Development and Application in Clinical Routine of Computer Aided Detection (CAD) Algorithms for the Identification of Pulmonary Nodules

Alberto Traverso[1,2,3]
[1]*Department of Applied Science and Technology, Polytechnic University of Turin, Turin, Italy*
[2]*Turin Section of INFN, Turin, Italy*
[3]*Diagnostic Image Analysis Group, Radboud UMC, Nijmegen, The Netherlands*

1 RESEARCH PROBLEM

Lung Cancer is one of the main public health issues in developed countries, accounting for about 19% and 28% of cancer-related deaths in Europe (Ferlay et al., 2010) and the United States of America (Jemal et al., 2009), respectively, with a five-year survival rate of only 10-16% (Jemal et al., 2010). Computed Tomography (CT) has been shown to be the most sensitive imaging modality for the detection of small pulmonary nodules: low dose high resolution CT-based screening trials are regarded as a promising technique for detecting early-stage lung cancers (Team et al., 2011). The identification of early stage pathological Regions of Interests (ROIs) in low dose high resolution CT scans is a very difficult and time consuming task for radiologists, because of the large number (300/500) of noisy 2D slices to be analyzed. In order to support radiologists, researchers have started developing CAD algorithms to be applied to CT scans. Several studies (Das et al., 2006)(Brochu et al., 2007)(Matsumoto et al., 2008) reported an improvement in the sensitivity of radiologists when assisted by CAD systems (Awai et al., 2004). In addition, CAD systems act as detection rates equalizers between observers of different level of experience (Brown et al., 2005). Currently, the usage of CAD inside clinical diagnostic routine has not been a common and widespread practice yet. So far, the most common way to make CAD algorithms available in the clinical routine of health facilities is the deployment of standalone workstations, usually equipped with a vendor-dependent Graphic User Interface (GUI). This approach presents several drawbacks, such as the high fixed cost of the software licenses, hardware and the obsolescence of both. Furthermore, the computational power required by CAD algorithms is often very high (increasing with the complexity of the algorithms), often requiring powerful and expensive hardware. The emerging of Cloud Computing solutions, accessible via secure Web protocols, solves almost all the previous issues. Furthermore, a solution pointing toward cloud computing facilities provides the possibility of combining several CADs, with demonstrated benefits to the overall performance (van Ginneken et al., 2010). I started my PHD project inside the Magic5 group coordinated by the Turin Section of INFN. This group is aiming at:

- Developing, validating and optimizing CAD algorithms for the automatic detection of pulmonary nodules in chest CT scans.
- Spreading the usage of CAD inside clinical routine, making CAD algorithms available without requiring the users to install any kind of additional software/hardware.
- Studying the impact of CAD algorithms on the performance of radiologists in clinical practice.

During my PHD I have also started an internship within the DIAG (Diagnostic Image Analysis Group) inside the Radiology Department of the Radboud University Medical Center in Nijmegen (NL). Part of the group is currently working to develop algorithms for the automatic detection and assessment of pulmonary nodules (and other diseases) in chest CT scans.

2 OUTLINE OF OBJECTIVES

In this section we intend to provide a detailed description of the objectives briefly enumerated in 1. We discuss each of these topics in dedicated subsections.

2.1 Development, Validation and Optimization of CAD Algorithms

As mentioned in 1, researchers have started developing CAD algorithms for the automatic detection of pulmonary nodules in chest CT scans. We believe that a very big challenge for CAD algorithms will be the capability not only to find pulmonary nodules, but being able to assess something about the malignancy

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of the nodules. In order to achieve this goal, CAD algorithms should be able to identify and compute some features of the nodules: among them, the volume is one of the most important. It has been shown (MacMahon et al., 2005) that the growing rate of the volume of a nodule can be a potential indicator of malignancy. Usually, this growing rate is computed considering the ratio between the volume of a nodule among two different temporal scans of the same patient. Despite this intuitive definition, the task represents a really challenge. In fact, the computation of the volume of a nodule passes through two fundamental steps:

- The registration (i.e the alignment of anatomical structures) between the two scans in order to avoid systematical errors due to different acquisition protocols.
- The delineation of the 3D contour of the nodule, usually referred as segmentation.

Preliminary objectives for the computation of the volume are, indeed:

- Developing a robust system for the automatic registration of two different CT scans of the same patient.
- Developing a robust system for the 3D automatic segmentation of pulmonary nodules.

Considering that segmentation is mandatory for the computation of the 3D volume, we also would like to consider the possibility to develop a tool for the interactive semi-automatic segmentation or for manual segmentation. The first case is needed when the result of the automatic segmentation is not satisfactory for the user. With a minimum user interaction (like drawing some boundaries of the nodule in 2D) the user can re-initialize the automatic algorithms. The second case is needed when the automatic segmentation totally fails and will allow the user to manually segment the nodule. We will present some methodological approaches to develop these solutions in 4.

