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The INFN TPS project

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Summary. — This work summarizes the motivations of different INFN groups to start a dedicated research project for the development of innovative treatment planning systems for hadrontherapy, with a particular attention to the case where carbon ions are used. Different tasks are identified according to the specific competence developed so far within INFN.

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1. – Introduction

Clinical results obtained with hadrontherapy have been positive for various tumours, with percentages of local control and survival higher than those gathered with conventional radiotherapy. So far, almost 50000 patients all over the world have been treated with charged hadrons. Most clinical data obtained with these particles are related

to protontherapy (more than 49000 patients at the end of 2006) but the implementation of carbon ion therapy has demonstrated to be of great interest in the last decade (more than 3300 patients at the end of 2006). These results, together with the progress in accelerator technology and calculation systems of the delivered dose, have caused over the past years an increased interest for the development of hadrontherapy, with the construction of new centers provided with equipments dedicated to clinical applications (LLUMC, Loma Linda and NPTC, Boston in USA; HIMAC-NIRS, Chiba, PROBEAT, Tsukuba, and Hyogo Beam Medical Centers in Japan; Heavy Ion Therapy Centre at Heidelberg, the Italian National Centre for Oncological Hadrontherapy, CNAO, at Pavia, Geisse-Marburg in Germany and the French National Hadrontherapy Centre, ETOILE, in Europe).

Two different beam delivery techniques have been worldwide implemented: active scanning and passive modulation. With the active system thousands of elementary pencil beams are aimed at an equivalent number of virtual voxels in which the tumor has been divided. The depth conformation is obtained by modulating the ion energy directly with the accelerator (synchrotron) or by inserting absorbers of different thickness (cyclotron). With the passive system the beam is wobbled over a fixed area and spread out by a complex system of absorbers: bolus, ridge filter and range shifter and the final matching with the beam eye-view of the target is obtained with a collimator. It is largely accepted that while the passive system is less expensive and the setting up to meet the clinical requirements is easier, the active scanning performances are superior. Indeed it is possible to obtain both excellent conformation to the tumor and reduction in fluences of unwanted secondary particles even at large distance from the target. Finally in long-term and stable conditions the active scanning requires less overheads and provides more safety.

In this context, hadrontherapy has been of direct INFN involvement since more than fifteen years, starting with the ATER project which eventually was extended to a total of 12 research groups in 12 different INFN Sections, covering several scientific aspects. Successful examples of cooperation between INFN, radiotherapists, and oncologists have been accomplished. In this framework, the development of the CATANA facility at the *Laboratori Nazionali del Sud* of INFN, for the treatment of ocular melanoma by means of a proton beam, has been an example of particular significance: hundreds of patients have been already treated. At present INFN is also deeply involved in the construction of the synchrotron for protons and ^{12}C ions at CNAO, the new Italian center for hadrontherapy in Pavia, based on active beam scanning technology.

Taking into account the various multidisciplinary expertises grown within the INFN research groups, a further contribute to the developments in the field of hadrontherapy could concern the design of new and advanced Treatment Planning Systems (TPS). In short the TPS is a set of tools that allow the translation of the dose prescription into a set of beam energies, positions and intensities needed for the treatment. Innovative contribution in this field is particularly needed in case of the use of ions.

Several INFN research groups, active in different scientific areas (experimental and theoretical/phenomenological nuclear physics, Monte Carlo calculations and techniques for numerical analysis, radiobiology and hardware/software development for dose monitoring purposes), propose to cooperate in order to develop an improved TPS for ion therapy with active scanning.

In the following sections we will give a short description of the relevant features of a TPS and of the scientific issues rising in the case of the treatment with ion beams, pointing out the reasearch areas where further scientific contributions are expected. The research directions for each area are then reviewed.

2. – Treatment planning in hadrontherapy

The TPS is a complex computer system that helps both to design radiation treatments and to compute the dose delivered to the patient. One of the main objectives in radiotherapy is the conformal delivery of the prescribed dose to the target volume, sparing as much as possible the surrounding healthy tissue and critical structures.

In intensity modulated particle therapy (IMPT) irradiation technique, many thousands, individually weighted, narrow beams are delivered to the patient using several fields (beam directions) in order to deliver a uniform dose to an arbitrary shaped planning target volume (PTV). Due to the very large number of degrees of freedom, computer-aided "inverse planning" techniques are mandatory to create reliable IMPT treatment plans. Within these techniques, beam spot positions, energies and particle fluences are determined from the prescribed dose distribution by means of an optimization procedure over an appropriate objective function.

