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Project description (11489 characters in main body)

Academic title and name: B.Sc. Casper Gammelmark Muurholm
Project title: Respiratory gated photon and proton radiotherapy guided by internal tumor motion monitoring with conventional standard imager systems

Background

Tumor motion during radiotherapy treatments

Most tumors move during radiotherapy delivery, in particular in the thorax and abdomen due to respiration[1] (Fig 1). The motion is normally accounted for by treating a volume that includes the anticipated tumor motion, which leads to increased healthy tissue irradiation [2], [3]. Real-time adaptation of the treatment to the tumor motion would be a better approach [4], but it requires reliable tumor motion monitoring.

Proton therapy has gained massive attention in recent years since it allows less toxic radiotherapy than conventional x-ray based radiotherapy. The Danish Center for Particle Therapy (DCPT) will soon start proton treatments with pencil beam scanning (PBS), which can sculpt the dose exactly to the tumor shape. However, tumor motion during PBS delivery is of major concern since it can lead to severe local under- and overdoses inside the tumor [5][6] (Fig 2).

Tumor motion monitoring with standard imager systems

Tumor motion monitoring during radiotherapy normally relies on implanted surrogate markers. One marker type is electromagnetic transponders that work similar to a GPS system[7]. The first clinical trial with this method for liver stereotactic body radiotherapy (SBRT) was recently performed at Aarhus University Hospital (Figure 1)[2], [8]. The technique is, however, expensive with limited availability. Monitoring based on the standard imager system of conventional accelerators would extend tumor motion monitoring to virtually all radiotherapy clinics.

Three methods exist for real-time tumor motion monitoring on standard-equipped linear accelerators[9]–[12]. The most promising methods for liver tumors are KIM (Kilovoltage Intrafraction Monitoring), where implanted markers are monitored by a gantry-mounted kV imager, and COSMIK (Continuous Optical and Sparse Monoscopic Imaging with Kilovoltage x-rays), where the kV imager is supplemented with respiratory monitoring. KIM was invented in 2007-08 by the main supervisor and co-supervisor Paul Keall at Stanford University[13] and has since been used in prostate cancer trials in Sydney [14][15]. COSMIK (Fig 3) was recently developed at Aarhus University to overcome limitations of KIM[9] and used for the world's first online real-time monitoring of internal respiratory tumor motion on a standard-equipped accelerator[9]. However, more work is needed for full clinical translation of COSMIK for real-time treatment adaptation.

Motion adaptation during stereotactic liver radiotherapy

The past decade has seen a large increase in the use of SBRT for both primary liver cancer and metastases[16]. Successful complication-free liver SBRT requires a high ratio between target dose and normal tissue dose[17], but the large tumor motion can substantially impair the tumor dose. Previous studies[8], [18], [19] have shown that various motion mitigation techniques can efficiently improve the dosimetric coverage. The most prominent are tumor drift compensation (adjusting the treatment couch when tumor drift exceeds a certain amplitude), MLC tracking (adjustment of the MLC aperture to the tumor motion), and respiratory gating (beam on when the tumor is in the correct position). This project will start out with COSMIK guided tumor drift compensation (part 1) followed by gating (parts 2-3) for liver SBRT. We will use gating rather than MLC tracking for real-time motion adaptation because it is simpler to implement clinically, provides excellent treatment quality [4], [19], and is directly portable to proton therapy.

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In a recent study of 15 liver SBRT patients (45 fractions) treated with Calypso-guided respiratory gating (Fig 4, [19]), it was found that the mean (standard deviation) improvement in the CTV D99 (dose delivered to 99% of the Clinical Target Volume) was 5.5% (10.4%) with tumor drift compensation compared to no motion adaptation and 4.3% (3.4%) with gating compared to tumor drift compensation. The same dosimetric improvements can be expected in Part 1 and Part 2 of this PhD project, respectively.

A power analysis of one sample by averages, using zero as the test value (testing for a significant dosimetric gain) shows that 22 fractions (7-8 patients) and 5 fractions (2-3 patients) are needed for Part 1 and Part 2, respectively, when using a beta error level of 20% and a 95% confidence interval. Both numbers can expectedly be obtained considering about 15-20 eligible patients per year.

Overall aim

The overall aim of this PhD project is safe clinical translation of real-time liver tumor motion monitoring with COSMIK and use hereof for real-time gating in photon and proton radiotherapy.

Part 1: Clinical translation of COSMIK for tumor drift compensation during liver SBRT

Background:

Real-time tumor motion monitoring with COSMIK has been implemented at AUH by in-house developed prototype software. It provides continuous monitoring of the internal respiratory tumor motion with 1-2mm accuracy by a combination of x-ray imaging of implanted markers and respiratory motion monitoring[9]. Fig 3 (left) shows the COSMIK program being used during a patient treatment.