2.2 Spreading the Usage of CAD in Clinical Practice

As mentioned in 1, the common approach so far is to provide stand-alone workstation with pre-installed CAD software, usually running on a proprietary operating system. We believe that this approach can really represent a big issue for the diffusion of CAD algorithm inside clinical structures due to these following reasons:

- High fixed cost of license for the software installation.
- Strict requirements for software (e.g. specific operating system) or hardware installation (usually the computational power required is increasing as the complexity of the algorithm increases).
- Difficulty to share CAD results among radiologists belonging to different institutions.

Our main objective is to propose a new approach for the usage of CAD algorithms in clinical routine without necessarily:

- Requiring user to install dedicated software.
- Requiring user to buy additional hardware for CAD computations.

The first goal can be achieved adopting a SaaS (Software As A Service) approach. SaaS is a software distribution model in which applications are hosted by a vendor or service provider and made available to customers over a network, typically the Internet. In order to adopt a SaaS approach these preliminary objectives have to be reached:

- Developing a dedicated web-fronted for the submission of chest CT scans for CAD analysis and the access to CAD results.
- Considering the possibility to allow the radiologist to insert medical annotations and review them according to CAD results directly on-line.

The second goal can be reached adopting an Infrastructure As A Service (IaaS) approach. Infrastructure as a Service (IaaS) is a form of cloud computing that provides virtualized computing resources over the Internet. IaaS platforms offer highly scalable resources that can be adjusted on-demand. In order to adopt a IaaS approach these preliminary objectives have to be reached:

- Developing a cloud back-end to handle the part of the computation of the algorithms.
- Creating a system in which computing resources (i.e. virtual machines) are created according to the required computational power.

The combination of both the SaaS and IaaS seems to be a very promising solution for the sharing of CAD algorithms in clinical facilities. Furthermore, the IaaS approach allows to easily combining different CAD algorithms with no particular effort. It has been proved (van Ginneken, 2010) that the combination of several CAD algorithm increases the overall performance of the detection.

2.3 Studying the Impact of CAD in Clinical Practice

As mentioned in 1, several studies showed the benefit given by the usage of CAD as support for radiologists in lung cancer detection. Despite these results, we are still far from a common usage of CAD inside clinical routine. Most of CAD algorithms have been validated using data-set coming from screening campaigns. On the contrary, there are few works which validated CAD algorithms on a clinical data-set (no more than few hundred of nodules). We believe that an important factor for the usage of CAD systems inside clinical routine we will be a detailed validation of these algorithms with CT scans from oncological patients undergoing staging or re-staging in hospital structures. CAD algorithms can be inserted in medical diagnosis in three different ways:

- Second-reader mode: the radiologist reads the CT scan first without knowledge of the CAD findings. In a subsequent step he/she reviews the findings of CAD and decides if each CAD marking highlights a previously overlooked lesion or a false-positive finding.
- Concurrent-reader mode: the radiologist reads the CT scan, and the CAD findings are displayed simultaneously. The radiologist can accept or reject the CAD findings and combine them with his/her own findings without the necessity of a second reading step.
- First-reader mode: after pre-selection by the CAD system only the slices with CAD findings are presented to the radiologist

In order to increase the usage of CAD in clinical practice we believe the following as mandatory objectives to be reached:

- Increasing sensitively the data-set used by previous studies from few hundred to some thousands.
- Performing observer studies to investigate the impact of CAD in clinical practice on oncological patients undergoing staging or re-staging.

Furthermore, the possibility to collect a data-base of annotated clinical data offers the great possibility to perform further clinical studies, such as the validation of malignancy prediction models. In addition, considering that most of available studies have been performed using the CAD as second-reader, we also would like to investigate the usage of CAD as concurrent-reader and compare the two approaches.

3 STATE OF THE ART

In this section we present, for each of the subsections enumerated in 2, available literature and previous works. We also try to highlight possible points of development and improvement.

3.1 Development and Optimization of CAD Algorithms

In the first part we present a CAD algorithm developed inside the Magic5 project, discussing briefly the main features and the result of the validation. In the second part we present the CAD workstation developed by the DIAG group, focusing on the algorithms for the segmentation of pulmonary nodules.