In general, the optimization is performed such that the probability to eradicate all clonogenic tumour cells without severely damaging healthy normal tissues is as high as possible. The optimal treatment plan should be also evaluated in real time and the TPS should be highly interactive, so that the user can almost instantly modify, calculate, and examine various plan outcomes.

Inverse treatment planning was first discussed by Brahme [1] in the early 1980s: the research activities in this fields can be classified in two main streams of studies. In the first one the effort is aimed to improve the knowledge on the biological effects of radiation by effectively including various physical, biological and other factors into the objective function. The second class of studies treats the different mathematical methods and algorithms to evaluate and to minimize the objective function, within the hardware constraints (computation time, memory management).

A central point in the development of the optimization techniques for a TPS is the huge difference between light ions ($A < 18$) and protons, mainly due to the increased biological effectiveness, *i.e.* a lower physical dose is required with light ions to obtain a given biological effect. For carbon ions, which are considered an optimal choice [2], the favourable physical dose distribution is particularly enhanced by the high "Relative Biological Effectiveness" (RBE) towards the end of the particle range, which offers an additional advantage for slow growing radio resistant tumours.

In the case of proton beam irradiation a constant RBE value is assumed through the irradiated volume. Furthermore such a value is very close to unity, *i.e.* the biological effectiveness is very close to that of traditional radiotherapy with e.m. source. As far as light ions are concerned, RBE shows complex dependences on several factors. It depends non-linearly on physical characteristics of the radiation, *e.g.*, the absorbed dose level, particle energy and atomic number. It follows that the biological effectiveness of primary ions as a function of depth in the irradiated tissues has to be evaluated carefully by taking also into account the effects due to all the secondary fragments produced in nuclear reactions within the irradiated volume. In general, the exposure to ion beams will result in a superposition of different radiation fields.

The ion RBE also depends on the type of the irradiated tissue. In particular, the medical dose prescription might be different from one tumour type to another and also for the same patient plan organs at risk might receive different absorbed doses. The TPS should hence be capable of dealing with separate biological data sets on a voxel-by-voxel basis to account for different endpoints in the target, normal tissues and organs at risk.

The exploitation of the light ion high RBE is the main point in ion therapy but needs a precise tumor conformal dose to be applied and this makes the treatment planning for radiotherapy with ion beams more complex than for protons: careful biological optimization has to be included in the TPS.

The state of the art of the ion beam TPS, which a new project must be compared with, is TRiP98 [3], the TPS developed at GSI, Darmstadt, and initially used within a pilot project. Within this project the SIS synchrotron has been upgraded to match the requests for ion radiotherapeutical treatment. Few hundred patients have been treated. TRiP98 included the analytical calculation of the Bethe-Block energy losses combined to the fragmentation processes to evaluate the physical dose [4]. A novel radio-biological model (Local Effect Model, known as LEM) was developed and included in the (TRiP98) TPS [5]. The GSI algorithm addressed the optimization of a single field. Very recently Siemens implemented a commercial version of TRiP98 and included it in a more general product [6]. In this application the LEM is largely approximated but the approach includes the multi-field solution.

3. – Towards an innovative treatment planning system

The considerations summarized in the previous section bring to the conclusion that the radiobiological model to evaluate RBE is a crucial and fundamental component of a TPS. The development of satisfactory models, possibibly predicting the damage mechanisms at microscopic level, such as the induction of complex lesions in DNA structure in correlation to the local energy deposition by ionizing particles, are one of the most important goals of radiobiology. The above-quoted LEM model is far from being a really satisfactory solution. However, at present it remains the only viable alternative for a project aiming to deliver in few years a product to be practically used in a clinical context. For this reason, in view of a dedicated applied research project, we consider LEM as a given baseline for our development. Given that, in the following we enumerate a list of some issues which could represent a substantial improvement resulting from a dedicated applied research project.

i) Multi field optimization: the GSI and Siemens implementation is based on quasi-Newton algorithm. A simulated annealing approach might greatly improve the performances.

