AARHUS UNIVERSITET

Project description

Project title: Three-dimensional dose measurements of proton therapy for tumour sites influenced by internal organ motion in human-like phantoms

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Background

Proton therapy (PT) represents the state-of-the-art method for treating cancer patients with radiotherapy. Protons are charged particles that can therefore be be accelerated to high energies with great precision. When penetrating tissue the protons have a depth dose distribution with a characteristic peak, the so-called Bragg peak (see Figure 1). The position of the Bragg peak depends on the energy of the particles and is where most of the energy is deposited. PT facilities have strongly increased in number over the last decade, because of these advantageous characteristics, including here in Denmark (with the Danish Centre for Particle Therapy (DCPT) now in clinical operation in Skejby).

PT is today most commonly given using the so-called spot scanning technique [2]. In spot scanning, the desired dose distribution is created by scanning a pristine proton Bragg peak throughout the volume that should be irradiated, adjusting the energy of the protons to reach different depths, and adjusting the spatial position by bending the proton beam using strong magnets. Although this is the most advanced and flexible form of PT, it is also highly sensitive to any changes occurring in the tissue traversed by the beam towards the tumour [3, 4] (see Figure 1). For tumours in the thorax and abdomen, e.g. lung, esophageal, pancreatic and liver tumours, considerable changes in anatomy occur both within and between every daily radiation fraction delivery (so-called intra- and inter-fractional motion). This represents an enormous challenge to treat these tumours with PT. These tumour sites still have a potentially great benefit from protons, and together represent approximately half of the candidates for PT in a business case for the DCPT [5]. Figure 2 shows how motion of a dosimeter can affect the dose distribution of a treatment.

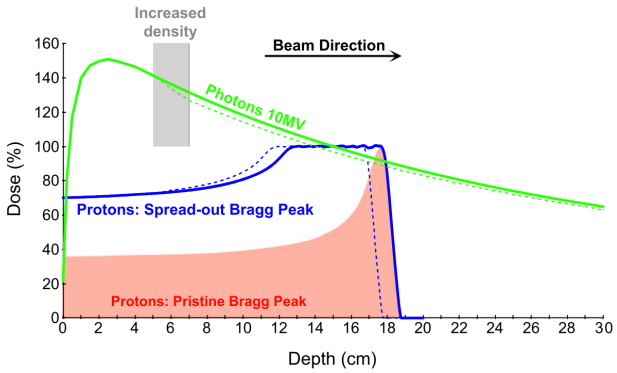

Figure 1: Depth dose curves of photons as used in x-ray radiotherapy (green curve), single proton beam (red highlighted area) and the sum of several proton beams resulting in a spread-out Bragg peak (blue curve). Figure from [1].

A deformable three-dimensional (3D) radiochromic dosimeter has been produced [6, 7, 8], where the dose distribution can be read-out by using high resolution optical computed tomography [9]. The mechanical properties of this dosimeter have been investigated [10] and showed promising elastic properties, which can be exploited to create deformable anthropomorphic (i.e. human-like) 3D dosimeters.

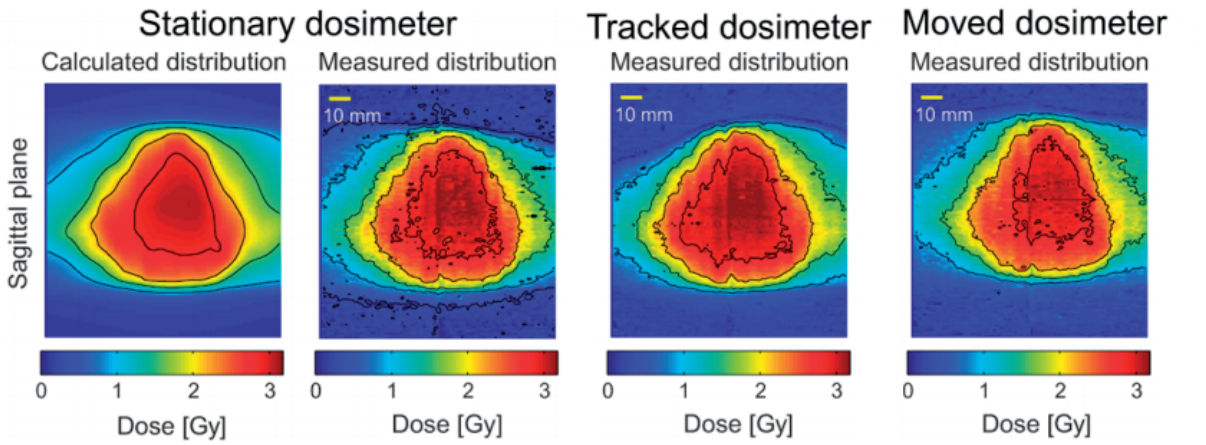

Figure 2: Calculated stationary dose distribution followed by measurements of the stationary dosimeter, the tracked dosimeter and the dosimeter with motion induced. The dose distributions are shown with 30%, 50%, 70% and 90% isodose curves. Figure from [11].