3.1.1 The M5L CAD

M5L is the combination of two independent CAD sub-systems: the Channeler Ant Model (CAM) and the Voxel-Based Neural Approach (VBNA). These two algorithms have a common start line, which is the parenchyma volume segmentation using a 3D region growing algorithm, which produces the separation of trachea, bronchi and lungs (De Nunzio et al., 2011). The CAM CAD algorithm is based on the reproduction of the life-cycle of colonies of virtual ants (Cerello et al., 2008). CT voxel intensity is interpreted as the amount of food available to the ants, which progressively is reduced by the feeding of the ants. The output of this stage is a pheromone map. The pheromone map is a collection of segmented objects, each object gets classified using 13 different features and a feed-forward artificial neural network performs classification. The algorithm has the capability to reveal both pleural nodules and nodules inside the lung parenchyma. The VBNA CAD uses two basically different procedures to detect nodules inside the lung parenchyma (CADI) (Li et al., 2003; Retico et al., 2008) and nodules attached to the pleura (CADJP) (Retico et al., 2009). Before combining the results of the two procedures there is an additional step aiming at reducing the number of false positives using a Supporting Vector Machine. The results, combined as described in (Torres et al., 2015), have been evaluated in terms of FROC (Free Response Receiver Operating) curves. The M5L sensitivity at 8FP/scan reaches 80% which, given the size and heterogeneity of the data-set, is quite satisfactory remarkable. We believe that an interesting point of development of the M5L CAD is the possibility to allow the user to compare baseline and follow-up scans[1] of the same patient. The idea is to perform *longitudinal analysis* studies, i.e. the study of the evolution of the volume of the nodule as a function of time in order to assess something about the growing rate of a nodule and relate it to its malignancy.

[1] A baseline scan is the first scan taken by a patient. Follow-up scans refer to next scans of the same patient.

3.1.2 Cirrus Lung Workstation

CirrusLung is a flexible workstation for a quick and effective extraction of quantitative imaging parameters related to COPD, lung cancer and TB (B. et al., 2013). The workstation loads an arbitrary number of CT and chest radiography studies of each subject simultaneously, allowing the user to instantly track the evolution of any lesion. Each CT scan is elastically registered to all prior CT scans of the same subject. CIRRUS Lung workstation has been developed jointly by the Diagnostic Image Analysis Group, Radboud University Nijmegen Medical Centre, Nijmegen The Netherlands, and Fraunhofer MEVIS, Bremen, Germany. It is based on the MeVisLab software platform. This work-station is a software which can be installed on PCs with a Windows operating system configuration. The algorithm for the automatic segmentation of pulmonary nodules performs quite well, with good results for all kind of nodules (solid, part solid and non-solid) (Lassen et al., 2015). However, sometimes there can be cases, especially for very subtle nodules, where the user cannot agree totally with the proposed segmentation and would like to correct the segmentation with few interactions through a semi-automatic segmentation tool. This feature is mandatory when reaching the goal to built a complete clinical workstation which allows the user to directly interact, within an intuitive interface, with the automatic algorithms (such as, for example, the possibility to manually tune some of their parameters).

3.2 Spreading the Usage of CAD in Clinical Practice

In the past, there have been some attempts to use an approach similar to the GRID infrastructure used in high energy physics to overcome problems related to the spreading of CAD in clinical practice (Bellotti et al., 2007)(Lamanna, 2004). The main issue with GRID computing is the rigidity, complexity of the structure and the man power required to manage the system. Furthermore, this solution does not fit the majority of Medical Physics projects, that require a custom environment. For previous reasons, the use of Cloud Computing solutions is progressively growing (Mell and Grance, 2011). Most of these works where focused on providing computing facilities for CAD computations, but they did not have the aim to develop a solution to manage the sharing of CAD results. The emerging of cloud computing seems to offer a great possibility to combine both computing resources and web solution for the sharing of CAD results.

3.3 Studying the Impact of CAD

As mentioned in 2, several studies proved the useful impact of CAD algorithms as as support for the radiologists in the diagnosis. Most of them were performed using the CAD as second-reader. However, second-reader approach leads to a sensitive increasing of the reading time if compared to the reading time without CAD. The concurrent-reader mode can have the appeal to substantially reducing the reading time when compared to the second-reader mode. Anyhow, an improvement of reading time is not enough to prefer concurrent-reader mode with respect to second-reader mode. A detailed analysis of the sensitivities reached through these two approaches needs to be performed over a big collection of nodules. In literature there were some attempts to perform studies about the comparison of CAD as *concurrent* or *second-reader* modes. All these studies measured time required for the radiologists to annotate cases in both modes, in addition with studies on the performances. In a work (Beyer et al., 2007), 4 radiologists were asked to annotate 50 studies two times (first using CAD as concurrent-reader and then as second-reader). The elapsed time between these two reading sessions was about 4 weeks. The gold-standard was formed by 340 nodules, most of them solid nodules and no presence of non-solid nodules. The results showed a reading time much higher for the second reader mode when compared to the concurrent reader mode as expected. Sensitivity of the concurrent reader mode was found to be lower than sensitivity achieved by second-reader mode. The authors claim that they cannot exclude possible biases due to memory-effects after only 4 weeks of elapsed time. Another work (Matsumoto et al., 2013) reached similar results in term of reading time. This study used a database formed only by not calcified nodules greater than 4 mm leading to a reference standard of 207 nodules. Results found about the comparison of sensitivities showed a discrepancy with work by Beyer, leading to conclude that concurrent-reader and second-reader modes lead quite to the same sensitivity. We believe that these improvements can be applied:

- Increasing the database size without limiting the research to solid nodules, but including also sub-solid and non-solid nodules.
- Eliminating the possible memory effect using one radiologist for the annotations with CAD in concurrent-reader mode and one radiologist for the annotations with CAD in second-reader mode.

