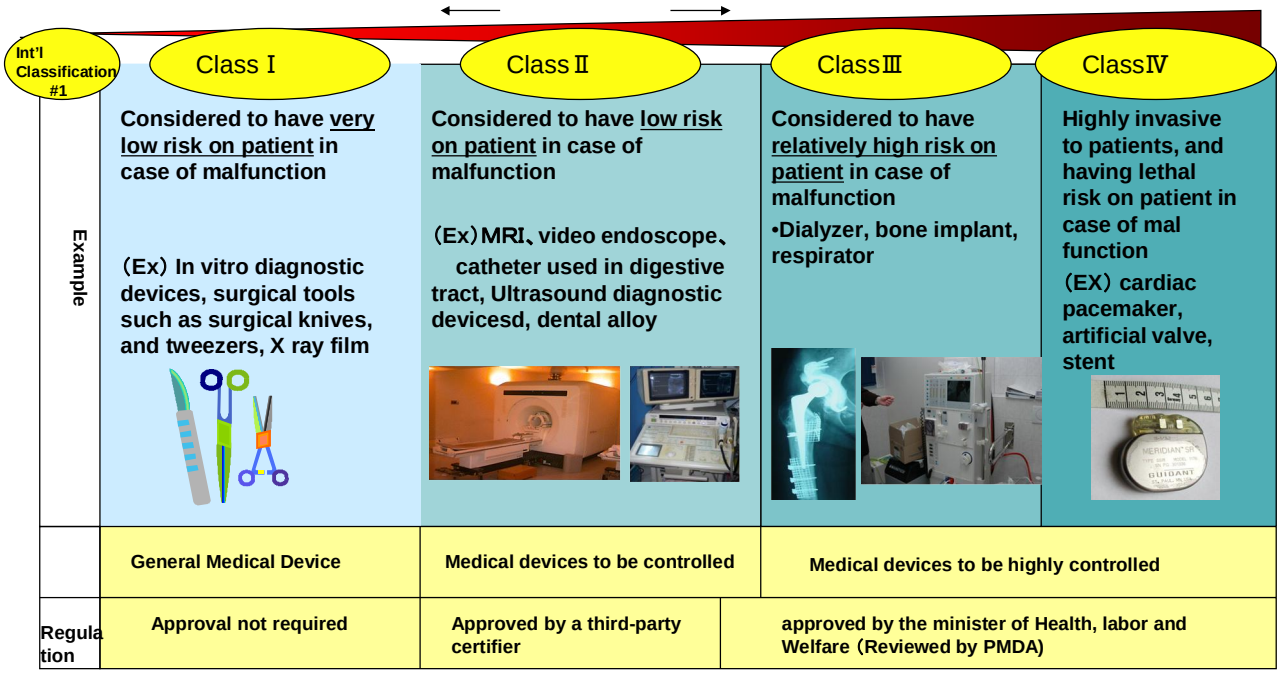

Fig. 5. Regulation and classification of medical devices in Japan [11]

As regards approval for software, it is important to note, that high risk health software running on non medical devices will be regulated after autumn, 2014. Specifically, software operated in non-medical devices (such as PC and tablet) used for high risk application will be reviewed by PMDA also after autumn, 2014. It can be expected, that the safety requirement defined in international standards will be referred to. Surgical navigation software running on conventional PC will also be regulated.

An important point of discussion in Japan relates also to the question whether the clinical data obtained in foreign countries is applicable to the review process in Japan. Specific issues are:

- clinical environment,
- differences in anatomy, pathology, depending on race, etc.,
- comparison with standard care.

In general, the PMDA profile of services as indicated in the 6 phases (top of Fig. 6), i.e. Research and development, Non-clinical tests, Clinical Test, Filing of application, Approval and Marketing, are similar to the FDA and European approval services. It is important to note, that standards development is considered to be a continuous activity in the PMDA profile of services.

It is also recognized by PMDA that, in order to improve on the profile of services [11], a promotion of regulatory sciences is important to accelerate R&D of medical devices as well as an enhanced international cooperation. PMDA, therefore actively promotes international activities in line with the PMDA International Strategic Plan and the International Vision formulated in 2009 and 2011, and as well as a road map for more specific action plans defined in 2013.

In order to build closer relationships with the EU and the US, PMDA has dispatched its staff members to regulatory agencies abroad including the European Medicines Agency. Moreover, PMDA's ties with other regulators from the US, Europe, and Asia have been reinforced by means of holding PMDA training seminars and the exchange of trainees.

