Improving Breast Radiotherapy Setup and Delivery Using Mixed-Reality Visualization

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1.) Title: Improving breast radiotherapy setup and delivery using mixed-reality visualization

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3.) Abstract:

Breast radiotherapy (RT) begins with an initial CT scan of the patient followed several days later by the actual treatment delivery where the patient is re-setup on the couch of the RT device. At this time, it is critically important to both reproduce the specific patient posture used during the initial CT scan and precisely align the patient (and lesion) with the RT device. Any difference in these two aspects can lead to under-dosing the lesion or overdosing critical structures like the lungs or heart. Currently, image-guided radiotherapy (IGRT) and surface-guided radiotherapy (SGRT) are the two main systems used to address these issues. IGRT is the gold standard for aligning an internal target with the radiation beam but 1) uses ionizing radiation which increases radiation dose to the patient and 2) lacks real-time feedback which prolongs overall setup time, potentially leading to further patient discomfort and anxiety. SGRT uses external light emitters and cameras to guide patient setup in real-time but lacks portability and is limited by line-of-sight obstruction, poor ergonomics, and prohibitive costs. Thus, there remains a tangible opportunity to improve the setup process for breast RT that would benefit patients and expand accessibility to advanced techniques.

To achieve this aim, we have developed a novel concept for patient posture correction and alignment using mixed-reality (MixR) visualization. MixR is an emerging domain whereby virtual objects (holograms) are overlaid upon physical environments via immersive technology. The concept is best implemented in optical see-through head-mounted displays (OST-HMD), like the Microsoft HoloLens v2 (Redmond, WA), that use a variety of sensors to map the surroundings, track physical objects, and render holograms at specific locations. Notably, these attributes are enabled while a user dynamically navigates a space, thereby affording natural viewing and even interaction with 3D virtual objects.

In our implementation of MixR, a user is able to simultaneously and directly view a patient and a reference hologram of their external surface derived from their initial planning CT scan. The hologram provides a visual reference for the exact posture needed during treatment and is initialized in relation to the origin of the RT device. Thus, by matching a patient to their hologram, the correct posture is achieved while subsequently registering the patient with the RT device. This is highly relevant in breast RT where setup is challenged by the independent movement of local anatomy and the deformability of pendulous breasts. Such a system removes the need for expensive and restrictive external

cameras and holds the promise to improve outcomes by improving accuracy and safety while reducing both setup time and imaging dose. By designing an application for a commercial off-the-shelf device with a cost of less than $4,000, we also believe the method capable of improving portability, reducing cost, and increasing accessibility for centers with limited resources. We have developed an initial version of this application using the HoloLens v2 and collected preliminary data using phantoms. The data supports an overall alignment accuracy of 3-4 mm.

The purpose of the current research is to extend this testing to patients by performing a pilot study to assess the accuracy, overall setup time, and amount of IGRT needed when utilizing MixRT for patient setup in breast RT. Comparisons will be made between MixRT and 3-point alignment for 3D conformal photon treatment, and MixRT/IGRT versus IGRT alone for pencil beam scanning proton treatment. This data will be used to establish viability and provide the framework for larger comparative effectiveness research studies and eventual FDA clearance.

4.) Background:

Radiotherapy workflow

Over half of all patients treated for invasive breast cancer will receive some form of RT.[1] The treatment workflow for external-beam RT involves three main steps. (1) Simulation; A CT scan of the patient is acquired with the patient in a predetermined position to provide an imaged-based, volumetric representation of the patient's anatomy. (2) Treatment Planning; This step links the patient's CT images with the radiation beams to be delivered by an RT device. Planning occurs within a computer-based platform where a radiation oncologist provides contours for the target and critical structures, and a dosimetrist optimizes beam design to meet dose-related objectives. In most cases, all beams share a common intersection point inside the patient (i.e., patient isocenter). (3) Treatment; Once the plan is ready (5-10 days after simulation), the patient returns and is positioned on the couch of the RT device. The patient isocenter is aligned with the radiation isocenter of the RT device, thus linking the treatment plan to the treatment delivery. Because the treatment plan is based on the specific CT acquired at simulation, it is critical that the patient's pose, orientation, and any ancillary devices used during simulation be reproducible at this time.