4 METHODOLOGY

In this section we present a description of the methodology which can be used to achieve goals presented in 2.

4.1 Development and Optimization of CAD Algorithms

We present two approaches for the improvement of CAD systems presented in 3.1.1 and 3.1.2. The first approach is aiming at developing a full automatic algorithm for the comparison of baseline and follow-up scans within the M5L CAD. The second is aiming at improving the algorithms for the segmentation of pulmonary nodules within the CirrusLung workstation.

4.1.1 Automatic Registration of CT Scans within M5L CAD

The starting point to have an algorithm for studying the evolution of the volume of pulmonary nodules is the development of a robust algorithm for the registration of CT scans. Registration means determining a geometrical transformation that aligns points (e.g. anatomical structures) between different scans of the same patient. There are some tools available for the automatic registration of CT scans based on topological transformation. The most famous and public available is called Elastix (Klein et al., 2010). Elastix is open source software, based on the well-known Insight Segmentation and Registration Toolkit (ITK) (Ibanez et al., 2003). The software consists of a collection of algorithms that are commonly used to solve (medical) image registration problems. The modular design of Elastix allows the user to quickly configure, test, and compare different registration methods for a specific application. A command-line interface enables automated processing of large numbers of data sets, by means of scripting. Registration algorithms depend on several parameters, usually not tuned or optimized for the registration of baseline and follow-up chest CT scans. The goal will be to find the best combination of parameters leading to the best registration of anatomical structures. In order to reach this objective a possible methodological approach can be:

- Collecting a data-set of pair baseline/ follow-up CT scans of different patients.
- Defining a set of points in both pair of scans corresponding to fixed anatomical structures which position should not change in two different scans. These points are usually called *landmark points*.
- Defining a metric for the quantitative evaluation of the goodness of the original scan and the registered one. The standard approach is to evaluate the performance of the algorithm, for example in terms of smoothness and DICE coefficient. The basic idea of the DICE coefficient is to measure the overlap of some structures between a pair of scans. Landmark points can be used to evaluate the DICE.
- Run the registration algorithms for a defined set of parameters
- Evaluate coefficients, change the value of parameters and re-iterate previous step
- Find the best combination of parameters

4.1.2 Editing of 3D Tumors Segmentation within CirrusLung Workstation

As described in 3.1.2 this workstation has an automatic algorithm for the segmentation of pulmonary nodules. The user can also change some of the parameters and re-inizialize the automatic segmentation. Even if the tool is performing quite well with all type of nodules, there are some cases in which the automatic segmentation fails or cannot be satisfactory for the user. This can happen with some very big (more than 15 mm of diameter) solid nodules usually attached to the pleura or with part-solid nodules where there is a difficult solid core to be segmented. The basic idea is to develop a tool for a semi-automatic correction of failed segmentation. The user will be allowed to draw some contours in 2D above the proposed segmentation and the algorithm, taking information from this manual correction, re-run the segmentation in 3D. A possible methodological approach to reach this goal can be:

- Create a data-set of nodules for which the automatic segmentation fails or is not satisfactory. This data-set can be composed looking at public available screening data set.
- Trying to segment them using the automatic tool already present in the workstation and store the binary mask of failed segmentation.
- Creating an editing interface for sketch editing segmentation in 2D.
- Developing an algorithm capable to, starting from the drawn contour by the user, perform the segmentation in 3D of the nodules using the information provided by the contour itself

Varational interpolation with radial basis function (Morse et al., 2005) seems to be a very prominent path for this desired algorithm. Without going into detail, the basic idea is to use the point belonging to the contour drawn by the user as constrained point for the interpolation. The segmentation will be a superposition of radial basis function centered in the constraint points.

4.2 Spreading the Usage of CAD in Clinical Practice

In order to make CAD algorithms available to radiologists without requiring any installation of software or hardware we believe that a possible way is the combination of the SaaS and Iaas approaches presented in 2. The methodology is intended to build:

- A web front-end accessible from every browser through tablet, laptops and mobile devices for managing CT uploading, on-line medical annotation of the exam and access to CAD results
- A cloud back-end for the computation of CAD algorithms

These two solutions were used to together to build what we have called the M5L on-demand system, which is basically composed by two main subsystems:

- A web front-end: available as a web application accessible from every browser from desktop and mobile devices. Having proper credentials, DICOM images can be uploaded to the remote repository and reviewers can insert their medical diagnosis and see other reviewers ones.
- A cloud computing back-end: thought to guarantee flexibility in the available computing resources. It allows to allocate computing resources according to the need of the user. The back-end handles the part of the computation of the CAD algorithms.

