Ultrasound Monitoring of Abdominal Soft Tissue

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1. **Abstract** (Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research)

Within the last decade, Linac based stereotactic body radiation therapy (SBRT) has been shown to be an effective treatment option for pancreas[1, 2] and liver[3, 4] tumors. SBRT delivers high doses of radiation therapy to the tumor over only 1-5 treatments. Because of the spatial precision of SBRT, it is feasible to administer a high radiation dose in only a few treatments. By minimizing the amount of radiation to surrounding healthy tissue, it is possible to decrease the rate of toxicity/complication and increase the radiation dose to cancerous tissue, thereby allowing better local control.

SBRT of the abdomen has been limited by the movement of intra-abdominal organs that naturally occurs with respiration and bowel movement. Organ motion occurs both intra- and interfractionally.

While intrafractional motion is a result of respiration, peristalsis and cardiac motion, the magnitude of interfractional target motion is dependent of daily variations in organ filling, weight change, tumor growth and radiation induced changes of tissue. Tumor movement may lead to tumor displacement and suboptimal dose delivery. Accurate localization of the target is very important to improve treatment delivery accuracy and reduce toxicity of the treatment. To evaluate tumor motion due to breathing motion, a 4-D CT simulation scan is performed. If the tumor moves more than 3 mm during a breathing cycle, breathing motion management is employed using Active Breathing Control (ABC) technique. ABC requires the patient to hold his/her breath within the proper tidal volume while treatment is delivered, while free breathing may be resumed between periods of treatment. This technique limits the delivery of RT to specific phases of the respiratory cycle so as to minimize the influence of breathing on the delineated tumor.

Despite significant progress made in ABC technique, tumor and organ motion could only be minimized and not eliminated completely. Assessing patient specific tumor/organ motion (both intra- and interfractional) throughout the course of SBRT treatment offers the possibility of ensuring delivery of the prescribed target dose while simultaneously minimizing normal tissue damage. In order to monitor the abdominal soft tissue motion, the Department of Radiation Oncology has developed a 4D ultrasound technique based on an ultrasound probe holder and a continuous motion monitoring software.

The 4D ultrasound image is acquired by using a motorized 3D ultrasound probe and image continuously. 4D ultrasound is a new non-ionizing and non-invasive imaging technique that allows continuous image acquisitions for real-time motion monitoring during the radiation treatment. Ultrasound is a proven modality for soft tissue localization (ref-prostate-breast). Several studies [5, 6, 7] have shown that even with older version of ultrasound system, the ultrasound images correlates with CT images within a small absolute magnitude of difference (about 3 mm), therefore we expect to have good agreement between the reference CT simulation and reference 4D ultrasound. Ultrasound motion monitoring during treatment delivery is based on real-time automatic registration of ultrasound images acquired on treatment days to reference ultrasound images acquired at the beginning of treatment, thus removing any inter-modality tracking uncertainty and inter-user variability. The ultrasound probe in the CT image will be contoured and radiation beams that directly pass through the ultrasound probe will be avoided. An SBRT treatment plan usually consist of multiple (9 – 12 beams for IMRT technique) co-planar beams delivered around the isocenter placed inside the tumor. Omitting the small range of angle directly passing through the ultrasound probe will not compromise the treatment plan dosimetry quality.

The first arm of this study is designed to validate the accuracy and stability of the ultrasound system and establish an efficient workflow to be applied for cancer patients. Healthy volunteers are able to perform more regular breathing patterns and longer breath-holds. Scanning healthy volunteers allows more predictable data acquisition time point and opportunity to develop a general workflow that can be continuously optimized for patient scanning. Anatomical abnormalities (surgical implant, fibrosis and metastases) in patients might produce artifacts in ultrasound images that can reduce motion tracking accuracy. Ultrasound of healthy volunteer with better anatomical landmark visualization helps us to evaluate the stability and accuracy of the ultrasound system and registration software.

