CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER:	CASE 6Y14
STUDY TITLE:	**Integrated 3D x-ray and ultrasound Guided Radiation Therapy of Soft Tissue Targets**
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1.0 Background and Rationale

Hypofractionated radiotherapy, the delivery of higher dose per fraction with reduced number of treatment fractions, is a promising treatment option for many disease sites. Hypofractionated radiotherapy inherently requires a smaller patient setup margin which in turn necessitates the use of image guidance to alleviate the increased risk of geometric misses and deleterious clinical outcomes.

The main thrust of modern image guidance is to localize the soft tissue target and represents a major paradigm shift from the verification of bony landmarks. The predominant form of image guidance is on-board kilo-voltage cone beam CT (KV-CBCT). Although KV-CBCT is highly effective in improving accuracy of the patient setup prior to treatment, CBCT has two major deficiencies when applied to verify hypofractionated radiotherapy or radiosurgery.

First, KV-CBCT only provides a "snapshot" of patient anatomy at the time of imaging, but not during actual radiation delivery. Secondly, flat panel based KV-CBCT employed in radiation therapy is less than effective in discriminating a soft tissue target in a low contrast environment. Localization of abdominal lesions for hypofractionated treatment is challenging with KV-CBCT. Alternative imaging methods are needed. Ultrasound imaging is one of the important technologies that are capable of soft tissue localization in the abdomen. We have a commercially available ultrasound system in our department. This system has been predominantly used for prostate patients, localizing the prostate prior to treatment. Ultrasound imaging alone, however, suffers insufficient of field of view to visualize a proper patient position for radiotherapy.

2.0 Objectives

Purpose of this protocol is to investigate the feasibility of combining on-board CBCT with ultrasound imaging to overcome the shortcomings of CBCT or ultrasound imaging alone for imaging guided radiotherapy delivery. Specifically, we will investigate (a) whether the ultrasound imaging can enhance soft tissue tumor localization; (b) whether the presence of a passive arm is interfering radiation delivery during each treatment; (c) whether the presence of the ultrasound probe will affect the choice of radiation beams and degrade treatment plan quality.

3.0 Patient/Sample Selection

We will recruit a total of 30 patients, 30 with prostate cancer that will undergo external beam treatment at the Department of Radiation Oncology.

All patients undergoing radiation treatment for prostate cancer, with EBRT or SBRT are eligible.

A completed patient eligibility checklist is required following the approved standard operating procedure of the enrolling institution.

3.1 Inclusion Criteria

Patients must meet <u>all</u> of the following inclusion criteria to be eligible for enrollment:

_____ 3.1.1 The patient must have prostate cancer by biopsy, with the intent of undergoing definitive dose radiation therapy to targets within the prostate. Patients with prostatectomy receiving post-operative radiotherapy are also eligible.

_____ 3.1.2 Age > 18 years.

_____ 3.1.3 Performance status - Karnofsky PS ≥ 70

_____ 3.1.4 Subjects must have the ability to understand and the willingness to sign a written informational form.

3.2 Exclusion Criteria

The presence of the following will exclude a patient from study enrollment.

_____ 3.2.1 Patients with uncontrolled inter-current illness or psychiatric illness/social situations that would limit compliance with study requirements.

4.0 Registration Procedures

All patients enrolled on study will be entered into the Oncore database

5.0 Research Plan

5.1 Investigate whether the ultrasound imaging can enhance soft tissue tumor localization.

(a) Following the standard clinical procedure, daily KV-CBCT image for each patient will be acquired and used to guide for patient setup prior to treatment delivery. Because of limited soft tissue contrast in KV-CBCT to observe the soft tissue organ, such as the prostate, the added ultrasound image may enhance soft tissue localization prior to treatment for these patients.

The ultrasound device will be calibrated to the treatment iso-center via an external camera system and infrared markers on the ultrasound (US) probe. A commercially available passive arm will be acquired and attached to the ultrasound probe. Following our current clinical protocol, the patient treatment position will be determined solely based the daily KV-CBCT. After KV-CBCT guidance, a pre-treatment US image will be acquired for the study but not used for patient positioning. The success of this specific aim is defined as that the tumors can be visualized in the ultrasound images in at least 80% of patients enrolled.

(b) **Investigate whether the presence of a passive arm will interfere with radiation delivery during each treatment.**

In order to monitor tumor or organ motion during radiation, the US probe will be placed using a passive arm, as shown in the figure below. This passive arm will be attached to the treatment couch and also in contact with the patient during the radiation. Although the passive arm is commercially available, we plan to test whether the presence of the US probe will interfere radiation delivery during each treatment. Specifically, we will test: (a) whether the passive arm reduces the clearance between the patient and the gantry of the linear accelerator; (b) whether the passive arm can hold a consistent contact pressure with the patient under normal breathing motion; (c) whether the passive arm can be automatically released if a patient makes a large movement. The success of this specific aim is defined as that at least 80% of patients are able have the ultrasound probe attached during the entire treatment course.