We will describe in details the M5L on-demand service we have developed in 5.2.

4.3 Studying the Impact of CAD in Clinical Practice

In this subsection we intend to present two possible different observer studies for the evaluation of impact of CAD in clinical routine. The first observer studying is aiming at evaluating the impact of CAD as second-reader in the performance of the radiologists. Our approach is to evaluate the performance of radiologist before and after having seen CAD results. Several papers cited in 1 proved an improvement of the performance of the radiologists when assisted in detection by CAD algorithms. However, most of these studies have been performed using a retrospective database coming from screening campaigns. These data-set were usually composed by no more than few hundred of nodules. Motivated by the goal of upgrading these works we have decided to setup a collaboration with the IRCCS of Candiolo (Italy). Using the M5L on-demand web service, three radiologists with different expertise are annotating cases of oncological patients staging or re-staging chest CT examination. The adopted methodology is composed by the following steps:

- Every week one or more bunches of CT scans from different patient is/are uploaded via the M5L web front-end. They are elaborated by the M5L CAD through the cloud back-end and results are stored in the web-server.
- The three radiologists annotate independently the exams through a dedicated web form without having access to CAD results (first-reader).
- After having completed the annotation, the radiologist can access CAD results, review them and insert CAD findings in his/her annotation (second-reader).

The web form for the annotation has been built similar to the LIDC/IDRI guidelines (Armato III, 2011). This approach was motivated in order to collect several features about the shape and malignancy of the nodules in a structured way, despite the common practice in clinical routine is not to have rigid guidelines. Another important motivation underlying this approach is the idea to create a database of structured annotated clinical data to perform further studies when looking at the features of pulmonary nodules. All the public available databases are coming from screening campaigns and all the most of CADs have been evaluated using screening data-set. No work has been performed usually a clinical dataset with oncological patients undergoing staging or re-staging. The second observer study is aiming at comparing the CAD as concurrent-reader and second-reader mode. The basic idea is to evaluate the difference of sensitivity between the CAD as concurrent-reader and second-reader. We are expecting from previous studies that using CAD as concurrent-reader reduces the annotation time with respect to the usage in second-reader mode, but a detailed analysis of the sensitivities is needed to prefer one solution with respect to the other. One of the crucial point is to eliminate possible memory effects which can bias the results. Furthermore, another bias which has to be considered when performing this analysis is that the results can suffer from inter-observer variability. In order to achieve this goal we propose the following methodology:

- Two radiologists with similar grade of expertise (A and B) will annotate independently a common data-set of CT scans.
- Radiologist A will analyze a first half of the scan, randomly chosen, in concurrent-reader mode. The other half of the scans will be analyzed in second-reader mode.
- Radiologist B, on the contrary, will analyze the first half in second-reader mode, the second half in concurrent-reader mode.

The results will be analyzed pairwise. For each scan not only the findings of the radiologist will be available, but also the reading time for each step. A comparison of the sensitivities and reading times could allow to assess and highlight the major differences and benefit of the two different reading approaches.

5 EXPECTED OUTCOME

In this section we intend to present some preliminary results already achieved applying methodologies described in 4. If the development has not start yet, we briefly delineate some expected results.

5.1 Development, Validation and Optimization of CAD Algorithms

In the first part, since no detailed development has started yet, we present a little bit in detail the expected outcome for the algorithm presented in 4.1.1. In the second part we will present some preliminary results on the analysis of the algorithm for the segmentation of pulmonary nodules presented in 4.1.2.

5.1.1 Automatic Registration of CT Scans within M5L CAD

We are expecting to develop a robust algorithm for the automatic registration of chest CT scans. This algorithm takes as input two scans of the same patient, the first is the baseline scan and the second is a follow-up scan. The first part is the determination of landmark points in the scan. This can be done manually or using some semi-automatic tools. An example of landmark point is shown in Figure 1. The next step is running the registration algorithm which produces a deformed (registered image) after applying topological transformations, as shown in Figure 2. The last step is the comparison of the same nodule in baseline and follow-up scans as shown in Figure 3.

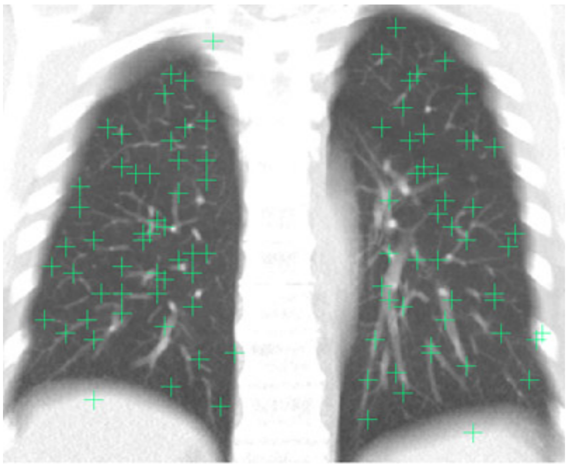

Figure 1: A sample fixed image showing the well-distributed landmark points projected in the coronal direction. (An average intensity projection is used to help to demonstrate that all points are within the lung volume).

