RadioBio data: A Moddicom Module to Predict Tumor Control Probability and Normal Tissue Complication Probability in Radiotherapy

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Abstract: In this work a system for analysing radiotherapy treatment planning dose-volume data is proposed. The work starts from the definition of a framework inside a statistical scripting environment (R) used for creating a software package. The analysis of dose-volume data in radiotherapy of malignant tumours is mandatory for evaluating the prescribed treatment and for feedback analysis of outcome, both in the direction of tumour control and in detection of parameters for estimating and predicting toxicity outcome. The statistical analysis of large amount of clinical data can be slowed by the lack of practice in statistical tools needed, by clinicians, to perform such kind of analysis. This is the reason that lead our working group in the creation of such a tool. Finally an example of clinical application of our software is given for the analysis of the outcome of patients undergoing to radiotherapy for prostate cancer.

1 INTRODUCTION

Radiotherapy is one of the most efficient and most used treatments in cancer therapy, together with the chemotherapy and surgery. In the external beam Radiotherapy (EBR) a radiation source is addressed to send radiation beams (X-ray, gamma-rays or electrons) on the patient, in specific locations, and the leafs of a collimator are configured in order to reproduce in the space a desired 3-dimensional conformation of radiation doses. Such doses are planned in order to be able to kill or severely damage the tumour cells. The 3-dimensional shape of toxic dose is delivered inside the patient body; therefore, attention must be payed in order to decrease as much as possible the delivery of radiations in healthy tissues, so reducing the likelihood of toxicity.

When planning a radiotherapy treatment, the radiation oncologists have two critical aspects to consider: (i) providing a total dose on the target that is adequate for damaging and killing; and (ii) limiting the dose received by normal tissue, in order to minimise iatrogenic side effects. Usually, radiation oncologists have to identify a reasonable trade-off between these two aspects. Because of that, physicians exploit complex mathematical models – called radiobiological models – for estimating the Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). Given such estimations, they can identify the plan that provides the largest total dose on target, while limiting the likelihood of normal tissue side effects.

Despite the fact that numerous models have been proposed, the identification and exploitation of radiobiological models is still considered an open and critical topic. Such models are currently in the aims of the most important international associations in the field: for example, the American Society for Radiation Oncology (ASTRO) in association with the American Association of Physicists in Medicine (AAPM) supported the creation of Quantitative Analyses of Normal Tissues Effects in the Clinic (QUANTEC). QUANTEC project exploits the large amount of data that modern technologies – like Linear Accelerator (LINAC) and Treatment Planning Systems (TPSs) – are able to export, in order to provide more accurate TCP and NTCP specific for the different involved human anatomical regions (Bentzen et al., 2010; Marks et al., 2010b).

One of the most common source of information exploited by radiobiological models is represented by

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the Dose Volume Histogram (DVH): an histogram showing on the x-axes the dose and on the y-axes the volume of the ROI receiving such dose. Each DVH is a "quick 2D recap", of the dose absorbed for each target or normal tissue volume, also called Region Of Interest (ROI). In literature, the analysis of DVHs is related to the actual clinical outcome, for effectively identifying some dose constraints under the form of clear rules, such as: the minimum dose to the Planning Target Volume is 95% of the plan reference point dose; in order to decrease risk of radiation pneumonia under 20% it is prudent to limit Mean Lung Dose within 20 Gy (Marks et al., 2010a) or "to avoid rectal bleeding or late rectal RTOG grade >= 2 less than 50% of rectal volume should receive 50 Gy or less than 35% should receive 60 Gy"(Michalski et al., 2010).

The classical empirical approach to define such constrains has been recently overcome by adaptive algorithms, which are able to adaptively find, with the evidence of the daily clinical practice, also new form of useful constraints. An important contribute come from (Naqa et al., 2006) which clearly highlights the importance of predictors built basing on DVH and a multi-variate modelling process. Nevertheless all those experiences are done locally, in different centres with different tools, and there is no common tools to build and tune new TCP/NTCP models by a specific dataset.

Despite collecting and analysing dose information is considered very important in order to build and improve maths models, there is a poor availability of easily to access tools for such task. VODCA is the oldest project and is able to collect DICOM-RT studies and to analyse them by using R, a well-known statistical engine. It should be noted that VODCA is not free and does not provide specific tools, libraries and function for TCP/NTCP models.