Image-Guided Radiotherapy

Patient alignment with the radiation isocenter and reproduction of the simulation setup is achieved in a variety of ways. A 3-point setup involves the alignment of surface marks (left, right, and anterior) with external lasers calibrated to intersect at the radiation isocenter. The 3-point setup is the most commonly utilized technique for the initial setup but is often supplemented with image guidance using portal imaging, stereoscopic radiographic imaging, fan-beam, or cone-beam CT (CBCT).[2] IGRT allows for the visualization of internal anatomy and is the gold standard for registering an internal target with the radiation isocenter, albeit at the cost of increased radiation dose to the patient. Such dose increases the risk of secondary malignancy and should be managed through minimization and the introduction of alternative, non-ionizing modalities when appropriate.[3]

In addition to aligning the patient and radiation isocenters, IGRT also helps verify patient posture. This involves an iterative approach of adjusting the patient, assessing posture based on imaging, and then re-adjusting to minimize any difference with the

simulation setup. For IGRT, this is a delayed process due not only to the time it takes to acquire, register, and analyze an image, but also the fact that image review takes place at a location separate from the immediate vicinity of the patient. Certain sites, like breasts, require more iteration than others due to independent movement of anatomy in the treatment field (e.g., breast, arms, shoulders, head and neck). This issue of non-rigidity distinguishes patient registration from other types of rigid registration encountered in medicine. Even when IGRT identifies differences in setup, it is not always intuitive as to how to make the appropriate corrections to patient posture in 3D based on 2D projections (either planar images or 3D datasets visualized in 2D axial, coronal, and sagittal planes), and in certain cases the treatment volume can exceed the field of view (FOV) of the imaging system. These limitations as well as the pressure to stay on schedule can lead staff to accept suboptimal setups with the hope that any difference in patient posture will have minimal effect on the dose distribution; ultimately, this depends on several factors, including the extent of the target and its relation to critical structures, the uniformity of the dose distribution, the type of delivery, and modality. Certain modalities, such as proton therapy, are extremely sensitive to changes in the amount of material between the beam entrance and target [i.e., the water equivalent path-length (WEP)].[4] Changes in body posture are a primary cause of WEP discrepancy and can lead to significant under-coverage of the target.

Surface-Guided Radiotherapy

Surface-guided radiation therapy (SGRT) is a technique that complements IGRT in many respects. While IGRT excels at aligning internal anatomy, SGRT emphasizes the matching of external surfaces.[5] In terms of setup, the strength of the technique is a real-time, 3D reconstruction of the patient surface, which allows for immediate correction of patient posture and alignment when compared to a reference body surface derived at the time of simulation. To accomplish this, SGRT systems utilize ceiling-mounted light emitters and optical cameras. The emitters project a known light pattern onto the patient's skin that is reflected and captured by the optical cameras; thereafter, the patient surface can be reconstructed in 3D and displayed on a conventional 2D monitor. Several studies have quantified the benefits of SGRT in comparison to a traditional 3-point setup (no IGRT) for patients with tumors of the breast, chest wall, and extremities.[6-10] The largest improvements are seen when treating intact breasts, which present challenges based on the independent movement of the local anatomy and the deformability of the pendulous target. By reducing the initial shifts, the need for iterative adjustment is reduced. In one study, this translated to a decreased setup time from 11 to 6 minutes, indicating reduced radiographic imaging and, consequently, reduced imaging dose to the patient.[11] Reducing setup time also minimizes patient discomfort that can occur with prolonged time on the treatment couch.

While SGRT represents a favorable complement to IGRT, it is not without limitations. For the patient surface to be recognized, the ceiling-mounted components must remain unobstructed during the setup procedure and map only the skin surface that can receive and reflect the light pattern. This line-of-sight approach often means a limited FOV and an inability to track surfaces in contact with the couch or behind other anatomy. Obstruction is also a limiting issue for certain room designs when components of the RT delivery system can block the overhead cameras during portions of the setup process. Besides obstruction and FOV limitations, SGRT is not currently optimized for the ways in which therapists set up patients. Because the real-time surface is displayed on a computer

monitor placed outside the immediate perspective of the user, the therapist must redirect their gaze from the patient, resulting in a cognitive delay and interruption of the natural hand-eye coordination used to perform patient adjustments. Furthermore, monitor size and distance limit the therapists' ability to observe small details, and the overall design eliminates the possibility of direct observation. For instance, it is currently impossible to make a direct eye-level inspection to determine registration accuracy between the patient surface and the reference body surface. This type of inspection comes naturally to a human observer and improves the perception of size, irrespective of distance.[12] Taken together, these issues portend a lack of human factors engineering, which seeks to optimize the fit between a user, technology, and the environment.[13] Finally, commercial SGRT systems lack portability and are prohibitively expensive for many cancer centers with limited resources. Three commercial products currently exist: Align RT (Vision RT, London, UK), Identify (Varian Medical Systems, Palo Alto, CA), and Catalyst (C-Rad, Uppsala, Sweden). While costs for these systems vary, the baseline price for a single, stand-alone system is in excess of $100,000.