Overall aim

The focus of this Ph.D. is on developing, testing and optimizing anthropomorphic deformable 3D dosimeters simulating inter- and intra-fractional movement. With the newly operational DCPT the opportunity to improve the planning strategies and modalities of the delivered dose to organs inside the thorax must be exploited for PT.
To achieve this aim, the Ph.D. project will be divided into four parts: ***i)*** Characterization of 3D dosimeter performance under simple deformations, ***ii)*** exploiting the spot scanning technique in PT to make dose calculations based on each spot on dosimeters deformed in time, ***iii)*** validating different algorithms simulating the deformation of a 3D dosimeter to prepare for simulations of more complex structures and ***iv)*** creating an anthropomorphic 3D dosimeter of a lung simulating the respiration process and optimizing the planned delivery system to compensate for intra-fractional motion.

Study 1: 3D Dosimetry using deformable materials (Q3 2019 - Q2 2020)

Background: Anthropomorphic (i.e. human-like) deformable 3D dosimeters for motion-including dose-verification can potentially increase the conformity in many clinical radiotherapy treatments. 3D tissue-equivalent deformable dosimeter material has been developed, consisting of a polymerising hydrogel in a latex membrane container, DEFGEL [12]. An anthropomorphic deformable radiochromic silicone-based 3D dosimeter was later on developed

[6, 7] and its dosimetric properties have been characterized [8, 13]. Furthermore, the mechanical properties of the radiochromic 3D dosimeter are characterized [10], which showed promising attributes with no plastic deformation, hence it retains its elastic abilities, which makes it a good candidate for deformable anthropomorphic phantoms. Silicone elastomers have already been used to simulate human tissue, because the elastic moduli can be adjusted to match values of various kinds of soft tissue [14, 15].

Aim: To characterize how the dose response in the deformable 3D radiochromic silicone dosimeters is affected by deformation.

Research plan: A cylindrical silicone-based radiochromic dosimeter will be produced. The dosimeter will be compressed by applying pressure on the top and the bottom in 10 steps of 5% of its rest length. In each step the dosimeter will receive a proton radiation dose of 3 Gy, accumulating to a total of 30 Gy. An identical, but non-deformed, phantom will receive an equivalent dose and this can be compared in order to investigate the differences. The deformation vector field can be assessed and compared to a deformation vector field calculated in a finite element simulation. Internal fiducial markers are used as a reference for these calculations.

Study 2: Proton dose calculations and measurements under dynamic deformations of a 3D dosimeter (Q2 2020 - Q4 2020)

Background: PT at modern proton centers is delivered as pencil beam scanning (PBS), where a narrow proton beam is scanned in three dimensions to cover the tumor target. While PBS offers superior conformality of the dose to the tumor shape it is also extremely sensitive to motion during treatment delivery, since interplay effects between tumor and pencil beam motion can create serious under- and overdosages in the tumor [4, 16]. At the moment DIR techniques are used to help estimate the dosimetric effects of intra-fractional motion [17, 18], but the conformity for the treatments regarding these techniques can be further improved. For conventional photon radiotherapy the world's first real-time calculation of the dose being delivered to a moving tumor in a patient was recently performed at Aarhus University Hospital [19, 20] based on in-house developed software. Implementing a program that can exploit knowledge of dynamic target deformations (from Study 1) synchronized with the delivered dose from the PT treatment can potentially be the first step in making a similar dose tracking system for PT and 3D dosimeters.

Aim: To calculate the delivered dose from PT to a deformable 3D radiochromic silicone dosimeter under dynamic deformations by exploiting known deformations synchronized with the PT beam and compare this to the dose measurements.

Research plan: The spot scanning deliveries are logged at PT facilities. By synchronizing the logged data to the deformations occurring in the 3D dosimeter, but exploiting deformation calculations, the actual dose delivered to a deforming dosimeter can be calculated. The dosimeter will receive complex dynamic deformations, such as compressing the dosimeter while simultaneously twisting it. Much of the work will lie in setting up a reproducible way

of conducting the experiment and programming the software to combine the deformation calculations with the PT facility data.

