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Medical physics aspects of the synchrotron radiation therapies: Microbeam radiation therapy (MRT) and synchrotron stereotactic radiotherapy (SSRT)

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ABSTRACT

Stereotactic Synchrotron Radiotherapy (SSRT) and Microbeam Radiation Therapy (MRT) are both novel approaches to treat brain tumor and potentially other tumors using synchrotron radiation. Although the techniques differ by their principles, SSRT and MRT share certain common aspects with the possibility of combining their advantages in the future. For MRT, the technique uses highly collimated, quasi-parallel arrays of X-ray microbeams between 50 and 600 keV. Important features of highly brilliant Synchrotron sources are a very small beam divergence and an extremely high dose rate. The minimal beam divergence allows the insertion of so called Multi Slit Collimators (MSC) to produce spatially fractionated beams of typically ~25–75 micron-wide microplanar beams separated by wider (100–400 microns center-to-center(ctc)) spaces with a very sharp penumbra. Peak entrance doses of several hundreds of Gy are extremely well tolerated by normal tissues and at the same time provide a higher therapeutic index for various tumor models in rodents. The hypothesis of a selective radio-vulnerability of the tumor vasculature versus normal blood vessels by MRT was recently more solidified.

SSRT (Synchrotron Stereotactic Radiotherapy) is based on a local drug uptake of high-Z elements in tumors followed by stereotactic irradiation with 80 keV photons to enhance the dose deposition only within the tumor. With SSRT already in its clinical trial stage at the ESRF, most medical physics problems are already solved and the implemented solutions are briefly described, while the medical physics aspects in MRT will be discussed in more detail in this paper.

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Introduction

The different contributions within the COST SYRA3 Action in this special issue highlight the history of the development of two new radiotherapies; MRT and SSRT, and their future potential medical applications. The phase I clinical trials in SSRT have allowed the community to move forward with synchrotron based therapies in particular from a safety point of view, requiring the implementation of a small hospital-like environment at the biomedical beamline ID17 at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. This milestone also helps to solve some of the medical physics aspects in MRT which are particularly challenging due to the microscopically small sizes of the beams and the very high dose rates. This high dose gradient requires accurate measurements of dose in microscopic volumes, something which is not necessary in standard radiotherapy. Despite the increasing computing power, Monte Carlo (MC) calculations in such small volumes for MRT applications are still time consuming and a recently developed solution using a convolution based algorithm now allows fast dose calculations from CT data to make a treatment plan. Dose measurements in MRT are difficult not only due to the demands on the spatial resolution but equally from the high dose rates used which are in the range of 8–16 kGy/s. Additionally, the low energy photons may require an important correction since the response of commonly used radiation detectors shows important variations for low energy X-ray photons.

Medical physics aspects in SSRT

The first clinical study of therapeutic applications of Contrast-Enhanced Synchrotron Stereotactic Radiation Therapy (SSRT) has been underway since June 2012 at the (ESRF) and at the University Hospital (CHU) in Grenoble (France). This phase I-II clinical trial is designed to test the feasibility and safety of SSRT through a dose escalation protocol. Two years after the start of the trial, this study has already included eight patients suffering from brain metastases of medium-to-small volume. Preclinical studies [1,2], based on the original work of Norman [3] had highlighted the potential of the technique and motivated this clinical trial. The treatment at the ESRF is based on stereotactic irradiations using high-flux, quasi-parallel, monochromatic medium energy X-ray beams (80 keV). The irradiation is performed, in the presence of an iodinated contrast agent, which previously was introduced into the tumor. At these energies, a localized dose enhancement occurs in the target, due to an increased photoelectric absorption of X-rays. This local increase in dose is due to the difference in the photon interaction mechanisms in the target volume where the contrast agent leaks from the capillaries when compared to the healthy brain where the iodine concentration remains negligible. The moderate kinetic energy of the photoelectrons and the iodine Auger electrons is deposited over a micrometer distance with a maximum distance of tens of micros, in the close vicinity of the heavy atoms; whereas Compton scattering predominates in the surrounding healthy tissues. Despite a strong falloff of the percentage depth dose (PDD) using 80 keV photons, a favorable dose deposition can be achieved at the tumor with better tissue sparing when compared to Co-60 irradiations using the same number of ports, thus generating interest for treating deep seated tumors.