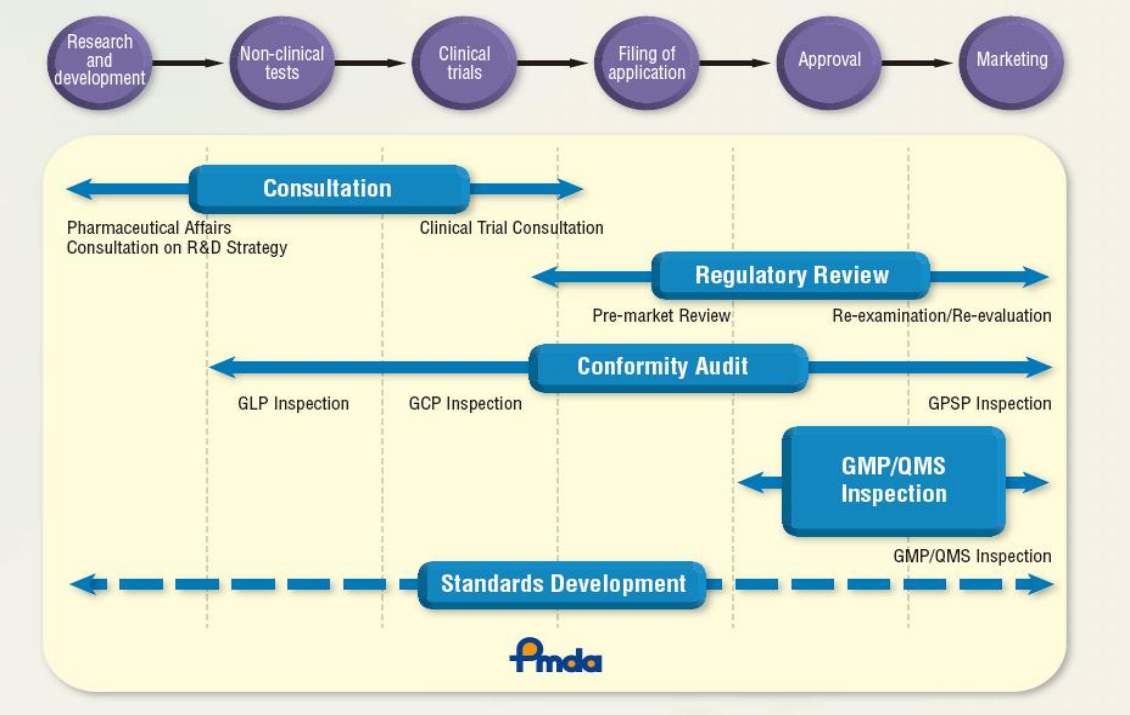

Fig. 6. PMDA profile of services 2013-2014 [11]

5. Conclusion

5.1 Observations and questions

A significant number of functionalities in the Operating Room require (real-time) exchange of data and control information. Based on the IT architectures discussed above and generic standard issues outlined in a Weissbuch on “Sichere Dynamische Vernetzung in Operationssaal und Klinik” [13], these functionalities may best be understood by means of clinical scenarios or use cases which address real clinical requirements for interoperability. Approval of devices and systems which claim to have features to support such interoperability should be based on tests which include compliance to standards. This, however, poses a number of questions which need to be addressed in the development of the DOR, some of these are:

1. What functionality/feature changes to an already approved device distinguishes a predicate device 510(k) procedure from a new or post-predicate device (for example, augmented with new interoperability features), i.e. when and when not is a device substantially equivalent to a predicate device and may need to be classified as Class 3 requiring something similar to a Premarket Approval?
2. How will specific software (including for example, new Apps) for “intelligent” or web-enabled interoperability be classified in Japan, USA or Europe (taken into account the differences in device classification systems)?
3. What strategic steps in national and international approval organizations and technical and legal developments are necessary to raise the importance of IHE Connectathon and certification, as a basis for safety assessment in the approval process?
4. What strategic steps in national and international approval organizations and technical and legal developments are necessary to raise the importance of a scientific approach, as a basis for safety assessment in the approval process?

Another interesting observation relates to the classification of medical devices, which perhaps will become a major issue comparing FDA, PMDA and corresponding EU Directives. The latter states [20]:

“Where a Member State considers that the classification rules set out in Annex IX require adaptation in the light of technical progress and any information which becomes available under the information system provided for in Article 10, it may submit a duly substantiated request to the Commission and ask it to take the necessary measures for adaptation of classification rules. The measures designed to

amend non-essential elements of this Directive relating to adaptation of classification rules shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 7(3)."

The question here to be addressed in the future relates to whether devices augmented with (intelligent) software for interoperability qualify for the label "technical progress" and may therefore require, for an appropriate classification, an adaptation of the classification rules as given by the regulatory agencies. It remains to be seen, whether the new drafts for Amendments of the EU Directives concerning medical devices or the expected new PMDA regulations will take account of these new technological challenges.