In order to provide a common tool for building and finely tuning TCP/NTCP models, in this paper we propose a software library, integrated in a more complete project called moddicom(Dinapoli et al., 2015b), that is able to effectively support the process of generating and improving TCP/NTCP models for the specific data of a radiotherapy centre. To foster the exploitation of the tool, and therefore allow a better use of the knowledge stored in the existing datasets, the proposed software is freely available as an R package at https://github.com/kbolab/moddicom.git. In this paper we provided an overview of the developed software library, and we show the results of an experimental analysis focused on evaluating the usefulness of the proposed system.

2 METHODS

The overall structure of the moddicom framework is shown in Figure 1. Currently, the modules grouped as *R environment* are available and ready to be used. The *R environment* includes:

- **geoLet**. This requires the DCMTK Office libraries (Eichelberg et al., 2004) and allows to load DICOM Images, DICOM RTStruct, DICOM RTDose, DICOM RTPlan studies in memory.
- **Image Feature Data Analysis**. This module allow to extract image features for Radiomics (Dinapoli et al., 2015a) analysis from the previously loaded DICOM studies.
- **RadioBio** data models. This module calculates DVHs (starting from the DICOMRT Struct/Dose/Plan previously loaded by geoLet) and can tune the parameters of six different radiobiological maths models for TCP/NTCP modelling.
- **Visualisation Module**. This module provides tools to visualise objects and images in 2D/3D in order to give a practical presentation of the stored data.

Part of the moddicom framework is still under development. The complete moddicom framework will be able to acquire information directly from modalities and PACS, via DICOM protocol, in order to populate its internal database, which will be subsequently able to automatically exploit the stored information. At the moment, the loading is done by searching a file system and for finding DICOM information.

The *geoLet* module can search the file system, from a given path, and load the data stored in DICOM RT-PLAN/RT-STRUCT and RT-DICOM-Distribution Doses. The corresponding information are then used by the *RadioBio data* module for generating and fitting a number of mathematical models. The fitting is also able to analyse the hidden clinical effects of dose constraint not yet identified as significant in literature. In the following, the implemented models are listed and briefly described. The interested reader is referred to the provided references for details about the mathematical functions and models.

- **Lyman.** It is a reformulation of probit model, that uses different parameters than mean and standard deviation (Burman et al., 1991).
- **Goitein.** This model is similar to the Lyman model, but it is function of *logarithm* of the Dose (Shipley et al., 1979; Bentzen and Tucker, 1997).
- **Niemierko.** It is the translation of a *loglogit* generalised linear model as function of TD_{50} and γ_{50} (Gay and Niemierko, 2007).

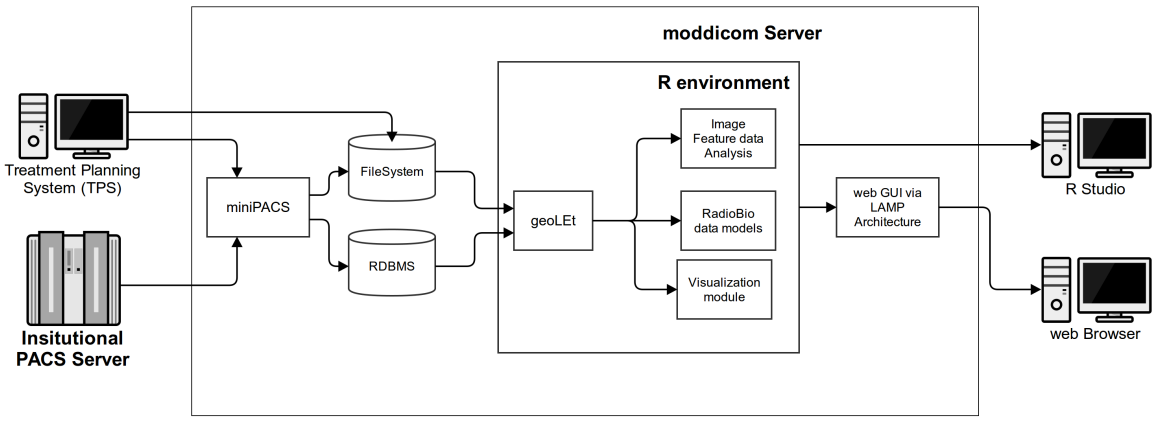

Figure 1: The overall structure of the moddicom architecture. The core is represented in the box titles *R environment* and is currently available. The structure includes also the PACS/TPS interface and the web based GUI.