Mixed Reality Visualization

Mixed reality (MixR) is an emerging domain whereby virtual objects (holograms) are overlaid upon physical environments via immersive technology. The concept is best implemented in optical-see-through head mounted displays (OST-HMD) which use a variety of sensors to map the surroundings, track physical objects, and render virtual objects at specific locations. Notably, these attributes are enabled while a user dynamically navigates a space, thus affording natural viewing and even interaction with holograms (Figure 1). MixR differs from both virtual reality (VR) and augmented reality (AR). In VR, the user is closed to the physical world and sees only the virtual environment. In AR, virtual content is displayed in the real world, but the content typically moves with the user and does not interact with the physical environment, e.g., Google Glass. MixR can be thought of as a more sophisticated version of AR, though the terminology is not completely settled. The first usage of MixR in medicine began in the early 2010's with physical simulators,[14] experimental HMDs,[15-16] and most recently with a commercial off-the-shelf system, HoloLens (Microsoft Corp., Redmond, WA) released in 2016.[17-21] Currently, the HoloLens (now on version 2) and the Magic Leap One (released in 2018 by Magic Leap Inc., Plantation, FL) are the only two devices competing in the consumer space for MixR implemented using OST-HMDs.

Figure 1. Example of MixR in an industrial setting using the HoloLens v2.

MixR offers incredible potential to the medical professional. At a basic level, MixR can be used to improve both situational awareness and information management by allowing for the optimal placement of relevant content in the user's local space. In the surgical suite this has been implemented using virtual 2D panels to display pre-operative planning materials (images, notes, etc.) directly within the surgeon's field-of-view.[17] These displays are visible through the OST-HMD thus absolving the need for the surgeon to redirect their gaze from the surgical site. A more advanced use-case is surgical navigation which spans a broad area related to the orientation and/or positioning of external tools in

relationship to a patient. Thus far, MixR-navigation has been used for pedicle screw insertion in orthopedic surgery[18] and needle insertion in brachytherapy.[19]

The novelty of these applications is the alignment of a physical object to a patient via a 3D hologram. The hologram itself is registered to the patient through inside-out tracking using only the sensors available on the OST-HMD. This differs from an outside-in approach, such as SGRT, in which external hardware is required to track and register objects. Outside-in navigation systems increase clutter in the operational space, suffer from line-of-sight obstructions issues, preclude optimal ergonomics, lack portability, and can be prohibitively expensive.[22-23] The type of inside-out tracking used for MixR can be categorized as either marker-based or marker-less. In the former, the position of the hologram is determined via its relationship to a known object placed in the physical space and subsequently recognized through feature detection. In the latter, the system utilizes visual simultaneous localization and mapping (VSLAM), a process that involves estimating the spatial relationship between the OST-HMD and multiple key points identified within a series of viewpoints.[24] Current OST-HMDs have a variety of sensors to draw upon for tracking purposes including IR cameras, RGB cameras, and inertial sensors. While marker-less tracking is native to current OST-HMDs, marker-based tracking is available via custom development or third-party SDKs using both RGB and IR data streams.[20,25]

MixR-Guided RT

As noted above, SGRT systems represent an *outside-in approach*. We propose to improve the setup process through *inside-out tracking* and the use of MixR visualization. To that end, we have developed a novel method for registering a patient with an RT device using a hologram as an intermediary [i.e., MixR-Guided Radiotherapy (MixRT)]. The hologram is generated based on the body contour derived from the patient's planning CT dataset (Figure 2A-B). The patient isocenter is linked to the hologram and registered to the radiation isocenter through a simple procedure using both marker and marker-less tracking (Figure 2C). In this way, the patient isocenter is linked to the radiation isocenter. The hologram can be viewed directly through a commercial device (HoloLens v2) and provides the reference posture to be matched during patient setup (Figure 2D-E). The approach improves upon SGRT in that the patient's surface (real as opposed to reconstruction) is matched to a reference surface. Obstruction, FOV, ergonomic, and economic limitations are all remedied through the use of the Hololens v2 and inside-out tracking, which allows the user to view the patient and hologram directly from multiple angles using one portable device. The key feature of the system is the way in which it transforms non-rigid registration into rigid registration by providing an efficient and cost-effective mechanism for reproducing patient posture without the use of ionizing radiation. While IGRT will still be required in certain cases to observe internal anatomy, by improving the initial setup the need for iterative IGRT is reduced, subsequently reducing setup time and the radiation dose associated with imaging. We thus envision MixRT being used independently or in conjunction with minimal IGRT to improve speed and accuracy while simultaneously reducing the radiation dose to the patient from additional imaging.