ii) Physical model for fragmentation: experimental data show a gap for carbon ion fragmentation between 20 and 200 MeV/u. From the complete knowledge of the processes in this crucial range all the nuclear physics community would benefit.

iii) Simulation tool to verify the implemented TPS: the outcome of the TPS, which is a numerical calculation, should be checked via independent tools. A Monte Carlo simulation of a statistically significant sub-sample of the full TPS can fulfill the requirements.

iv) Tools to verify the implemented TPS: a quasi online measurement of the decay of the induced isotopes using the Positron Emission Tomography technique leads to a precise determination of the implemented TPS.

v) Factorization of the RBE computation from the cell type: LEM predictions and the (very few) experimental data agree rather well. Simulation results (as well as experimental data) are cell line dependent: further understanding of the biological nature of the radiation induced cell damage could lead to a better radiobiological model.

vi) TPS in 4D: organ can move during treatment (*i.e.* lung tumor) mainly during respiratory movements. Neglecting the organ displacement can lead to severe deviations

from the prescribed dose. The implementation of a TPS which deals with the above problem would be beneficial for a large number of pathologies.

vii) Water equivalent approximation: this is a twofold approximation. At the interface between two voxels of largely different Hounsfield number the use of a well-tuned Monte Carlo can describe the density gradient effects on the delivered dose. Furthermore the translation from Hounsfield numbers as from CT to a length-modulation coefficient has to be evaluated with care when the density gradients are important.

viii) Optimization of the field definition: the search of the best field angle can be introduced in the overall optimization. The objective function can improve by far by optimizing the average beam direction with subsequent sparing of the healthy tissues.

ix) Factorization of the dependence of the TPS on the accelerator and beam control system: technically this improvement would greatly simplify the refitting to any given complex.

x) Finally there is a stream of problems which have never been challenged due to lack of resources and manpower such the impact of the objective function definition on the TPS output. As an example: the objective function, which leads to the optimization, should be written as dependent on several factors as fractionation, long-term effects due to far-away dose, patient radiosensitivity.

It must be stressed that the fruitful improvement of each item needs deep synergy with the activities on the other items.

4. – The scientific areas of the project

Within INFN different research groups have been working on several topics essential to develop an innovative TPS. As pointed out in the introduction, we can identify five main areas: nuclear physics, radiobiological aspects and their practical implementation, the development of Monte Carlo models and tools, the progress in the numerical optimization techniques and the development of dose delivering monitoring tools such as the technique of in-beam PET.

In the following we shall summarize the main goals for each of these areas.

4˙1. *Nuclear physics.* – The study of the fragmentation processes is relevant in different fields of the physics concerning both basic research as well as the applications. We plan to fill the lack of data at intermediate energies of ^{12}C fragmentation on different targets. This energy range is of fundamental importance for hadrontherapy and is interesting also for different aspects concerning nuclear physics. For this purpose we propose to perform extensive measurements of projectile fragmentation with the ^{12}C beams, delivered by the CS of the Laboratori Nazionali del Sud. We plan to study ^{12}C at 62 and 80 MeV/A on several targets, using an apparatus already working at LNS.

Since it is mandatory to extend these measurements up to 200–250 MeV/A to fill a gap of data in the literature [7], after the measurement campaign in Catania, we propose to perform measurements at laboratories abroad, where higher ^{12}C energies are available (BNL, MSU, Chiba, etc.). To perform this kind of measurements at higher energies with respect to the ones available in Catania, it is necessary to use a different experimental apparatus with optimized features to detect and identify higher energy fragments.

The detector that we want to use in the first stage of our experimental campaign is installed into the TRASMA scattering chamber in the 20° experimental cave for the FRIBs experiment, that tagged intermediate energy radioactive ion beams at the Laboratori Nazionali del Sud.

The detection system consists of two Si-CsI hodoscopes with different granularity, called Hodo-small and Hodo-big, respectively. The Hodo-small, placed at a distance of 0.8 m from the target, consists of 81 two-fold telescopes: 300 μm silicon detectors $1\times1\,\mathrm{cm}^2$ of active area followed by a $1\times1\,\mathrm{cm}^2$ and 10 cm long CsI(Tl). The Hodo-small covers the angular range $\theta_{\mathrm{lab}} = \pm 4.5°$.

