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Quality assurance

Design of and technical challenges involved in a framework for multicentric radiotherapy treatment planning studies

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ABSTRACT

This report introduces a framework for comparing radiotherapy treatment planning in multicentric *in silico* clinical trials. Quality assurance, data incompatibility, transfer and storage issues, and uniform analysis of results are discussed. The solutions that are given provide a useful guide for the set-up of future multicentric planning studies or public repositories of high quality data.

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In radiation oncology, *in silico* clinical trials or planning studies are increasingly popular for investigating different treatment options without harming the patient [1–3]. They can be described as modelling studies that, based on virtual patient material (imaging), validated procedures (including *a priori* sample size calculation) and models, providing an alternative method of exploring

or generating hypotheses. The modelling results should then be validated in real life with prospective clinical trials [4].

The concept of treatment planning comparison studies is not new. Starting in the early 80s, the National Cancer Institute funded various projects to evaluate and compare different treatment modalities [5,6]. Back then, a lot of tools and procedures we now take for granted (e.g. 3D dose evaluation, multi-modal image registration, and plan optimisation) were missing or insufficiently implemented. This hindered the proceedings of those projects. In the three decades that followed a lot of these issues were overcome. Although the comparison of radiotherapy treatment options in a multicentric setting is still challenging it is much less problematic as in the early days.

One such multicentric *in silico* clinical trial that is based on the MISTIR (acronym for “Multicentric *In Silico* Trials In Radiotherapy”) framework presented here is ROCOCO (**R**adiation **O**ncology **C**ollaborative **C**omparison) [7]. This is an emulation of clinical trials in photon, proton and heavier particle radiotherapy for tumours with high incidence. It comprises the treatment planning (TP) comparison of lung, prostate and head and neck tumours for 25 patients in each group. Currently, eight international institutes are performing TP for conventional and intensity-modulated photon, passive scattered, scanning or intensity-modulated proton and carbon ion

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radiotherapy. MAASTRO CLINIC serves as the coordinating Data Centre (DC) as well as being a participant.

During the course of the project various organisational and technical issues arose and were solved, thus maturing the framework into its current state (Fig. 1). As we believe that the set-up is an *all-in-one* solution that can be used for a wide range of *in silico* clinical trials in radiotherapy, planning studies and/or for public repository of anonymised datasets, our intention with this technical note is to provide a step-by-step guide for building such a framework. All major action blocks will be discussed and critical issues on data exchange will be explored. Information that is kept up-to-date can be found online on the MISTIR website: <http://www.mistir.info>.

Methods

For an international, multicentric *in silico* clinical trial that started in January 2008 a framework was built using five major action blocks (Fig. 1). A centrally hosted database (DB) was designed to host the protocol, the patient datasets, the TP results and the analysis thereof. Secure access to the database was granted to authorised project participants by means of the FTPS (secured File Transfer Protocol) and HTTPS (secured Hyper Text Transfer Protocol) protocols [8,9]. We used Public Key Infrastructure (PKI) certificates (the gold standard security method in data exchange of medical data [10–12]) to verify the user's identity before login was allowed.

To facilitate data sharing, the participants agreed to use the internationally accepted Digital Imaging and Communications in

Medicine standards (DICOM) [13]. In the event of a participant being unable to comply, the RTOG (Radiation Therapy Oncology Group) format [14] was accepted.

The five action blocks of the framework, as described below, were: initialisation, preparation, treatment planning, analysis and reporting.

Initialisation

Following the template of a real clinical trial, a protocol was set up in which the trial hypothesis, the sample size and the methodology were described. The structure and management of the project were defined by project goals and milestones. With respect to the topic that was studied (the comparison of treatment techniques or modalities) the protocol described the study endpoints, differentiating primary and secondary endpoints and how differences were analysed. Furthermore, it described the available data and means to access it in a secure manner. A Material Transfer Agreement (MTA) was formulated in which the participants' roles, rights and liabilities were described. After signing the MTA, the participant was granted access to the central database. Templates of the protocol and MTA are available online.

Preparation

With the prepared protocol, eligible patients were accrued and their datasets were gathered. By consecutively including patients that satisfied the protocol, no selection bias was introduced. A set of CT images and delineations of targets and critical organs in the DICOM RT STRUCT format were de-identified and uploaded to the database. Furthermore, fluor-18-fluorodeoxyglucose (FDG) PET and MR images were added. For the available 4D CT/PET data, the 3D motion vector of the target was determined and included in the dataset [2]. Because the FDG-PET images were used to automatically delineate high-uptake regions with a method validated with pathology [15–17], the standardised uptake value (SUV) conversion curves of data-supplying institutes were calibrated [18]. This guaranteed that the auto-delineation algorithms used in the data-supplying institutes created equivalent contours.

Treatment planning

To perform TP, the centres downloaded the datasets from the database. It was mandatory for each centre to test if any shift occurred in the structure sets during data import. To validate the import, screen captures in JPG format of representative slices were uploaded for verification. The centre then proceeded with TP according to the strict criteria as described in the project protocol. The TP results were exported by the participants in DICOM RT format and uploaded to the DB.