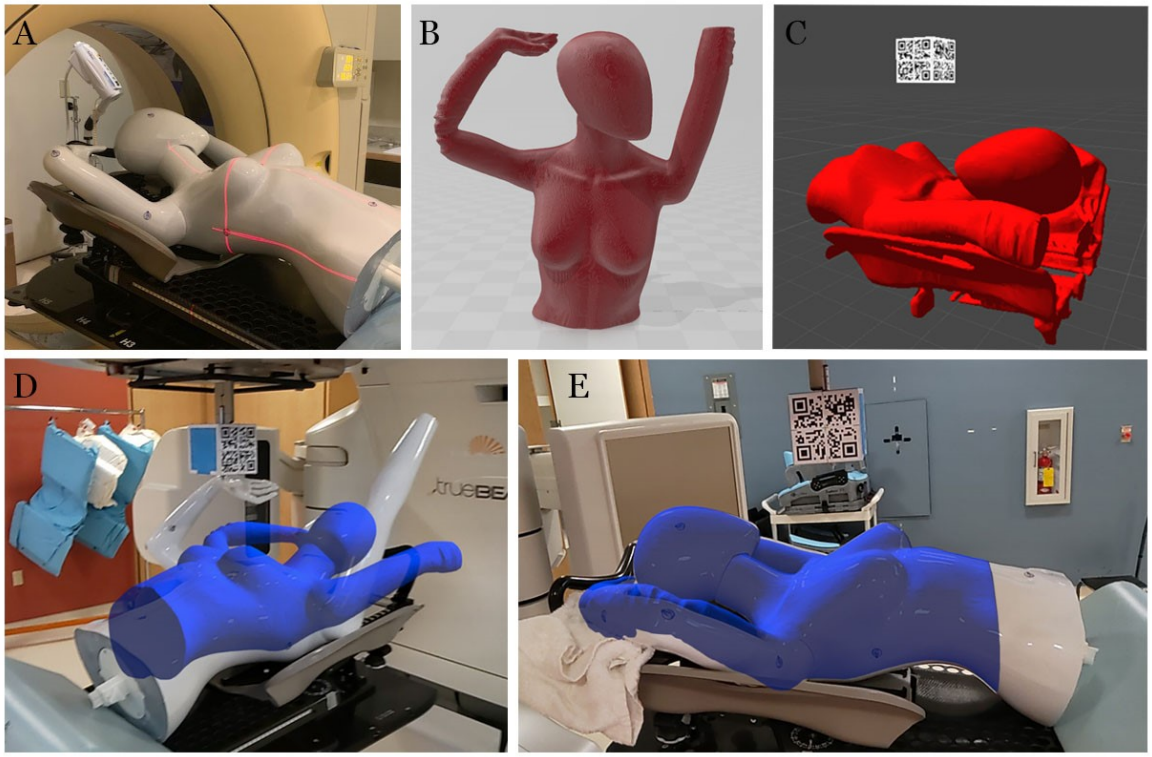


Figure 2. System for patient alignment via hologram: A) Initial simulation CT scan, B) Creation of 3D object file from body contour, C) Development platform where patient isocenter is linked with virtual representation of physical marker, D) Physical marker attached to machine at pre-determined location linking patient isocenter with radiation isocenter; patient hologram (blue) is visualized through HoloLens v2 highlighting the mis-alignment of the mannequin (white), E) Physical mannequin adjusted to match the reference hologram, thus reproducing the required posture and registering the mannequin with the RT device.

Table 1. Preliminary accuracy of MixRT for rigid alignment.