The Hodo-big, placed at a distance of 0.6 m from the target, consists of 89 three-fold telescopes 50 μm + 200 μm Si detectors, both having $3\times3\,\mathrm{cm}^2$ surface followed by a 6 cm long CsI(Tl) of the same surface. It covers the angular range $\pm 4.50 \leq \theta_{\mathrm{lab}} \leq \pm 16.50$ degrees, both hodoscopes were used to measure the yields of isotopically resolved fragments.

4˙2. *Radiobiological research.* – In the previous paragraphs we have already mentioned that the central issue for a TPS is the availability of a radiobiological model to calculate RBE. We have also stated that our baseline choice for a practical development is the LEM approach. Actually this model is built in such a way as to give a prediction of cell survival (or, in principle, of other biological end-points) as a function of dose by means of a set of parameters (in the literature knows as the α and β parameters). These in turn must be derived from a fit to a set of experimental data as wide as possible. The construction of this radiobiological database is the heart of the proposed project. In order to achieve this result, we are planning the following activities.

1) A systematic radiobiological investigation in terms of cell survival *vs.* dose (survival curves) in different tissues and human cell types (normal and tumoural, with different radiosensitivity) by ion beams of different energies.

2) In addition to human cell lines, a biological reference system has to be used to allow the radiobiological check of the specific hadrontherapy center and TPS along the time as well as the comparison with other worldwide hadrontherapy centers. Chinese hamster V79 cells are widely used in ionizing radiation cell survival studies: this is a radio-resistant (repair proficient) cell line and is considered as a reference cell system due to its cellular radiation response which is highly reproducible and radiation-quality/LET selective.

3) As mentioned above, also other biological end-points turn relevant to be investigated after irradiation of normal and tumour human cell lines with therapeutic beams, in order to assess the success of the ion treatment as well as the short- and long-term effects due to unwanted irradiation of healthy tissues. Among all, the induction of apoptosis, micronuclei, chromosome alteration, DNA damage and its repair can be investigated to build a dose-response curve and derive a measure of the radiosensitivity. In this project, we propose to measure the kinetics and proficiency in double strand breaks repair. It will be evaluated in normal and tumour cell lines irradiated with selected dose levels (0.5 and 2 Gy) and harvested from 0.5 up to 24 h. In parallel, the irradiated cells will be scored for the evaluation of the induced micronuclei, providing a measure of the cytogenetic damage in the form of whole chromosomes or acentric fragments arising from mis-repaired lesions that have not been incorporated into daughter cell nuclei at mitosis.

The radiobiological characterization of the therapeutic beams requires an appropriate experimental set-up. To take into account the various physical processes that may affect the ion beam transport in the patient body, a water-phantom can be used where flasks with cultured cells can be placed in different x-y-z positions along the primary therapeutic beam trajectory. The physical dose delivered in a given point has to be evaluated as well as measured in order to be correlated with cell surviving fractions gathered at each position. Fixing the dose to be delivered at a defined z-depth and fixing the beam

energy, cell survival, and therefore RBE, is measured along the beam direction ($x = y = 0$) and in lateral positions ($x, y \neq 0$) in order to evaluate the possible unwanted contribution of laterally-scattered particles as well as the primary beam attenuation and then the effective delivered dose. This measurement has to be repeated, at a defined beam energy, for different z-positions along the beam in order to cover the whole target volume (including the surrounding healthy tissues).

An inhomogeneous layered phantom (tissue-like phantom) could be a further useful tool for a more realistic description of the target volume (healthy and tumour tissues): in such a way the primary ion beam attenuation and the RBE map can be built over the target volume including the effects due to its in-homogeneities (*i.e.* different densities of different tissues and organs and interfaces between different tissues or organs).

4˙3. *Developments of optimization techniques.* – Within the TPS project optimization algorithms must be developed able to derive the particle energies and fluences from a prescribed dose distribution, not just to calculate the absorbed dose from given particle fluences.

From the computational point of view, optimization techniques should guarantee the best tradeoff between robustness and speed of calculation. The GSI and Siemens implementation of TPS is based on a standard quasi-Newton algorithm. Our study will lead to the implementation of a variety of algorithms with the purpose of sorting out the most robust and performing. In particular, an approach based on simulated annealing techniques might greatly improve the results.