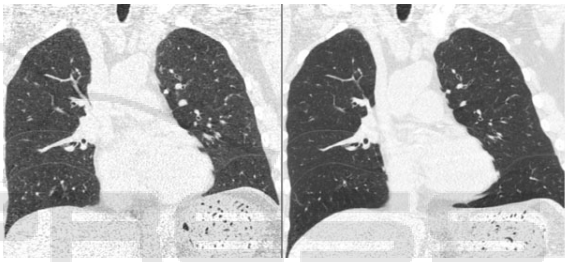

Figure 2: On the left the fixed (target) image in an example pair. On the right the deformed moving image after registration. It is clear that the fissures are relatively well aligned in this example, but the lung boundaries in the lower lungs are not).

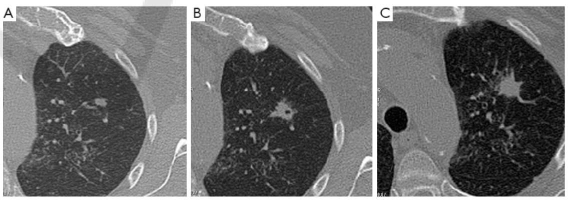

Figure 3: 74-year-old man with rheumatoid arthritis had solitary pulmonary nodule in left upper lobe. (A) Nodule volume was 175 mm3 on first CT scan; (B) six months later, nodule volume was 749 mm3, with doubling time of 114 days; (C) spiculate margins and nodule growth compatible with malignant nodule.

5.1.2 Editing of 3D Tumors Segmentation within CirrusLungScreening Workstation

We have started segmenting a list of nodules bigger than 10 mm from some screening data-set public-ally available. Our data-set was including all kind of nodules: solid, calcified, part solid and non-solid. We have tried to segment them first without interacting with the automatic tool and then tuning some parameters (like threshold or shape) trying to reproduce a satisfactory segmentation. We collected all the binary masks of nodules with failed segmentation. In the LIDC/IDRI data-set for example, there were more than three hundred nodules greater than 10 mm. We found that almost 10% of those nodules could not be segmented well by the algorithms. This sub-set was mainly formed by very big solid nodules (usually attached to the pleura) as shown in Figure fig:solid or part-solid with a difficult solid core to be segmented as shown in Figure 5. Starting from this list of nodules we are extracting the contour from binary mask of segmentation and we are, as starting point, developing the possibility for the user to manipulate and correct the wrong contour in 2D.

5.2 Spreading the Usage of CAD in Clinical Practice

A first proof of concept of the prototype of the M5L on-demand web service was presented some years ago (Nakayama et al., 2012). The entire system has been recently completed and tested by some institutions. Its features will be presented in Section 6.

5.3 Studying the Impact of CAD in Clinical Practice

We briefly present the preliminary results achieved for the clinical validation of the M5L CAD in collaboration with the IRCCS of Candiolo. 20 cases out of 80 already submitted to the web site have been annotated independently by two radiologists with a difference in expertise of 20 years. After having completed the annotation of a case, CAD results have been shown to the radiologists. They were able to mark CAD findings as False Positive, Irrelevant or True Positive. In this last case they were asked to specify the malignancy of the finding. In order to be consistent with the validation of M5L CAD performed within the LIDC/IDRI data-set only nodules with a diameter greater than 3 mm were considered. Furthermore, to be consistent with the previous validation we took as gold standard nodules annotated by both radiologists. This procedure leads to a group of 27 nodules identified by both radiologists. The sensitivity of the CAD with respect to the gold standard was of the 74% at about 3.3 FPs/scan. The CAD added 7 more nodules, so the sensitivity of both radiologists plus the CAD reaches the value of 80% showing, as expected, an improvement of performances also in clinical practice. We are expecting to proceed with this studies, increasing the validation data-set and performing further statistical clinical studies.