5.2 Recommendations

It can be expected, that the complexity of the clinical and non-clinical tests for safety is very high and a solid scientific foundation [16] is necessary to show that a safe interoperability has been achieved. The PMDA drive to promote **regulatory sciences** is important in this context and may be of particular significance when devices and systems are planned to be employed in an international environment. From this and the observations made above, a number of recommendations can be derived:

1. In the middle or long term a **Centre for interoperability in the OR** with a strong focus on scientific methods and tools may have to be established on an international level, not least to establish completeness and reproducibility of testing procedures for clinical and non-clinical tests for interoperability of medical devices and systems for the OR, thereby enabling a higher confidence level for safety of medical device software and systems in the OR [19].
2. As can be expected that the role of **IHE integration profiles** will increase in importance for approval agencies in the future, IHE generally and IHE Surgery Connectathons specifically, can be considered to be the first steps in this direction and should become a focus of OR.NET, MD PnP and similar (follow-up) projects in the near future.
3. **Leading industry for integrated ORs** should be encouraged to take an active role in promoting activities towards recommendations 1 and 2. This does imply In particular, taking steps towards the definition of a set of promising IHE integration profiles which may then provide the basis for work items in the appropriate IHE domains.
4. A regular annual international **OR interoperability forum** for the exchange of views, concepts, R&D results, clinical and non-clinical safety testing, classification standards to facilitate conformity and predicate device testing, technical documentation, quality assessment and control of notified bodies, regulatory developments, etc. should be established. This forum should be of particular interest to SMEs engaging in the development of medical devices, in order to obtain a better understanding of resources required to achieve medical device approval on a national and international level. The CARS 2014 Workshop on "IHE Integration Profiles, Implementation and Approval Issues" [21] may serve as a template for such a forum.

Acknowledgement

The lecture contributions to the CARS 2014 workshops relating to IHE and approval issues, etc. by Prof. Ichiro Sakuma, the University of Tokyo, Japan and Prof. Kevin Cleary, the Children Medical Centre, Washington DC, USA as well as discussion contributions by over 20 international participants have been very much appreciated.

References

[1] Goldman JM (2007): The OR of the Future: Current activities and Health IT implications, HIMSS07 New Orleans. http://www.mdpnp.org/uploads/HIMSS_2007_ORF_Goldman.pdf

[2] http://www.mdpnp.org/about.html, accessed August 2014

[3] Lemke HU, Berliner L (2011): DOR Maturity Levels (2005-2025 and beyond): Evolutionary growth path. International Journal of CARS, Vol 6, Suppl 1, Springer Verlag, Heidelberg, Germany

[4] Lemke HU, Vannier MW (2006): The operating room and the need for an IT infrastructure and standards. Editorial, International Journal of CARS, Vol 1, No 3, Springer Verlag, Heidelberg, Germany

[5] The FDA (CDRH) Workshop on Medical Device Interoperability: achieving safety and effectiveness, Co-Sponsored by The Continua Health Alliance and The Center For Integration Of Medicine &

Innovative Technology (CIMIT), Medical Device "Plug-and-Play" Interoperability Program (MD PnP), January 25-27, 2010

[6] www.accessdata.fda.gov/cdrh_docs/pdf11/k110875.pdf

[7] www.accessdata.fda.gov/cdrh_docs/pdf7/k073272.pdf 2008-01-08

[8] Don S, The Alliance for Radiation Safety in Pediatric Imaging, 2011, www.fda.gov/downloads/medicaldevices/newsevents/workshopsconferences/ucm313229.pdf

[9] The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notification, July 28, 2014

[10] General principles of software validation; Final guidance for industry and FDA staff, 2002

[11] PMDA profile of services 2013-2014.pdf

[12] G. Strauß et al. Procedure Point Navigation (PPN): Erste klinische Erfahrungen mit einem Assistenzsystem zur Ablaufsteuerung für die FESS. submitted to Journal "HNO", Springer, 2013

[13] Moser H. et al (2014) Weissbuch on “Sichere Dynamische Vernetzung in Operationssaal und Klinik, VDE, Frankfurt, Germany

[14] http://www.ornet.org

[15] IHE International Board, Strategic Meeting Minutes 2012-11-28 Approved. https://docs.google.com/document/d/1KMTBNrXGr9EYMUQV2Fk486_rqPL4wwVly0tfhDmY01Q/edit?pli=1

[16] Pace DK, Modelling and Simulation V&V Challenges, Johns Hopkins APL Technical Digest, Vol.25, Number2 (2004) 163-172

[17] Lemke HU, Ratib OM, Horii SC (February 2005): Workflow in the operating room: Review of UCLA Arrowhead 2004 seminar on imaging and informatics. In: Proceedings of Medical Imaging 2005, PACS and Imaging Informatics. Editors: Ratib OM, Horii SC, Vol 5748, SPIE.

[18] CAR/CMI Joint Session on Integrating the Health Care Enterprise – IHE, Panel on Integrating the Real World: IHE in Practice, CARS 2004 Congress, Chicago, IL, U.S.A.

[19] Lee I, et al., High-Confidence Medical Device Software and Systems. Published by IEEE Computer Society (April 2006).

[20] Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007

[21] http://www.cars-int.org