- **Munro**. This model is an empirical dose/response curve that fits experimental data. The model is based on the assumption that this curve is equivalent to a Poisson model (Munro and Gilbert, 1961).
- **Okunieff**. This model is the equivalent of the *logistic* generalised linear model, where the covariates and their coefficients have been reported as function of TD_{50} and γ_{50} (Okunieff et al., 1995).
- **Warkentin**. This model is the equivalent of the Warkentin *Poisson* model where the covariates and their coefficients have been reported as function of TD_{50} and γ_{50} (Warkentin et al., 2004).
- **Bentzen**. Bentzen described dose/response curves both for tumour and normal tissue response. In our implementation, *log Poisson* model starts from equation used in Warkentin equation, but the subsequent evaluation of the relationship of response with the *log* Dose (Bentzen and Tucker, 1997).

The previously cited models are considered in order to automatically find the most significant Dose/Volume constraint able to fit the model with the clinical outcomes. A similar approach has been proposed in the past (Naqa et al., 2006), but it is worthy noting that moddicom represents the first shared and freely available software tool able to do that.

The *RadioBio data* module also provide a simulation environment where DVH can be artificially created (Van den Heuvel, 2006) and associated to clinical outcome according with a known statistic. This represents an useful sandbox to test the implemented mathematical models and see their details in action. As previously cited, *RadioBio data* module is also linked with the *geoLet* module for being able to work with real clinical data directly taken from DICOM sources.

For providing a complete environment to the researches, a range of tools –including calibration plots and fitting curve– have been implemented and can be exploited within the moddicom framework.

3 EXPERIMENTAL RESULTS

In order to test effectively the applicability and the capability of the proposed *RadioBio data* moddicom module, a clinical investigation was performed on a real dataset of 123 patients treated with Radiation Therapy for prostate cancer: this cohort was taken from a study performed between September 2010 and May 2014 at the Radiation Oncology Centre of Gemelli Hospital. Acute and late rectal (GI) and bladder (GU) toxicity data were collected. Referring physician clinically examined patients a median of 5 times during RT treatment, unless otherwise requested by patient himself. RTOG score (Cox et al., 1995) and CTC-AE v.4.03 (of Health and Human Services, 2010) were used to stratify grade of toxicity. Patients' DVH were collected to evaluate bladder and rectum dose-volume distributions. Dose from treatment planning and simulated delivery was evaluated using the Equivalent Uniform Dose (EUD) (Niemierko, 1997). For normal tissues, the EUD represents the uniform dose which leads to the same probability of injury as the examined inhomogeneous dose distribution. The EUD was calculated from the corresponding dose-volume distributions (histograms).

To calculate the EUD-based normal tissue complication probability (NTCP), we used parametrisation of the dose-response characteristics using Lyman

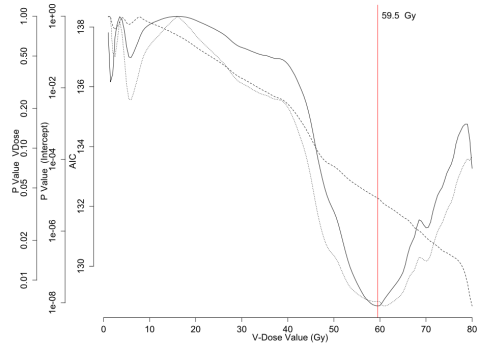

Figure 2: Correlation between rectal G1 late toxicity and a Vdose=59.5 Gy.

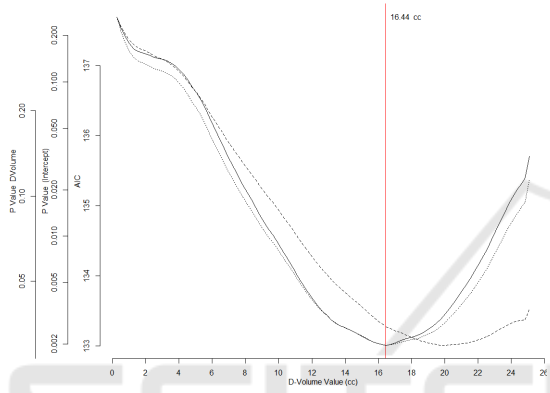

Figure 3: Correlation between rectal G1 late toxicity and a Dvolume=16.44cc

NTCP formula (Burman et al., 1991).