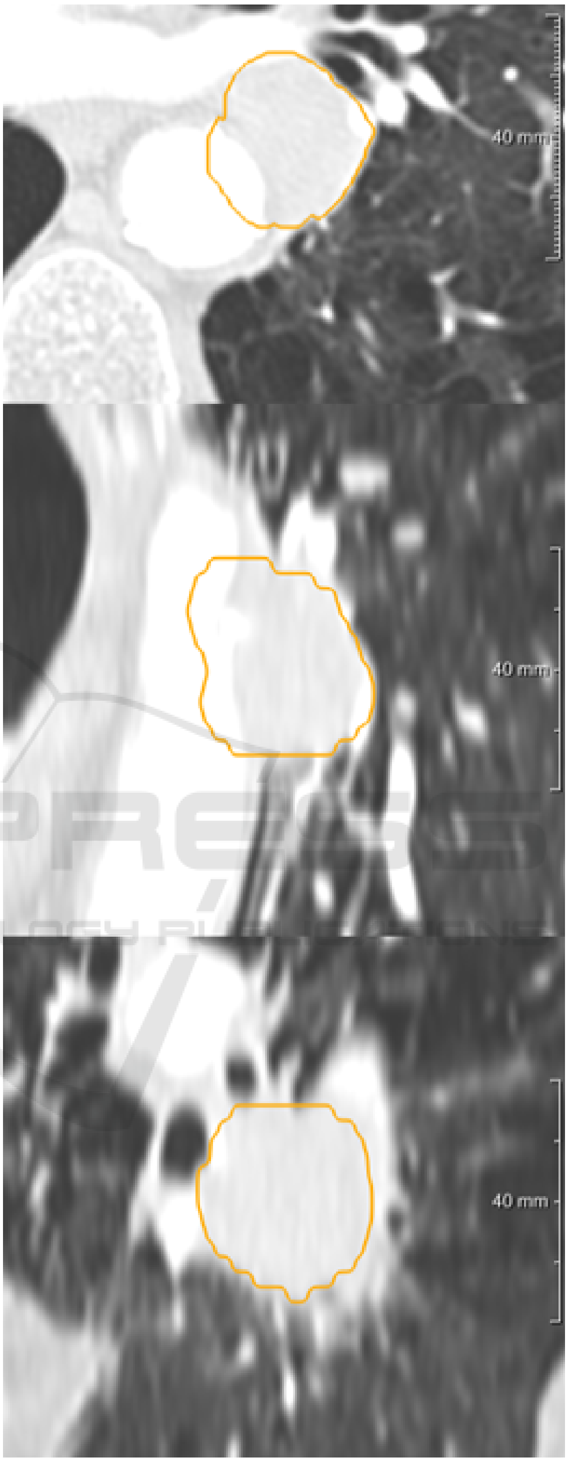

Figure 4: Screen shot of a big solid nodule with failed segmentation.

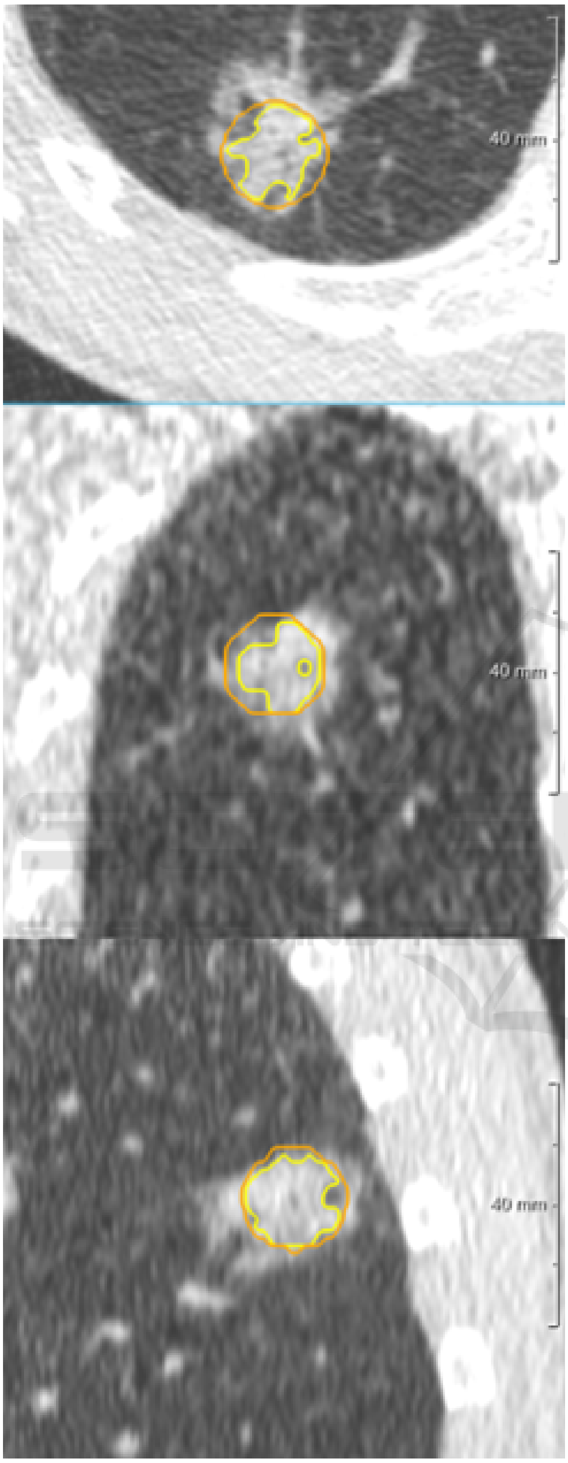

Figure 5: Screen shot of a part solid nodule with failed segmentation, Orange line is the contour of the lesion, while yellow line is the contour of the solid core.