Figure 1.

(c) **Investigate whether the presence of the ultrasound probe will interfere with the choice of radiation beams and degrade plan quality**

The presence of the US probe and the passive arm may block the access of some radiation beams. The specific aim of this study to investigate whether altering the radiation beam directions will affect the treatment plan quality. Our preliminary planning data[1] showed that it is necessary to choose different radiation beam angles, but the impact on treatment plan quality is not clinically significant for most patients. Patients for whom treatment plan quality is in the opinion of the treating physician adversely impacted by alteration of beam angles required by presence of the US probe will be treated with the non-altered plan, and thus be included in step 5.1(a), but excluded from 5.1(b&c), as US probe will be removed prior to treatment in these cases to allow for treatment with the best possible plan. We expect this to be rare. The success of this specific aim is defined as that the quality of the plans for 80% of patients will not be affected in the presence of the

ultrasound probe, defined as no more than a 2% decrease in tumor coverage, and also no more than a 2% increase in the dose to the most critical normal tissue for that tumor location (Prostate: dose to hottest 10 cc of rectum.)

6.0 Study Parameters

The study parameters collected are the US images acquired prior to each treatment and during radiation delivery. Pre-treatment KV-CBCT images will also be collected for dosimetric analysis. Specifically, the tumor location detected from combined US/KV-CBCT images will be compared with using KV-CBCT alone. Using the KV-CBCT the gold standard, 3D radiation dose distributions will be re-calculated according to the tumor localizations using KV-CBCT alone and using combined US/KV-CBCT. For SBRT prostate cancer, we will compare the following dosimetric endpoints, extracted from dose volume histograms.

Organ Name	Endpoint 1	Constraints
PTV_HD*	**V5000 cGy**	**> 50%**
PTV_LD*	**V3625 cGy**	**> 95%**
PROSTATE	**V3625 cGy**	**> 95%**
BLADDER	**D0.03 cc**	**< 5250 cGy**
RECTUM_ANT	**D0.03 cc**	**<5000 cGy**
RECTUM_LAT	**D3cc**	**< 4000 cGy**
RECTUM_POST	**V0.03 cc**	**< 2250 cGy**
URETHRA	**V0.03cc**	**< 5000 cGy**
URETHRA	**D1cc**	**< 4500 cGy**

PTV_HD = planning target volume in high dose prescription dose of 5000 cGy

PTV_LD = planning target volume in low prescription dose of 3625 c Gy.

For patients treated with conventional multiple fractionation, we will compared the following dosimetric endpoints, extracted from dose volume histograms.

Organ Name	Endpoint 1	Constraints	Planned	comments
CTV_7800	**V7800 cGy**	**> 99%**		
PTV_7800	**V7800 cGy**	**> 95%**		
BLADDER	**V7000 cGy**	**< 10%**		
BLADDER	**V6000 cGy**	**< 20%**		
RECTUM	**V7000 cGy**	**< 10%**		
RECTUM	**D10cc**	**< 7000 cGy**		
RECTUM	**V5000 cGy**	**< 30%**		**Without pelvic nodes**
RECTUM	**V5000 cGy**	**< 50%**		**With pelvic nodes**
FEMORAL HEAD_L	**V5000 cGy**	**< 5%**		
FEMORAL HEAD_R	**V5000 cGy**	**< 5%**		
PENILE BULB	**Dmean**	**< 5250 cGy**		

For patients with prostatectomy receiving post-operative radiotherapy with conventional multiple fractionation, we will compared the following dosimetric endpoints, extracted from dose volume histograms.

Organ Name	Endpoint 1	Constraints	Planned	comments
CTV_7000	**V7000 cGy**	**> 99%**		
PTV_7000	**V7000 cGy**	**> 95%**		
BLADDER	**V6500 cGy**	**< 40%**		
BLADDER	**V4000 cGy**	**< 60%**		
RECTUM	**V6300 cGy**	**< 10 %**		
RECTUM	**D10 cc**	**<6300 cGy**		

RECTUM	**V4500 cGy**	**< 30 %**		**Without Pelvic nodes**
RECTUM	**V4500 cGy**	**< 50%**		**With pelvic nodes**
FEMORAL HEAD_L	**V5000 cGy**	**< 5%**		
FEMORAL HEAD_R	**V5000 cGy**	**< 5%**		
PENILE BULB	**Dmean cGy**	**< 5250 cGy**		