Analysis

In order to analyse the results and to compare TP modalities, the DC used the CT, the delineations and the dose matrices stored in the DB. Visualisation of the TP results was done using MATLAB (The MathWorks, Natick, Massachusetts), CERR [19] or VODCA [20].

For the calculation of dose-volume histograms (DVHs), user-developed MATLAB code was used instead of requesting DVH parameters from the participants. The centrally performed calculations reduce any uncertainties that can arise due to differences in the algorithms of the various treatment planning systems (TPSS).

The DVHs were then used to derive relevant dose metrics of the different structures such as mean, maximum and minimum dose, conformity indices (CI), inhomogeneity coefficient (IC) and tumour

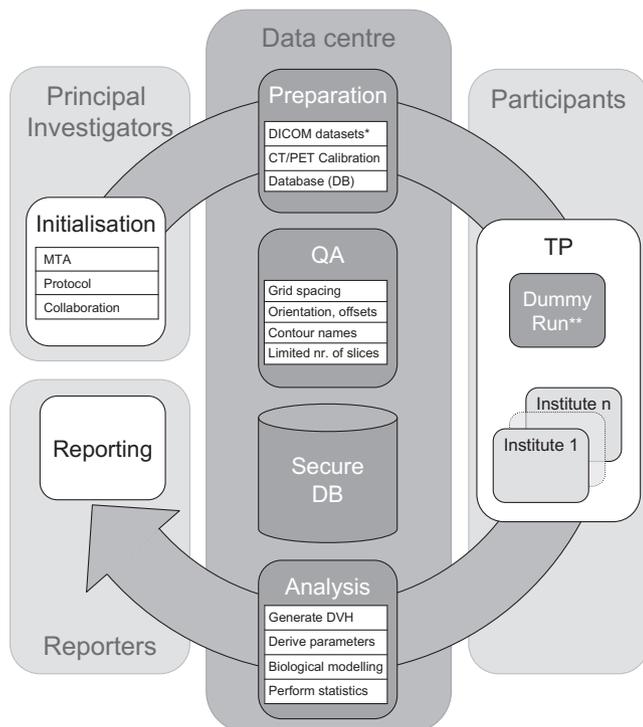


Fig. 1. A diagram illustrating the major actions of a project that is based on the currently presented *in silico* trial framework. After uploading data to the DB it is checked for integrity and validity by various QA procedures (some items shown). The blocks surrounded by the “Data centre” frame are performed centrally to avoid data corruption and minimise uncertainty due to the use of different algorithms. DICOM images can originate from multiple institutions. However, before allowing other participants to use them the DC performs the initial QA procedures. ** The dummy run is a joint action by the DC and participants as part of the QA programme.

control probability and normal tissue complication probability (TCP and NTCP, respectively) where models were available. The abovementioned metrics were calculated using the strict formulation described in the project protocol. The results were made available by entering them into the DB.

Reporting

Finally, the validated data in the DB were available for publication by the designated project members.

Quality assurance

A large collaborative project such as ROCOCO needs a well-designed data exchange set-up. Data supplied to all participants originate from multiple sources including CT, PET and MR scanners and from the TPS. TP will be based on the data available in the DB and participants will upload their data from their systems to the DB. Currently, TP has been performed using XiO/Focal (CMS Software, Elekta), Pinnacle (Philips), Virtuos/TRiP (in-house: DKFZ Heidelberg/GSI Darmstadt) and HIPLAN (in-house: NIRS). With such a variety of programmes involved and due to the fact that the DICOM standard allows vendors to incorporate proprietary information, interoperability problems easily arise with data import/export [21]. Therefore, it is essential to define a proper Quality Assurance (QA) programme.

At MAASTRO CLINIC, an in-house developed programme called DIGITrans is used in daily clinical routine that normalises all DICOM (RT) data to prevent interoperability issues and guarantees data consistency. This includes matching the patient demographics of exported data from the scanners, TPS or record-and-verifying system to the electronic health record. Furthermore, we “brand”

the images by invisibly adding referencing DICOM tags to the image data.

During the set-up of the MISTIR framework many issues were addressed (Table 1) for which we reused part of the DIGITrans procedures or developed new ones. The MISTIR QA procedures now prevent and correct problems with:

- SUV (PET) calibration
- CT calibration (Hounsfield unit to electron density conversion)
- correct media assignment, if needed (e.g. in Monte Carlo dose calculations)
- DICOM (RT) data connectivity
- de-identification
- 4D data phase consistency
- orientation/transformation errors
- number of slices
- contour names
- contour interpolation
- multiple contours on a single slice
- invalid dose grid sizes
- other protocol violations.

To test the set-up of the protocol, DB and QA procedures, first a dummy run is performed with a representative sample of the dataset. The participants are asked to perform TP according to the protocol and send their results to the DB. Upon receiving the datasets, the QA procedures are applied to ensure consistency and validity of the data. In cases where the TP data do not conform to the protocol, the participant is asked to adapt its procedures and redo TP. Then the data are checked again for validity. After acceptance, the participant is asked to proceed with the entire dataset.