Aim:

To improve robustness and optimize COSMIK for tumor motion monitoring during liver SBRT and use it clinically to compensate for liver tumor drift.

Hypothesis:

COSMIK can be used clinically to reposition the patient in case of tumor drift, which will increase the dosimetric accuracy.

Research plan:

The COSMIK method will first be improved for higher robustness in its identification of implanted markers in x-ray images. Improvements include handling of overlapping markers and considerations of the entire marker group instead of individual markers. The optimization will be based on two large databases with ground truth segmentation: (1) Projections from 317 CBCT scans and intra-treatment fluoroscopy sequences of 10 lung cancer patients with implanted markers in mediastinal lymph nodes[20], [21], and (2) projections from 501 CBCT scans and intra-treatment fluoroscopy sequences of 21 esophageal cancer patients with implanted tumor markers.

Following the optimization of COSMIK, a 3-month research stay in Sydney with co-supervisor Paul Keall will start. Professor Keall has been leading the clinical translation of KIM. The research stay will include quality assurance development for clinical translation of COSMIK and further software development with access to Sydney image data and marker identification algorithms.

The next generation of the COSMIK software will then be used prospectively during treatment of all liver SBRT patients with implanted gold markers at Aarhus University Hospital in the approximate period between March and November 2019. The monitoring will be used for tumor drift compensation by couch corrections in

case of drifts exceeding 2mm. About 10 eligible patients (30 fractions in total) can be expected, which is sufficient to show a dosimetric benefit over no motion compensation according to the power analysis.

Part 2: Respiratory gated photon radiotherapy guided by COSMIK

Background:
A recent study of Calypso-guided respiratory gating for liver SBRT showed substantial dosimetric benefits of gating compared to unmonitored treatments without intrafraction adaptation[8]. Gating also gives substantial improvements compared to the drift correction strategy of Part 1 (Fig 4 , [19]), but it is more difficult to implement since it requires more robust real-time target localization. Gating will therefore be introduced as a second step after Part 1.

Aim:
To clinically implement respiratory gating guided by COSMIK for improved liver SBRT treatments.

Hypothesis:
Respiratory gating guided by COSMIK is feasible for liver SBRT and will significantly increase the dosimetric accuracy.

Research plan
Real-time monitoring with COSMIK will first be optimized using the dataset of Part 1 and then used in a prospective trial with respiratory gating for the liver SBRT patients treated at Aarhus University Hospital between approximately September 2019 and July 2020 (~10 patients expected, i.e. ~30 fractions, satisfying the power analysis above). The treatment will only be delivered when the tumor is inside a narrow region near the exhale phase. The delivered tumor dose will be calculated after each treatment and compared with the dose of simulated drift compensated treatments to quantify the dosimetric benefit of the gating.

Part 3: Respiratory gated proton therapy guided by COSMIK

Background:
DCPT has a strong wish to use proton PBS for liver SBRT due to the superior dose deposition with less normal tissue doses. However, proton PBS is much more susceptible to motion effects and a motion management strategy must be developed before clinical use of proton PBS in the liver.

Aim:
To develop COSMIK for the imagers available at DCPT and apply it for respiratory gated proton PBS for liver SBRT.

Hypothesis:
COSMIK allows accurate liver tumor motion monitoring and respiratory gating during proton PBS treatments.

Research plan
After Part 2 COSMIK will be transferred to proton therapy at DCPT, where gating based on internal tumor monitoring is essential for safe thoracic and abdominal treatments. The monoscopic x-ray imaging will be replaced by stereoscopic imaging by the dual x-ray imagers at DCPT. A 1-month research stay at Maryland Proton Treatment Center (MPTC) will kickstart this process since MPTC has the same Varian proton facility and imaging systems as DCPT. The group of the main supervisor already works closely with MPTC.

A clinical trial with COSMIC-gated stereotactic proton therapy for 10-15 liver patients will be conducted at DCPT. As in Part 2, the dose delivered to the moving tumor will be evaluated after each treatment session, now using a method for motion-including dose reconstruction for proton PBS developed in our group[23].

Time Schedule

Parts 1-3 will gradually implement COSMIK guided respiratory gating.

Part 1: Fall 2018 and the beginning of 2019 will be used for COSMIK optimization and the research stay in Sydney. Concurrently, the preparation for the patient study will be done, including ethics approval if needed. The following nine months' patients will be recruited for the study.

Part 2: Parallel with the clinical translation of Part 1, COSMIK will be improved further and prepared for respiratory gating. This includes protocol writing and ethics approvals. Following the conclusion of Part 1, the clinical translation of Part 2 will begin and run for about 9 months until mid-2020.