For patient study, organ motion registered by ultrasound will be compared to motion recorded by CBCT and the accuracy of the ultrasound system will be evaluated. In addition, imaging and setup efficiency, cost and volume acquisition rate will be compared between CBCT based and 4D ultrasound based intra-fraction motion monitoring.

2. **Objectives** (include all primary and secondary objectives)

Primary objectives:

a. Establish effective workflow for real time monitoring of abdominal soft-tissue motion due to respiration using 4D ultrasound system
b. Evaluate feasibility of real time motion monitoring of tumor and surrounding organ/tissue during pancreas and liver SBRT treatments using 4D ultrasound system
c. Evaluate accuracy of the 4D ultrasound motion monitoring system compare to CBCT based intra-fraction motion monitoring during pancreas and liver SBRT treatments

Secondary objective:

a. Evaluation of dosimetry differences due to target/organ motion observed

3. Background

SBRT of the abdomen has been limited by the movement of intra-abdominal organs that naturally occurs with respiration and bowel movement. Currently at Johns Hopkins Hospital, breathing motion management is employed using ABC technique for patient treated with pancreas and liver SBRT if the tumor and/or abdominal organs move more than 3 mm during a breathing cycle. While ABC device has been reported to reduce respiratory motion to below 2 mm, small variation of breath-holds may lead to tumor displacement and suboptimal dose delivery. Assessing patient specific tumor/organ motion (both intra- and interfractional) throughout the course of SBRT treatment offers the possibility of ensuring accurate delivery of the prescribed target dose while simultaneously minimizing normal tissue damage. This can be achieved by using Clarity 3D ultrasound system together with ABC device for real-time tracking of the pancreas and liver during SBRT treatment.

4. **Study Procedures**

a. **Arm 1:** Validate the ultrasound tracking and establish reference range of motion for abdominal soft tissue motion from healthy individuals.
Fifteen healthy volunteers will be enrolled and informed consent obtained per study guidelines as described. A reference ultrasound scan will be conducted on each subject during breath-hold. Subjects will be required to lie in supine position and engaged with ABC; an ultrasound probe will be placed at the abdomen area with minimal pressure applied. Continuous motion monitoring is achieved by acquiring 4D ultrasound images using a motorized 3D ultrasound probe to image the pancreas, liver and other intra-abdominal organs continuously. Several 4D ultrasound scans will be collected during subsequent breath-holds that serve as secondary images. Registration of the reference and secondary ultrasound scans will be performed with automated registration algorithm built-in with the ultrasound system to evaluate abdominal soft-tissues and organs motion. Additional registration of ultrasound images will be performed with Velocity software to evaluate accuracy of automated registration software in the ultrasound system.

b. **Arm 2:** Monitor the abdominal soft tissue motion of pancreas patients treated with SBRT during the whole course of treatment.
Thirty pancreatic cancer patients receiving SBRT treatment with ABC will be enrolled and informed consent obtained per study guidelines as described. A 4D ultrasound scan will be acquired at the time at simulation and used as a reference ultrasound image for localizing

tracking target. The ultrasound probe will be placed at the abdominal area to monitor the pancreas motion. The probe will remain in place during the CT scan. Patient setup and the ultrasound probe location will be recorded so that the same setup can be reproduced during treatment delivery. The ultrasound probe in the CT image will be contoured and radiation beams that directly pass through the ultrasound probe will be avoided.
On each treatment day, 4D ultrasound images will be acquired continuously during beam on time to monitor pancreas motion. The system will record all relevant images, but will not be used in clinical decision making. These data will be used to evaluate the magnitude of target motion and dosimetry deviation due to the motion. Intra-fraction CBCT images acquired during treatment will be registered with reference CT images. Organ motion registered by ultrasound will be compared to motion recorded by CBCT and the accuracy of the ultrasound system will be evaluated.