6 STAGE OF THE RESEARCH

The outcomes of the PHD thesis can be divided into two parts. The former is a more technical part aiming at:

- Improving exiting CAD algorithms with the enhancement of some functionality useful for relating CAD outcomes to clinical results.
- Build and test a system, to be inserted in clinical practice, which allows radiologists:
  - Submit case through a dedicated front-end for CAD computations.
  - Having the possibility to directly insert their medical annotations through a dedicated web-form.
  - Having the possibility to access to CAD results and operate both in concurrent-reader or second-reader mode.

The M5L on-demand system can be considered as the first main outcome of my PHD thesis. The entire front-end web interface has been developed using the DRUPAL free and open source tool (Coombs, 2009). DRUPAL easily allows the development of custom modules in PHP code. We have basically developed two modules:

- Submission module: this module is conceived to be used by a technician operating with a submitter role, who uploads one or more CT studies to be analyzed and selects a radiologist (not necessarily belonging to the same institutions) who will review the studies. The module layout is shown in Figure 6.
- Review module: this module is conceived to be used by a radiologist. After logging in with his/her credentials and reviewer role, the radiologist can insert the medical annotation of studies assigned for review during the submission process. The M5L results are available in different formats, such as DICOM Structured Report, HTML, XML and PDF. The M5L marks can then be reviewed ad assessed, with the options to include them into the annotation, as shown in Figure 7, or reject them.

The M5L CAD on- demand service is hosted by the INFN Torino Computing Center, which is a Tier-2 of Large Hadron Collider Computing Grid (Turner IV et al., 2006). A Private Cloud infrastructure has been created. The facility is managed by OpenNebula, a free and open-source Cloud Management Platform which allows hardware and virtual infrastructure control and monitoring, adding the possibility of virtual machine life-cycle management (Milojičić et al., 2011). OpenNebula orchestrates storage, networking, actualization, monitoring, and security technologies to deploy computing services as virtual machines on distributed Resources infrastructures. The resources used by M5L are:

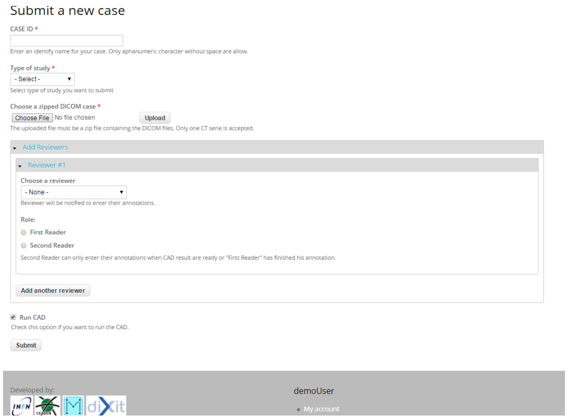

Figure 6: Screenshot of the submission page as seen buy a submitter.

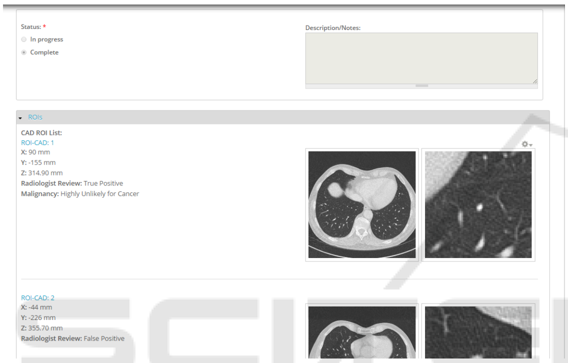

Figure 7: Screenshot of CAD review page as seen by a radiologist.

- One physical host for the web-server.
- Several Virtual Machines (VMs) as computational power.

At this moment M5L is allowed to deploy up to 18 VMs, with a total of 48 cores. An elastic cluster based on CernVM Online (Buncic et al., 2010), a service that can create clusters with a head node and many workers based on CernVM OS, was configured so as to achieve the capability to scale resources up or down. Using CernVM Online VMs can be contextualized, so as to define the use of resources, user settings and automatically install and enable some specific tools, which in our case are like HTCondor (Tannenbaum et al., 2001) and Elastiq (Berzano, 2014). The second part of the PHD thesis is more a clinical part, aiming at performing observer studies to investigate the impact of CAD in clinical routine and to diffuse the usage of CAD as support for cancer detection. We believe that technical aspects cannot be divided from clinical requirements. CAD algorithms have to fit clinical guidelines. The link between technically aspects and clinical requirements is mandatory if we really want to insert CAD in clinical practice. CAD workstations should we built according to requirements provided by clinicians.

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