Part 3: Concurrently with Part 2, the adaptation of COSMIK to DCPT will take place and protocol writing and ethics approvals will be performed. Patients will be recruited for proton treatments from mid-2020 to mid-2021.

The Research Group

All work will be performed by the applicant, Casper Gammelmark Muurholm, unless stated otherwise. The patient recruitment will be done by co-supervisor Professor Morten Høyer and Britta Weber. The applicant holds a BSc in physics from Aarhus University (MSc in June 2018). He has taken multiple programming courses and has worked with Monte Carlo simulations for a proton beam-line in his bachelor's project. He currently works on fast rotation- and translation-including dose reconstruction for prostate in his MSc project. The MSc project will form a strong basis for the proposed PhD project, as the underlying theme of motion mitigation and management is the background for both. The applicant will work in close collaboration with the research group led by the main supervisor Per Poulsen whose specialty is motion management. Furthermore, the project involves collaboration with the research group of co-supervisor Professor Paul Keall at the University of Sydney, which is internationally leading in tumor tracking. Also collaborating is Professor Katja Langen of MPTC whose principal focus is organ motion in proton therapy. The applicant will have access to all required equipment including accelerators and proton beamline with image guidance, motion stages and dosimeters for development, evaluation and quality assurance of the gating treatments.

Collaborators

Per Poulsen, A/prof, AUH (main supervisor)
Paul Keall, Prof, Director of Rad. Phys. Lab., Sydney (co-supervisor)
Morten Høyer, MD, Prof, AUH (co-supervisor)
Peter Munro, Principal Imaging Product Manager, Varian
Britta Weber, MD, AUH
Katja Langen, Prof, Chief physicist, MPTC
Thomas Ravkilde, Med. Physicist, AUH

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Perspectives

The project will, for the first time, allow respiratory gating based on real-time internal motion monitoring with standard-equipped radiotherapy accelerators. It allows widespread use of accurate respiratory gating with a large gain in treatment accuracy and a higher ratio between tumor dose and normal tissue dose. This will likely increase the cure to complication ratio in radiotherapy. Extension of the developed methods to other tumors undergoing respiratory motion will be straightforward.

For proton therapy, the proposed research is essential for safe treatments of many abdominal and thoracic tumors. The combined methods for motion monitoring and motion including dose reconstruction will set a new standard for quality assurance in radiotherapy. It enables detailed evaluation of current treatment practice and helps defining the future clinical practice. The accurate knowledge of the actually delivered dose will likely lead to better understanding of dose-response relationships in photon and proton radiotherapy trials.

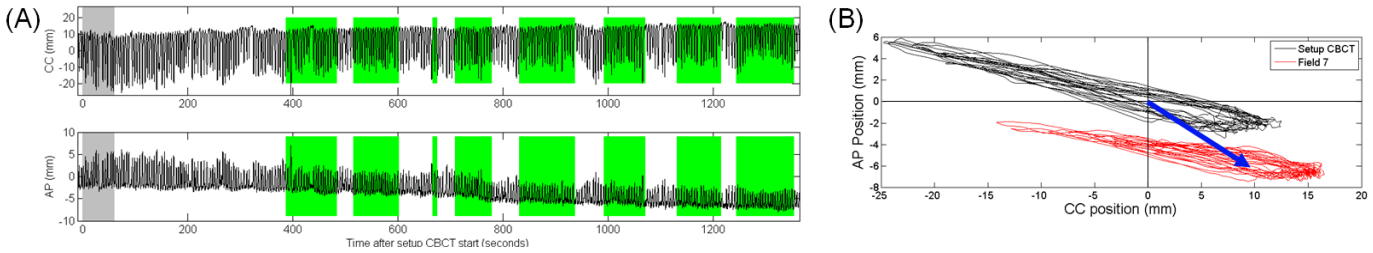

Fig 1: Intrafraction motion of a liver tumor measured by implanted electromagnetic transponders at Arhus University Hospital. (A) Motion in cranio-caudal (CC), and anterior-posterior (AP) direction from time of setup cone-beam CT scan (gray area) throughout all field deliveries (green areas). (B) Tumor motion in the sagittal plane during the setup cone-beam CT scan (black) and during delivery of the last treatment field 20 minutes later (red). Note the large intrafraction tumor drift in the cranial and posterior directions (Adapted from [8]).