Table 1

A selection of problems, solutions and remarks on the implementation of the MISTIR QA procedures.^a

Topic	Problems occurred during dummy run	Solution	Remarks
De-identification	The TPS, discards breathing phases in 4D datasets, due to reduced DICOM references in TPS export	Write code to directly modify the needed tags	We use <i>dcmodify</i> from DCMTK ^b
Integrity	The TPS does not handle PET or MR export TPS changes coordinate systems during DICOM import/export	Check for transformations whenever data is entering another system	We use screenshots to visually check for translations, rotations, inversions etc. We use the offset vector to restore transformed datasets
Slice thickness	TPS drops the <i>Frame of Reference UID</i> during DICOM import/export TPS cannot handle CT images and contours with varying slice thickness	Encode the <i>Frame of Reference UID</i> into the CT image data Resample the CT data, re-import into TPS and use the interpolation function to generated contours on new slices. Manually correct contours (e.g. in case of bifurcations)	
Nr. of slices	TPS cannot handle difference in reconstruction thickness and slice spacing TPS could not handle >99 CT slices	Make the slice thickness equal to the difference between the slice locations Make a subset of the data or resample if critical areas would be cut off	Radiologically this is not the same, however, it can be ignored for radiotherapy Add ~5 cm margin around beam edges to account for patient scatter
Structure names	TPS could not handle structure names starting with a number	Change the structure name to begin with a letter	
Internet protocols	Secured network transfer between institutes using FTPS not possible as the protocol is often blocked by hospital firewalls	Use an HTTPS as well as an FTPS server	We use DRUPAL ^c and FileZilla Server ^d , respectively. We use PKI certificates to guarantee security
File management	An HTTPS server does not always allow easy file manipulation	Add a module for file management	We use the WebFM module ^e
Data corruption	With many files in large datasets, upload is prone to errors	Pack the datasets before upload	We propose checksums to verify data (e.g. MD5 or SHA1)

^a Refer to MISTIR: <http://www.mistir.info> for more details.

^b OFFIS Dicom Toolkit: <http://dicom.offis.de/>.

^c DRUPAL: <http://drupal.org>.

^d FileZilla: <http://filezilla-project.org/>.

^e WebFM: <http://drupal.org/project/webfm>.

Results

The presented MISTIR framework has been successfully used for a multicentric, *in silico* clinical trial that is currently being conducted by the ROCOCO consortium. Twelve institutes are participating and several more have expressed interest in the study.

To ensure data integrity, a series of QA tests were performed manually on any item (including that from the host institute) that is uploaded to the DB before releasing it to the project members. The QA procedures are designed to detect and correct issues regarding the readability of data, compatibility with DICOM (RT) standards and transformations in structure delineations and/or in image coordinates.

The design of the framework has successfully been tested for several different sectors of the trial. Implementation of the mentioned procedures has successfully led to TP results for prostate and lung cancer [22,23].

Discussion

We have demonstrated that building a functional data management and analysis framework for an international, multicentric *in silico* clinical trial are feasible. Its QA procedures are able to detect data inconsistencies and prevent incorrect data analysis.

In its current state, MISTIR is used for file-based data exchange and manual data analysis. To support large multicentric trials with improved data transfer and warehousing of the DICOM RT objects and data mining capabilities we are working on implementing a DICOM RT compliant DB (PACS). To ensure semantic and technical interoperability, recommendations from standardising initiatives for healthcare and clinical research such as caBIG [24], CDISC [25] and IHE [26] are taken into account.

One application that would strongly benefit from the availability of large validated, multicentric datasets is the modelling of radiotherapy outcome [27,28]. For satisfying significance of the predictive models a large number of datasets are necessary, while for robustness it is best to validate the models on foreign datasets. We believe that public sharing of these datasets would stimulate this research on a global scale, as it already has done in genomics research where public data repositories are common practice [29]. Whether a centralised set-up based on the current MISTIR platform is needed or that it should evolve into a de-centralised, grid-based solution such as the GridCAD and GridIMAGE initiatives for radiology [30,31] remains to be determined. This is considered to be beyond the scope of this paper. A very recent series of papers of the QUANTEC consortium summarised the currently available dose/volume/outcome data for normal tissues [32]. In a vision paper of the same series they concluded that storage of high quality datasets in repositories should become a common strategy [33]. We believe that the described technology will help to realise this goal.

Conclusion

We presented MISTIR: a complete and secure framework for *in silico* clinical trials using the output of treatment planning on prepared datasets. It is successfully being used in the *in silico* clinical treatment planning trial that the ROCOCO consortium currently is conducting. By defining strict planning protocols and using validated algorithms, the results of the *in silico* trials can be used as a starting point for validating and/or generating hypotheses, without harming any patient and at a reasonable cost. These hypotheses need further testing in prospective phase II/III trials.

The step-by-step description of the different building blocks and procedures that are used in MISTIR offer a useful guide for the set-up of future *in silico* trials and/or public repositories.

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