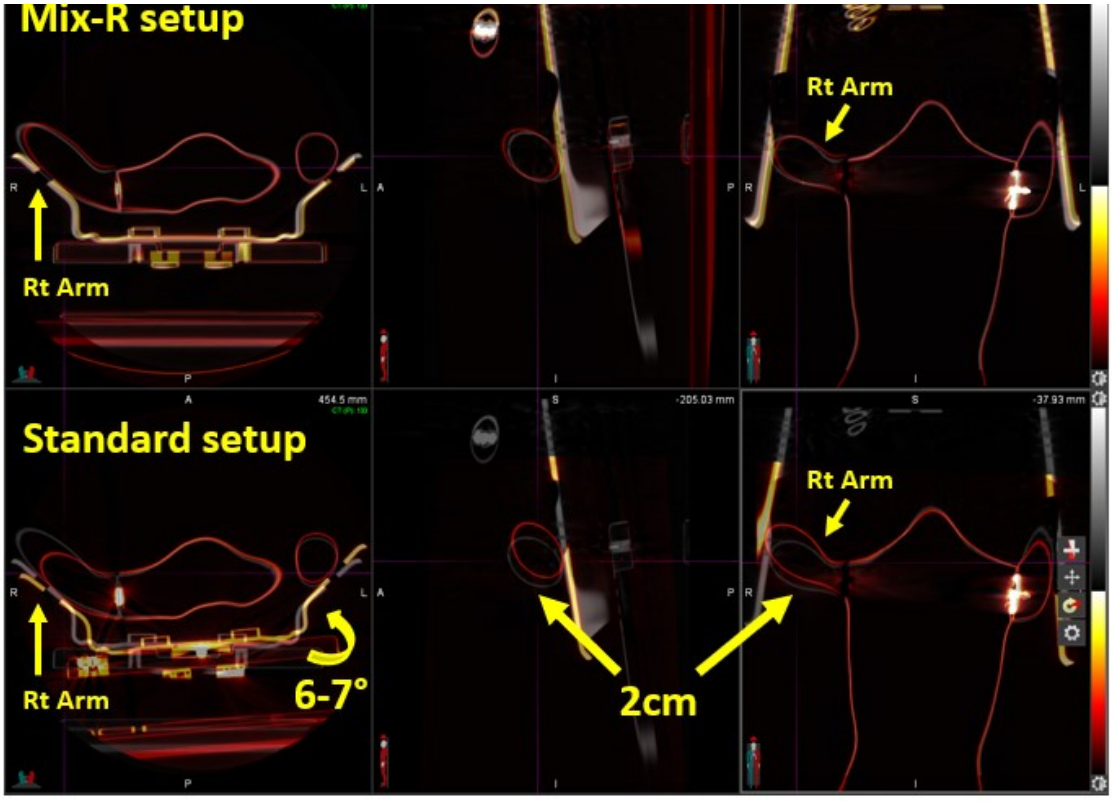
	User 1	User 2	User 3	Mean	StDev
Shift (mm)		n = 5		n = 15	
Vrt	0.8	0.6	1.5	1.0	0.8
Lng	1.1	1.3	1.2	1.2	0.7
Lat	2.0	1.8	2.4	2.1	1.5
RMS	**2.4**	**2.6**	**3.3**	**2.8**	**1.4**
Shift (°)					
Rtn	0.4	0.7	0.7	0.6	0.6
Pitch	0.1	0.1	0.0	0.1	0.1
Roll	0.1	0.1	0.1	0.1	0.1

In preparation for this study, we have developed a preliminary application to enable MixRT and provide initial estimates of hologram stability, alignment accuracy, and user variability. In one experiment, three users were tasked with aligning a rigid anthropomorphic phantom with an RT device (linear accelerator) while wearing the HoloLens v2. Each user performed the alignment five times, and accuracy was quantified using IGRT. For each user, all five measurements were completed within the same session. Between measurements, the setup was disassembled and reset. The results shown in Table 1 preliminary estimate an overall accuracy of 3±1 mm. These results were consistent between all users across all sessions. Considering the preliminary nature of the study, these results

are extremely encouraging, achieving less than the 5 mm alignment tolerance for 3D photon treatments and approaching the 2 mm alignment tolerance for proton treatments.