A dedicated treatment room has been built at the ESRF medical beamline [4]. The patient is installed on an armchair with his or her head tightly maintained by the same stereotactic frame used at the CHU for complimentary irradiations. The current dosimetry protocol in SSRT uses monochromatic X-rays at 80 keV with a dose rate of ~1 Gy/s which is slightly higher but in the same order of magnitude like typical dose rates at the clinic. The specificity comes from the use of a 2 mm high beam, requiring the regular scanning through the beam to obtain a homogenous coverage of the tumor volume to be irradiated. A dedicated treatment planning system (TPS) was adapted to SSRT. The synchrotron beamline geometry was modeled and included as a phase space file in the TPS. The dosimetry is based on parallelized Monte Carlo simulations of low to medium energy electrons and polarized photon transport in presence of high-Z material [5]. Dedicated quality assurance protocols were implemented. An absolute dosimetry protocol was adapted according to the gold standard used in conventional RT [6]. The treatment plans and absolute dosimetry are validated with measurements performed in a dedicated water tank as well as in solid water with and without bone slabs. A 2D dosimetry technique is being developed in anthropomorphic phantoms using EBT3 Gafchromic films.

The contrast agent uptake has been previously studied on 12 patients who received an intravenous bolus of iodinated contrast agent (40 mL, 4 mL/s), followed by a steady-state infusion (160 mL, 0.5 mL/s) in order to ensure stable intratumoral amounts of iodine during the treatment. Absolute iodine concentrations and quantitative perfusion maps were derived from 40 multi-slice dynamic conventional CT images of the brain (recruitment day) or from quantitative synchrotron radiation CT (treatment day). For three of these patients, iodine concentrations reached in the tumor were compared between the recruitment day and the treatment day (~10 days interval). The post-infusion mean intratumoral iodine concentration (over 30 min) reached 1.94 ± 0.12 mg/mL (200 mL of contrast injected) [7].

In this first clinical trial phase, the patients receive a fraction of their overall treatment by SSRT (5 Gy), while the remaining of the treatment is delivered by standard stereotactic irradiation at the CHU (6 Gy and 2 × 11 Gy). All patients were in good general condition [8]. Future developments in medical physics for SSRT are expected to include in *invivo* dosimetry and static irradiations using minibeams [9].

In vivo dosimetry based on optically stimulated luminescence (Al_2O_3 crystals) has already been tested on one patient [10] but requires a complex set-up and offline reading. A new *in vivo* dosimetry protocol is currently being developed, based on 2D entrance and exit fluence measurements using dedicated pixelated transmission detectors. The dose retrieval will be performed using inverse problem methods (iterative reconstruction of the dose) adapted to local and limited projection tomography problems [11]. The monochromatic minibeam technique is being developed in parallel to further improve the normal tissue sparing effect and simplify some of the delicate safety issues because of the lower dose rate. The first experiments in monochromatic Minibeam Radiation Therapy (MBRT) (600 μm-wide beams, 1200 μm ctc) confirmed that this technique keeps (part of) the sparing tissue capability observed in the thinner microbeams, while significant tumor growth delay was still observed [12]. The next development is the transfer of this technique to clinical trials I in order to be able to perform the SSRT dose escalation protocol to its end maintaining a suitable bone radiation tolerance [13].

The non-homogenous dose distribution due to the irregular uptake in the tumor environment of the dose enhancing drug leads to in-homogeneities, which may complicate the interpretation of the outcome of the treatment [7]. The contrast agent, moreover, remains extracellular and is not optimal for dose enhancement at the cellular and molecular levels with respect to the DNA. An interesting perspective would be to influence importantly the microscopic dose distribution from Auger electrons through photon activation processes [14] or from optimized radio-chemotherapy protocols [15], which would more selectively damage the tumor cells with non-repairable double strand breaks.

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