In principle, standard optimization developed for intensity modulated radiotherapy (IMRT) with photons can be applied to IMPT, including simultaneous multi-field optimization as well as the integration of multiple objectives for target volumes and organs at risk. However, these techniques need to be modified for ion beams, since the optimization has to be done in terms of the biological dose (RBE×dose) instead of the physical dose distribution. This task is not trivial, since, as pointed out before, RBE depends not only on the type of irradiated tissue, but also non-linearly on the absorbed dose level, particle energy and atomic number. This will lead to discontinuities in the RBE× dose spatial distribution with sharp steps at organ boundaries, which the optimization should address.

In a multi-field optimization the weights and the energies of each pencil beam that composes each field (beam port) will be optimized simultaneously in a treatment plan. While each field separately would deliver an inhomogeneous effect in the target volume, when combined together they will produce the desired distribution of the biological effect. Multi-field optimization enhances the quality of the resulting treatment plans, *e.g.*, by improved sparing of normal tissue and organ at risk and by a better conformity of the high effect region to the target. Existing TPS includes the multi-field solution. However the approach suffers of important limitations since it does not include an optimization over the possible angle of irradiation, and the directions of the fields have been previously assigned. It follows that an innovative aspect of multi-field technique is the optimization of the field directions. This task will require higher computational power with respect to the TPS optimization implemented so far, since several geometrical configurations have to be computed in few seconds.

The possibility to have a fast computing of several geometrical configurations will also unlock the innovative possibility to the implementation of 4D optimization in TPS. Organ can move during treatment (*i.e.* lung tumour) mainly during respiratory movements. The correct optimization procedure should be combined with time-dependent Computed To-

mography (CT4D) [8] information and should be done effectively over several geometries that correspond to different displacements of the organs with a time-dependent structure.

Another innovative aspect in the TPS will be the implementation of multi-criteria optimization techniques to facilitate the planning process in the common case of mutually conflicting objectives, *e.g.*, target coverage *versus* sparing organs at risk, introducing proper importance factors to all the solutions found by the algorithm. A criterion could be a solution with a reduced number of slices of the irradiated volume by each beam-port, with a clear advantage for the clinical procedure due to the decrease of the time required to the irradiation. To estimate this reduction in the case of multi-field optimization, one can exploit the fact that each beam-port irradiates effectively only a sub-volume of the PTV. The choice of the optimal sub-volumes should also be performed directly within the TPS, by means of the implementation of a proper heuristic-based method.

4˙4. *Monte Carlo development for TPS*. – The use of a reliable Monte Carlo is one of the major improvements in the development of an innovative TPS, since it is now recognized that this is the only way to overcome the shortcomings of analytical calculations in case of mixed radiation fields and complex geometries. Monte Carlo simulation is also necessary in the workflow to produce the database for the optimization process. For this purpose the simulation code is the necessary tool to take into account the mixed radiation field, the production of fragments and the 3D effects due to angular spread of secondaries. The baseline choice for the proposed development is FLUKA [9]. The application of this code to hadrontherapy is reported elsewhere in these proceedings [10]. The planned activity will proceed along two main directions: the improvement of physics models and the practical application of Monte Carlo in the TPS. Both these directions find support also on the activity of the FLUKA2 group in INFN which already gets benefit from its international collaboration and are more extensively reported in [10].

There are two main directions which are envisaged from the point of view of Monte Carlo application to TPS. A first fundamental goal is the development of a reliable and accurate validation tool, while the second is the direct use of Monte Carlo to calculate a treatment planning. The last goal is at present very far from being realistically achievable and we shall almost exclusively consider the work to produce a validation tool. The purpose is the following: for a given clinical situation, a TPS provides a first result which in general is subject to validation on the basis of specific measurements using phantoms. This procedure, which is of course necessary at present, is expensive and time consuming. If a reliable Monte Carlo tool can be made available in order to avoid the experimental validation, this would be already considered a major improvement. Furthermore, the same Monte Carlo tool would be necessary to correct the results of a standard TPS when complex geometries are present (for instance at interfaces between tissues of very different density and composition). In order to be able to accomplish such a function, the Monte Carlo has to meet a list of requirements, the most important being:

a) capability of treating the detailed geometry of human body as resulting from a CT scan;

b) capability to identify the different organs and provide the correct tissue assignment in terms of composition and density;

c) capability to embed the radiobiological model used by the TPS;

d) capability of providing a numerical result within the time period required by the clinical personnel;

e) capability of giving results through a powerful interface in order to minimize the post-processing time and to facilitate the use by the clinical personnel.