c. **Arm 3:** Monitor the abdominal soft tissue motion of liver patients receiving SBRT treatment with ABC during the whole course of treatment.
Twenty hepatic cancer patients being treated with SBRT treatment will be enrolled and informed consent obtained per study guidelines as described. A 4D ultrasound scan will be acquired at the time at simulation and used as a reference ultrasound image for localizing tracking target. The ultrasound probe will be placed at the abdominal area to monitor the liver motion. The probe will remain in place during the CT scan. Patient setup and the ultrasound probe location will be recorded so that the same setup could be reproduced during treatment delivery. The ultrasound probe in the CT image will be contoured and radiation beams that directly pass through the ultrasound probe will be avoided.
On each treatment day, 4D ultrasound images will be acquired continuously during beam on time to monitor liver motion. The system will record all relevant images, but will not be used in clinical decision making. These data will be used to evaluate the magnitude of target motion and dosimetry deviation due to the motion. Intra-fraction CBCT images acquired during treatment will be registered with reference CT images. Organ motion registered by ultrasound will be compared to motion recorded by CBCT and the accuracy of the ultrasound system will be evaluated.

5. Inclusion/Exclusion Criteria

a. Inclusion Criteria:
   I. Arm 1: Healthy adult (age $\geq$18 years)
   II. Arm 2: Pancreatic cancer patients (age $\geq$18 years) currently receive SBRT treatment at JHU
   III. Arm 3: Hepatic cancer patients (age $\geq$18 years) currently receive SBRT treatment at JHU

b. Exclusion criteria: Children (age < 18 years) are excluded.

6. Drugs/ Substances/ Devices

Probe holder (passive): FISSO surgical arm (FDA approved)
Probe holder (active): active arm with robotic control (developed by JHU robotic lab)

7. Study Statistics

a. Analytic plan for primary objectives:
   An effective workflow for real time monitoring of abdominal soft-tissue due to respiration using a 4D ultrasound system will be developed through the use of healthy controls. As

described earlier, these controls will provide data for estimating the background reference for abdominal soft tissue. Data collected on controls will be summarized with descriptive statistics. Quantitative analysis of target/organ motion and displacement recorded in 4D real-time ultrasound scan will be carried out to assess both intra- and interfractional variation as described above in the study. This study will help us to ensure delivery of the prescribed target dose while simultaneously minimizing normal tissue damage. We will consider the approach feasible if we are able to successfully complete the procedure and output the associated data for 50% of the study participants. The software will output a motion curve over time. We will calculate the difference between values on the curve and the values from CBCT at the specific time points that CBCT is performed, and summarize the differences using descriptive statistics. A 95% confidence interval for the difference will be reported. These data will be used to evaluate the accuracy of the 4D ultrasound system.

b. Analytical plan for secondary objectives:
Quantitative analysis dosimetry deviation due to patient specific tumor/organ motion (both intra- and interfractional) throughout the course of SBRT treatment will be carried out. The actual dose received will be compared to the intended dose, and their difference will be summarized with descriptive statistics.

c. Sample size justification:

The goals of this study are to test the feasibility of the approach and subsequently generate data for describing the accuracy of the 4D ultrasound motion monitoring system during pancreas and liver SBRT treatments. The variability of the data obtained is currently unknown, so it is difficult to give preliminary estimates of the precision that specific sample sizes will yield. We plan to enroll 15 healthy controls, 30 pancreatic cancer patients, and 20 hepatic cancer patients for generating the pilot data.

8. Risks

a. Medical risks: None; data will be acquired but there will be no change in the radiation therapy intervention.
b. Legal risks such as the risks that would be associated with breach of confidentiality: While data will be stored data in secure locked files (computer files will be password protected and any paper records will be stored in the research office at Johns Hopkins under lock and key) in which only the research team has access, there is always the risk that confidentiality will be lost
c. Financial risks to the participants: None

9. Benefits

There is no benefit to the patient from participation in the study. Potential benefits to society include those to future patients undergoing Linac based SBRT treatments, who may receive improved treatment as a direct result of the research performed in this study.

10. Payment and Remuneration

N/A

11. Costs

There will be no additional cost to the patient as a result of participation in this study.

References:

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