7.0 Statistical Considerations

Because of limited funding from NIH, the number of patients that are planned to be enrolled into this protocol will be small and potentially lacking of the statistical power. The primary purpose of this study is a feasibility study to test whether a combined CBCT and ultrasound image guidance is clinically feasible. Our analysis is primarily descriptive and does not require any advanced statistics to analyze the endpoints. As a measure of protocol success we expect that:

1) Over 80% of patients have ultrasound images which are clinically adequate for treatment set-up in the judgment of the treating physician.
2) Over 80% of patients are able to undergo ultrasound based tumor tracking during treatment.
3) The quality of treatment plans for more than 80% of patients will not be affected.
4) No adverse events related to the ultrasound probe are noted during treatment.

8.0 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

8.1 Data Storage

Data will be stored electronically on a secure server in a password protected file. Access to data will be restricted with only principal and co-investigators as well as study coordinators and appointed regulatory reviewers having access to the file's contents.

8.2 Adverse Events and Data Monitoring

This protocol is a feasibility study. No clinical adverse events are expected. We will record number of patients who have the ultrasound probe attached during treatment and number of patients who have the ultrasound probe removed. When the treatment completed, no study related follow up is required.

8.3 Written Informed Consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

8.4 Sources of Materials

The research project will involve acquiring ultrasound images in addition to the standard x-ray images acquired for the treatment procedures. All other medical records and data will also be collected per standard practice to manage the treatment of the patient.

The medical records and data collected during the studies will consist of identifiable information that can be linked back to the patient (e.g. patient names, treatment dates, history numbers, dates of progression and/or response). We will obtain privacy authorizations from patients before we collect and store data and medical information. Only the research team listed in this proposal will have access to the subjects' identities and any data or records disclosed to a third party will be de-identified.

8.5 Potential Risks

Other than the potential of mild discomfort from the placement of the ultrasound probe, there is no risk associated with the additional on-board ultrasound imaging. During treatment planning, we will make sure that the US probe and the passive arm are not blocking the radiation beams, and conduct a run dry run (before radiation treatment) to make sure adequate clearance between the passive arm and the gantry of the linear accelerator.

All other potential risks are associated with the standard clinical practice of radiation treatment. These will be managed with established procedures in place.

8.6 Protection Against Risk

No adverse effects are expected from the additional ultrasound imaging in the research.

<u>Protections against Breach of Confidentiality:</u>

All research personnel involved in this study will comply with HIPAA regulations. The following measures will be taken to minimize the risk of breaching patient confidentiality:

- Patients' clinical data (hard and soft copies) will be stored in electronic format and stored in a password protected server located in a locked sever room at main Campus of Cleveland Clinic.

- Only research staff and authorized regulatory agencies will have access to the data. The secured data includes: case report forms, source documentation, signed consent forms, and any material containing patient identifying information.
- This data will be securely stored in electronic format in Cleveland Clinic and data pertinent to this protocol will be stored in a password protected server that is located in a locked server room.
- No information by which patients can be identified will be published.

8.7 Potential benefits of the proposed research to the subjects and others

There is no additional benefit to the study participants. However, participants could potentially receive an indirect benefit of a feeling of altruism knowing their participation will pave the way for future patients whose treatment may be guided by the integrated 3D x-ray/ultrasound imaging system.

8.8 Importance of the knowledge to be gained

The research aims to develop a novel non-invasive approach of image guidance of hypofractionated SBRT of patients with abdominal and pelvic tumors with the capability of continuous monitoring during radiation delivery. Successful monitoring of target position during treatment is expected to reduce margins required during radiation treatment, and thereby reduce dose to surrounding normal tissue. This has been demonstrated clinically using real-time tracking technology using implanted markers in prostate cancer, but in this study would be able to be done non-invasively using ultrasound.

The analysis of the recalculated dosimetry will show the uncertainty of dose delivery using current CBCT and ultrasound image guidance methods and shed light on the degree of improvement that can be achieved when they are combined. The data from the feasibility studies will be immensely useful for designing a treatment protocol with adequate statistical power to prove the improvement in treatment accuracy and efficacy. In turn, a cost-benefit analysis can then be made in terms of resource allocation, treatment efficiency and margin reduction. The information will be most significant as a baseline for assessing the cost-effectiveness of the next generation of advanced IGRT machines such as those employing on-board MRI.

8.9 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, and all correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

8.10 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to

systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

References:

1. Zhong, Y., et al., *Assessing feasibility of real-time ultrasound monitoring in stereotactic body radiotherapy of liver tumors.* Technol Cancer Res Treat, 2013. 12(3): p. 243-50.