As reported in [10], FLUKA has already shown to be able to meet some of the quoted requirements. In particular, we emphasize the successful attempt to embed LEM in the Monte Carlo code. Other achievements concern the possibility to translate the human body structure in the FLUKA code that is possible thanks to the use of a voxel geometry and the "import" of a CT scan into the FLUKA geometry that can thus be accomplished through a one-to-one relation between CT pixels and FLUKA voxels. In this respect the work to establish both the CT-Voxel relation and the issue of the correspondence between the CT density and the actual material (*i.e.* elemental composition and density of the medium) must be mentioned. Both issues are being addressed in a common effort from FLUKA developers and colleagues from the Heidelberg research centre [11-13]. There are other important technical developments which must be scheduled in the development of a Monte Carlo tool, and probably the most important of them is the capability of considering time-varying geometries, so to take into account cases such as those related to the target movement due to breathing. Also in this aspect there are plans on the methods to be employed in the framework of FLUKA.

Another output which is expected from a Monte Carlo tool of this kind is the accurate prediction of the distribution of beta-emitters after the irradiation. This is essential in order to make use of the online PET to monitor the patient treatment, which is the object of the next section.

5. – Dose delivery monitoring: the application of in-beam PET

Beta-emitters isotopes are produced during irradiation. Simulation studies have been already initiated to predict the 3D distributions of the production of these radioisotopes. In particular Monte Carlo applications for proton and carbon ion therapy have been developed using FLUKA. Comparisons of FLUKA simulations with experimental data can be found, for instance, in [14]. Successful comparison of calculations with real patients' tomography after treatment with proton beams can be found in [11, 12, 15]. In order to achieve results of the same quality in the case of ion beams more work is needed in both model developing and technical implementation of algorithms.

We propose to develop a complete in-beam PET detection system for ^{12}C ion therapy monitoring. A detection system able to perform the measurement of the β^+ [15-17] activity produced during the light ions irradiation can be deviced starting from the experience acquired within the DoPET collaboration of INFN. Dedicated hardware and software reconstruction codes [18, 19] are necessary.

A 3D activity distribution reconstruction algorithm and the following unfolding filter for the dose calculation are the two steps that have to be performed to obtain the requested dose delivered spatial distribution monitoring. To perform the reconstruction of the created isotopes, an appropriate iterative reconstruction method has to be applied. We already implemented a fully 3D iterative reconstruction algorithm and its refinement is one of the future goals. In fact, we would like to include correct normalization factors in our algorithm, which are mainly given by crystal efficiency factors. Furthermore, we are planning to estimate the random coincidences, in order to filter and subtract them appropriately during the reconstruction. We envisage to improving the system model and in order to include all physical aspects, we are planning to set up a fully Monte Carlo generated system model. After the reconstruction process, the following step is the calculation of the spatial distribution of the delivered dose from the measured activity

distributions. To fulfill this goal a dedicated code, able to calculate the light ion range inside the irradiated medium starting from the measured activity is necessary. Our approach is based on the description of the activity image as a convolution of the dose distribution with a special filter function. We have already applied this approach in the energy range of interest for the proton treatment of ocular melanoma (40–70 MeV), with promising results. Since the final aim is to obtain direct information about the dose localization from the measured activity, our goal will be the calculation of the inverse filter.

6. – Conclusions

The TPS project is a typical case where a mature application can be developed starting from the competences emerging from the R&D activities carried on so far by INFN and with strong connections to radiobiology. It belongs to a more general branch of projects of interest for medical applications which derive from nuclear and particle physics, together with imaging, accelerator techniques, and particle detectors applied to diagnostics. Like many of these projects, the TPS proposal is intended to be developed with the partnership of a company. In this respect we expect that the commercial partner will provide the interfaces to assure the necessary flexibility and tools for the proposed new TPS to be successfully inserted in the typical workflow of clinical operation. The main contributions deriving from the expertise of an industrial partner are the following:

1) the tools to read out the Computed Tomography (CT) input data;
2) the geometrical limits of the Planning Treatment Volume (PTV);
3) the tools to output the results, as isodose curves and dose volume histograms (DVH) to be used for standard clinical applications;
4) archiving procedures;
5) finally, compliance with the procedures for the product certification.

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