Study 3: Optimization of deformation image registration for anthropomorphic 3D dosimetry (Q4 2020 - Q3 2021)

Background: Deformable image registration algorithms are methods used in radiotherapy to track the movement of the body during multiple time points. DIR algorithms compute a deformation vector field to uniquely map out each voxel in a specified geometry. This technique is entirely built on intensity images and is typically based on homogeneous material. There exist many algorithms for DIR, which can be used to increase conformity of PT such as the Horn and Schunck algorithm [21] and the Lucas and Kanade algorithm [22]. Studies have previously looked into the sensibility of providing a deformation strategy to improve PT treatments and how deformation can affect a dose delivery [12, 23] and another study attempts to provide an overview over a set of these algorithms to see which provides the best results for the DEFGEL dosimeter [24]. Determining which algorithm works best with the deformable 3D radiochromic dosimeter plays a vital role, when investigating complex anthropomorphic models because a process like respiration causes considerable organ deformation.

Aim: Finding the optimal algorithm for predicting complex deformations in order to best model anthropomorphic 3D dosimeters.

Research plan: DIR is based on images and have methods only exploiting these [21], but there are also developed finite element hybrid methods [25, 26]. Comparing these different types of algorithms is therefore the focus of this study to prepare for modeling of complex anthropomorphic 3D dosimeters. This will be done by making a 3D model of a lung and using all the chosen algorithms to simulate its movements. The lung will be driven with a pump simulating the motion of a lung similar to one depicted in a new study creating 3D printable organs [27].

Study 4: Anthropomorphic 3D dosimeter models in the thorax (Q3 2021 - Q2 2022)

Background: In order to make anthropomorphic dosimeters, read-out methods are needed in 3D and of course dosimeters that can absorb dose in 3D. The first attempts at producing anthropomorphic dosimeters for PT was by using radiochromic 2D films [28, 29] in water phantoms, where the dose can be optically read-out or with thermoluminescent dosimeters, which does not allow for spatially restricted read-out [30]. Constructing anthropomorphic 3D dosimeters so the densities and structures are similar to that of real organs are challenging. Gel dosimeters with tissue-like densities have been produced and can be cast into many shapes [23, 31], where one is cast into an anthropomorphic and are shown to have a high spatial resolution with PT [32]. A deformable cardiac dosimeter phantom is produced using the radiochromic silicone material [33]. Here the heart is encapsulated in a thorax phantom and driven by a pulsating hydraulic actuator that mimics the pulsation of the heart. An

irradiation is then performed with an x-ray photon beam under pulsation as a proof-of-principle. Producing such anthropomorphic dosimeters for PT can become an important tool in verifying patients specific treatments. End-to-end tests on alanine dosimeters with PT spot scanning have been conducted [34], therefore research into the first silicone-based deformable 3D dosimeter with a high spatial resolution for PT [35] is urgent.

Aim: To construct deformable anthropomorphic 3D dosimeters for patient specific cases simulating lungs and its respiration process and performing planned dose deliveries on them.

Research plan: Clinically relevant anthropomorphic 3D dosimeters imitating lungs will be moulded with air pockets enabling a way of simulating the respiration process. The lungs will be inserted into a thorax surrogate to imitate a patient geometry and the height of the thorax under the respiration process can serve as the basis for the DIR calculations. A planned dose delivery will be performed on each lung while using DIR to account for the intra-fractional movement and hereby verifying the process on a truly complex model. This will act as a precursor for clinical use of patient specific anthropomorphic 3D dosimeters and implemented DIR features.

Perspectives

Treatments of lung, oesophageal, pancreatic and liver tumours, are strongly influenced by internal organ motion and make up around half of the expected patients at DCPT. Our goal is to produce anthropomorphic 3D dosimeters that through analysis can help increase the conformity of future PT treatments. The matter in question have not been more pressing than now, with the newly operational PT facility at DCPT.

Collaborations

This project will be based at the DCPT located at Aarhus University Hospital, which provides state-of-the-art treatment for PT. The DCPT facility is scaled to allow the world's largest proportion of patients being treated with PT in clinical trials (including sites in the thorax and abdomen). A collaboration between the Departments of Oncology and Medical Physics, and the Department of Physics and Astronomy, both part of Aarhus University, will be the backbone of this project. Part of this collaboration is Per Rugaard Poulsen's group, which is the leading group in motion management in radiotherapy. This collaboration has previously led to the discovery of the first 3D dosimeter for PT [35] and to a new dosimeter type using optically-stimulated luminescence. [36]

This Ph.D. project will be performed by: The Ph.D. student performs all parts of the described project. Creating and characterizing the deformable dosimeters, and developing methods and software accounting for deformations. He will be supervised by the following research group:

- Ludvig Paul Muren, professor, Department of Medical Physics, Aarhus University Hospital (main supervisor)

- Peter Balling, professor, Department of Physics and Astronomy, Aarhus University
- Per Rugaard Poulsen, professor, Department of Medical Physics, Aarhus University Hospital
- Jørgen B. B. Petersen, medical physicist, Department of Medical Physics, Aarhus University Hospital

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