In a second experiment, an attempt was made to reproduce the posture of a non-rigid, female mannequin placed on the couch of a CT scanner. The first setup was done using only setup photos and room lasers, typically the only tools available for this type of "verification CT scan".[4] The second setup was performed using MixRT. In both cases, CT scans of the mannequin were acquired and registered with the initial, simulation CT scan using the torso as the area of focus. With the torso aligned in both registrations, the difference in arm position provides a way to assess the correctness of the overall posture. As seen in Figure 3, the MixRT setup outperforms the standard setup which showed a difference in arm position of 2 cm and further required a roll of 6-7 degrees in order to align the torso. In a real treatment scenario, this misalignment would require further manual correction, increasing the utilization of IGRT, overall setup time, and with no guarantee of a result matching that provided by MixRT. As previously noted, sub-optimal setups are often accepted, even with IGRT, due to the pressure to stay on schedule, minimize patient discomfort that can occur with prolonged time on the treatment couch, and the limitations of current methods. Thus, MixRT, with its ability to naturally guide both patient alignment and adjustment in real-time, provides a mechanism for increasing the overall accuracy of the treatment delivery and associated outcomes.

Figure 3. Preliminary accuracy of MixRT for non-rigid alignment demonstrating the elimination of roll and accurate arm placement compared to standard alignment methods. Left-to-right (axial, sagittal, coronal views).



5.) Specific Aims:
Perform a pilot study to assess the feasibility of MixRT. Feasibility will be based on the accuracy, overall setup time, and amount of IGRT needed when utilizing MixRT for patient setup in breast RT and in comparison, with current methods. Comparisons will be made between MixRT and 3-point alignment for photon treatment, and MixRT/IGRT versus IGRT alone for pencil beam scanning proton treatment. This data will establish viability and provide the framework for larger comparative effectiveness research studies and eventual FDA clearance.

6.) Research Plan:

- **Describe the inclusion and exclusion criteria for this project:** This study will target adult patients who are planning to undergo photon or proton radiation therapy at UFHPTI for treatment of the breast or chest wall. As this type of treatment is rare in men, the study will focus on female patients only.

- **Provide a thorough step-by-step description of what you intend to do throughout the course of the study in a logical and sequential format:**

  Hologram creation
  For all patients included in this study, we will create holograms based on the external body contour derived from their planning CT dataset. This contour is routinely segmented during treatment planning; thus, we will only need to access the existing contour located in the software system MimVista and export it to our software system. We will also access patient setup photos located in a clinical file system and export these to our application.

  Mixed-reality guided patient setup
  At UFHPTI, we treat breast/chest wall patients using various modalities and techniques. In all cases, patient setup begins with a 3-point alignment. The additional use of IGRT depends on modality, approach, and patient-specific variables. Most patients treated with 3D conformal photon therapy (3DCRT) receive only weekly IGRT, including kV orthogonal and MV portal imaging. The 3-point alignment, thus, represents the standard setup for the majority of treatment, both here and across the nation, as 3DCRT is the most common technique for breast RT. As such, one of our primary aims is to pilot the clinical implementation of MixRT with the goal of accuracy similar to or better than a traditional breast setup involving 3-point alignment (5mm tolerance).

  We will recruit 12 patients scheduled to receive whole breast or chest wall RT using a supine, 3DCRT or IMRT approach. All patients will be consented for a study comparing the accuracy of MixRT with a traditional 3-point alignment as quantified using CBCT. To control for setup variation which typically decreases after the first few treatment fractions, we will stratify patients into two groups using an alternating method. In the first group, the therapists will position the patient using 3-point alignment during fractions 1-5 (5 total), then using MixRT for fractions 6-10 (note:

16 fractions is a common course of breast RT). For the second group, we will reverse the order, using MixRT for fractions 1-5 and 3-point alignment for fractions 6-10. In this way, each patient will serve as their own control. In all cases, patient alignment will be verified using CBCT which will be registered to the simulation CT by the treatment therapists using the standard clinical workflow. The magnitude of the resulting shift will be recorded. If further adjustment is necessary, the number of repeated CBCTs will be recorded along with the shift magnitude. All registrations will be reviewed by a board-certified radiation oncologist (one of the co-investigators) who will qualitatively assess the accuracy of the setup while blinded to the setup method. The process for mixed-reality alignment is noted below:

1. Identify the patient and initialize their hologram by detecting a QR-coded cube attached to the treatment device.
2. Setup the patient according to their setup photos, related immobilization devices (typically only an inclined breast board), and 3-point alignment. Further match the patient to their hologram as viewed through the HoloLens 2 device.
3. Utilize IGRT to verify proper alignment per protocol or departmental standards.
4. Make corrections as needed based on IGRT.
5. Repeat steps 1-3 if necessary.