In such comparison DVHs have been clustered according with the induced toxicity (Figure 4). The dose-volume toxicity parametrisation has been conducted by identifying respectively the volume of a structure receiving a given level of dose (as known as *Vdose*) and the dose received by a given volume of the structure (as known as *Dvolume*). Such dose-volume parametrisation is extensively in radiotherapy for correlating outcome and dose distribution data (Marks et al., 2010b). We observed a correlation between development of late G1 or superior GI toxicity and a Vdose equal to 59,5 Gy (see Figure 2) and a Dvolume equal to 16,44 cc (see Figure 3). In particular we found a significant correlation with D16cc by Mann-Whitney Test ($p = 0.019$).

Finally, to elaborate a predictive model for G1 GI toxicity, we build up a DVH-reduction model by Lyman Model Maximum Likelihood Estimation, based on estimated NTCP under uniform irradiation (EUD) of the rectum. We found that our patients were distributed on or close to an S slope showing that 50% probability of acute toxicity is present with a mean delivered uniform dose of 66,5 Gy (see FIgure 4).

The results of the analysis, performed using the

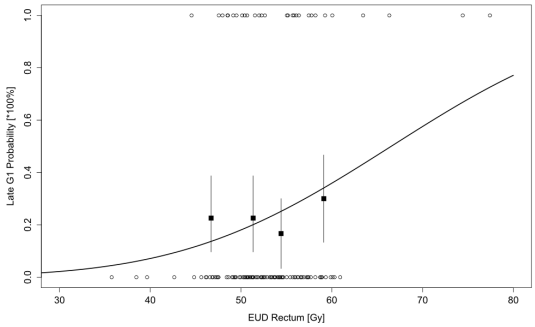

Figure 4: The DVH-reduction model based on estimated complication probability (NTCP) under uniform irradiation (EUD) of the rectum.

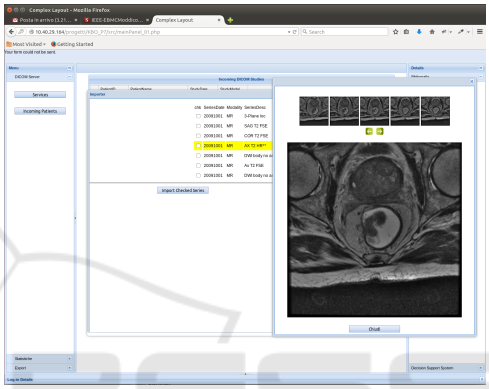

Figure 5: The proposed graphical user interface.

proposed moddicom module, confirmed the evidence known in literature and also suggested a new possible significant dose constraint. While the former result clearly indicates the validity of the approach, the latter provides some insights into the usefulness of the *RadioBio data* module. However, due to the limited number of recruited patients, further investigation should be done to confirm the identified constraint.

Remarkably, the analysis was performed by a physician –although expert user of R– rather than a technician. Therefore, the use of moddicom can provide an effective support to physician in their every day research or clinical activities.

4 CONCLUSIONS

In this paper we presented the *RadioBio data* module of moddicom, which is a free and open source library born to support the adaptive TCP/NTCP modelling.

We tested *RadioBio data* with 123 patients treated with Radiation therapy for prostate cancers and we obtained results in accord with literature. The performed analysis focused on investigating the usability and usefulness of the proposed module, and it showed

that *RadioBio data* can be an useful tool to mine effective dose constraints hidden into the shape of Dose Volume Histograms. Moreover, the considered case-study can be extended by considering a larger sample of patients, in order to provide stronger evidences and better optimise planning procedures in treatment validation and predict possible toxicity. The future challenge will be the personalisation of treatments and complications rates reduction.

Future work include the development of a user-friendly graphical user interface, as proposed in Figure 5, an experimental analysis considering a larger number of patients, and the involvement of a larger number of medical experts.

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