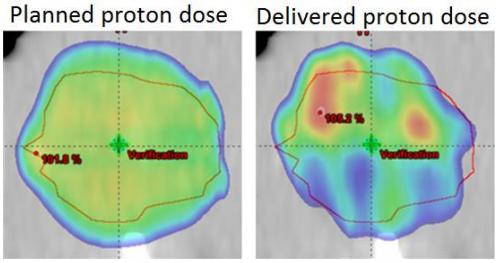

Fig 2: Left: An example of a planned homogeneous dose distribution using pencil beam scanning to treat a liver tumor (red contour). Right: Distortion of the planned dose with both hotspots and coldspots caused by tumor motion during the pencil beam scanning delivery (interplay effects). The color wash shows doses above 95% of the prescribed mean tumor dose. [Simulation and dose reconstruction by Per Poulsen, unpublished].

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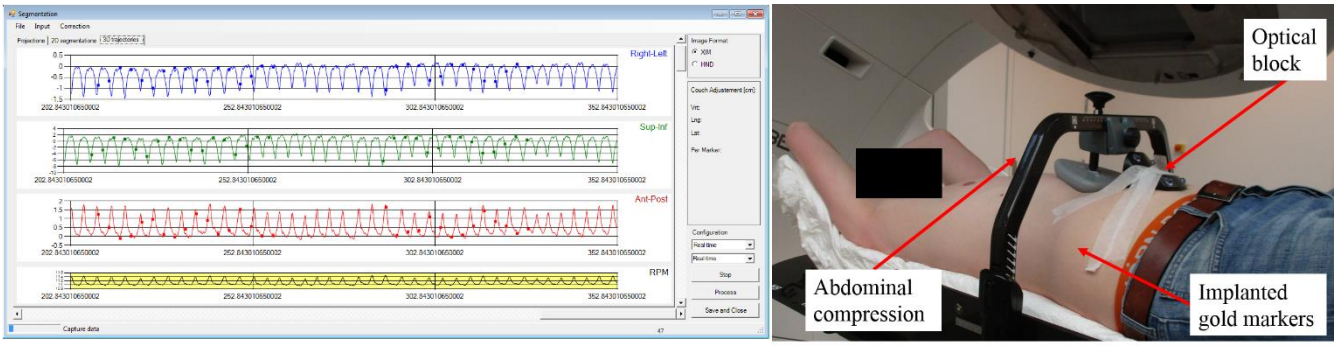

Fig 3: Left: Screenshot of the COSMIK user interface during a real-time patient treatment. The top three graphs represent the motion in each direction and the last graph shows the external optical block signal. The dots on the graph show the internal 3D marker position as determined every 3 s by intra-treatment x-ray images. Right: Patient setup for stereotactic liver radiotherapy with tumor motion monitoring by COSMIK.

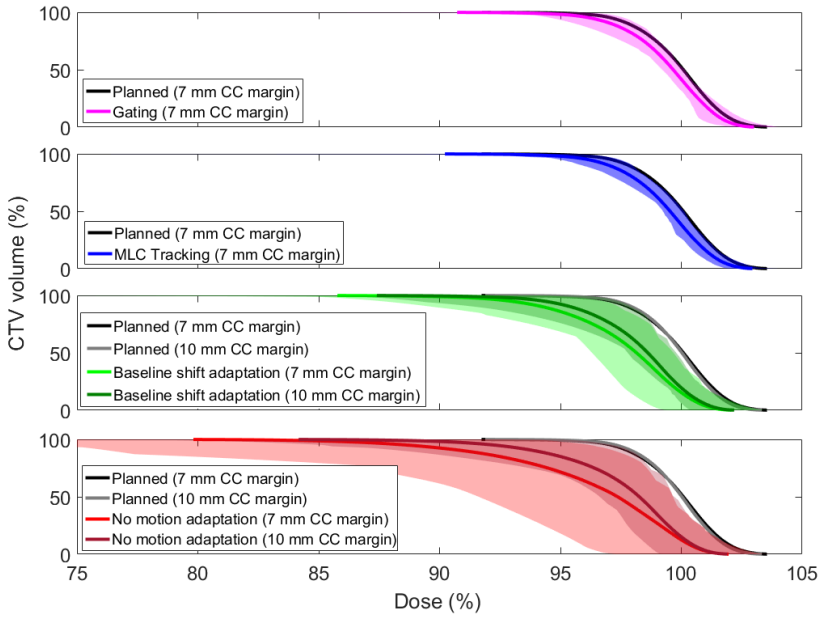

Fig 4: Mean CTV dose volume histogram (DVH) for 15 liver SBRT patients as treated by Calypso-guided gating at Aarhus University Hospital,and in simulated treatments with MLC tracking, with couch corrections in case of baseline drift of the tumor position, and without intrafraction motion adaptation (i.e. with the current standard of care). The shaded areas show the 10-90 percentile DVH range. (Adapted from Ref [19]).

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