For patients receiving proton therapy, setup typically includes routine CBCT, the challenges of which were previously discussed for non-rigid alignment including prolonged setup time and increased imaging dose. The primary goal of this sub-aim is thus to show that MixRT can reduce setup time and the amount of imaging dose in cases requiring CBCT alignment. To evaluate this, we will recruit an additional 12 patients scheduled to receive RT using a supine, pencil-beam scanning approach. As with 3DCRT/IMRT approach, we will divide patients into two groups using an alternating method and alternate the setup approach between fractions 1-5 and 6-10, reversing the order between the two groups. Setup time will be tracked from the moment the patient lies on the treatment couch to when the final position is confirmed by the therapist prior to treatment. Patient alignment will be verified/quantified in a similar manner as noted above.

A window period of 2 additional fractions is permissible for the collection of study data. This window period is provided to allow a patient to remain on study through her 12^{th} fraction of treatment if the patient is not able to receive the study intervention during one to two of her first 10 fractions.

To summarize, we intend to enroll 12 patients receiving either 3DCRT or IMRT and 12 patients receiving proton therapy. Within each modality, patients will be randomized into two groups using an alternating method. The order in which MixRT will be utilized will be reversed between the groups. The measured data will include registration accuracy (6 DoF shifts), setup time, and number of CBCT's utilized. Registration accuracy will be quantified using the image registration module that is used as part of the IGRT process. Setup time will be quantified using a stopwatch.

The number of CBCT's will be quantified via counting the number that are used during the setup process. Patients receiving photon IMRT receive daily CBCT as part of the standard of care. Thus, this investigation would likely not introduce additional imaging dose for these patients. For proton therapy CBCT is used weekly, and for 3DCRT it is not routinely used. Thus, this investigation would represent a marginal increase in the utilization of CBCT for these patients, up to 10 extra CBCT's nominally.

Setup during Verification CT

Radiotherapy patients at UFHPTI often receive repeat CT scans (verification scans) at periodic timepoints during the course of treatment to assess for anthropomorphic changes that could have dosimetric effect. Reproducing the posture from the initial CT simulation is critically important yet difficult to achieve due to the lack of real-time feedback. For patients who receive a verification CT (likely all proton patients), we will implement holographic alignment during this process and assess its accuracy in comparison to CT acquisition without the aid of holographic alignment. The procedure will be as follows:

1. Identify enrolled patients scheduled to receive a verification CT scan.
2. Setup patient without the aid of holographic alignment (standard method).
3. Acquire verification CT scan.
4. Dismantle the setup.
5. Utilize holographic alignment to correct patient posture. This involves a therapist wearing the HoloLens 2 device and viewing the patient's reference hologram overlaid the patient. The therapist will manually adjust the patient to match the hologram.
6. Re-acquire verification CT scan.
7. Export datasets to MimVista software.
8. Register each dataset with the simulation CT using mutual information based automatic alignment.
9. Quantify registration accuracy of the outer body contour both qualitatively and quantitatively, the latter of which will utilize similarity metrics such as the Hausdorff distance and symmetric mean absolute surface distance.

- **Discuss procedures for recruiting and consenting potential study participants:** Eligible patients who are planning to undergo radiotherapy at UFHPTI will be approached by consent and protocol trained staff to participate in this study. Since this will not affect the patient's actual treatment course, they may be simultaneously enrolled in any of the other protocols open at the time.

- **Describe the targeted study population (the target population should be representative of the population that may potentially benefit from the research) and the setting in which the research will take place:** Our application should

benefit all patients undergoing radiotherapy, but benefit will be greatest for cases where non-rigid alignment is a critical aspect of patient setup. Breast-RT is a perfect example of this, and the study will focus on patients undergoing this type of treatment.

- **If you intend to use a vulnerable population, describe the scientific and ethical reasons for including them and what, if any, additional safeguards are needed to protect them:** We do not intend on targeting vulnerable populations. However, UF/Shands staff and students will be considered for participation. We feel we cannot refuse them potential enrollment if they present to us, meet the eligibility criteria, and wish to participate in the study. We will adhere to the strict policies and confidentiality and the informed consent process with these patients as with all our patients. Potential subjects are presented with treatment alternatives as part of the informed consent process. It is stressed that participation in the clinical study is entirely voluntary, and that consent can be withdrawn at any time without penalty.

- **Describe how potential subjects will be identified and recruited:** Patients will be identified and recruited during their pretreatment workup.
- **Describe how subjects protected health information will be accessed and by whom:** Data will be accessed and collected from the treatment planning system, RayStation, clinical database software, MimVista, and the radiation oncology information system, Mosaiq. These are all clinical systems used to facilitate patient treatment at UFHPTI. Only the investigators and research staff will screen or access patient medical records for the purpose of this study.

- **Describe how consent will be obtained, by whom, and in what setting, and how and where consent will be documented:** Patients will be consented during standard of care clinic visits by protocol/consent trained staff. Documentation of informed consent will be noted in the patient's chart in Mosaiq.

- **Describe the number of subjects that will be screened, and the number of evaluable subjects needed based on power analysis:** Up to 40 patients may enroll, but approximately 24 patients are needed in this pilot study. We recognize the study is underpowered, however, this is a pilot study where the purpose is to collect preliminary data to help establish viability of the method.

- **Describe completely all drugs, devices, or instruments that are being proposed:** This study involves no drugs. The specific device, HoloLens 2, will be worn by the therapists during patient setup. This device will display relevant information needed during the setup procedure including setup photos and the patient's hologram as registered to the radiotherapy device. Final positioning will be made according to IGRT which is standard of care.

- **Provide a clear and concise description of the treatment, intervention, or observation to be carried out in the study:** The intervention for the study is the use of the HoloLens v2 device to aid in patient alignment. As noted in the study

description above, this device utilizes mixed-reality to display a hologram of the patient as registered to the treatment machine. The patient will be matched to the hologram by a radiation therapist who is wearing the device. The patient will not wear the device. The device will not come into contact with the patient. The sensors on the device emit only non-ionizing signals such as IR.

- **Clearly state the nature of the experimental control (placebo, other treatment, historical) or the absence of a control:** Patients who receive verification CT, each patient will have their own control represented by the verification CT acquired without the use of holographic alignment. During the use of MixRT during patient setup, each patient will also have their own control represented by the sub-set of fractions where data is collected but holographic alignment is not employed.

- **Describe any randomization procedures:** Randomization is included during the use of MixRT guided patient setup where the patients are segmented into two groups. The order in which holographic alignment is introduced into the course of treatment is reversed for the two groups. The purpose is to control for setup variation which typically decreases after the first few fractions of treatment.

- **Describe completely all physical examinations, blood tests, x-rays, any special tests or procedures, surveys, questionnaires, and/or observations that will be used to obtain information about subjects:** No additional tests will be done that are outside the radiotherapy workflow. The study does include an increased utilization of specific aspects of the radiotherapy workflow, namely addition CT and CBCT acquisition.

- **Describe who will be responsible for obtaining the information and in what type of setting the information will be obtained:** Data will be collected during the course of radiotherapy treatment and during the acquisition of verification CT scans. Either the study investigators or trained radiation therapist will be responsible for collecting this data. The PI will serve as the primary data manager based on familiarity with the data.

- **Describe how these activities will answer the study questions:** The main question we seek to answer is whether mixed reality visualization is a feasible method for patient alignment in radiation therapy. To answer this question, we will collect relevant clinical data including registration error, registration time, and the amount of imaging used during the registration process. While we are not yet attaching power or a formal sample size structure to this data, we believe this data work together as our primary endpoints to answer the question of feasibility.

- **Clearly describe the procedures you will use to protect the privacy of subjects and ensure confidentiality of all data and study records including hard copy and computer files:** For a given patient, we will export from our treatment planning system a DICOM structure and plan file. This data will exist within computers

controlled by the study investigators and stored in protected folders. This type of information is commonly exported and temporarily stored for clinical operations. The files will be converted to a new file type that is readable by the HoloLens v2 device. The data will then be uploaded to the HoloLens v2 device. The HoloLens v2 is basically a wearable computer system. Data encryption is enabled on the HoloLens v2 by default using BitLocker. The HoloLens v2 device will remain on-site (UFHPTI) at all times and be securely stored when not in use.

Data collected during patient setup, e.g., setup time, registration shifts, number of CBCTs, will stored in an excel spreadsheet located in a secure folder on computers controlled by the study investigators. Each patient will be given a study ID to anonymous the data stored in the excel spreadsheet.

- **Discuss how research interventions differ from standard therapies, and alternatives to participation in the study, if they exist:** As noted in the background section, IGRT, SGRT, and 3-point alignment are the mechanisms used for patient alignment in breast radiotherapy. The current method using mixed-reality improves on these approaches by allowing natural viewing of the patient and a reference surface derived from their CT scan. We believe by using our system, patients can be aligned faster and with less utilization of ionizing radiation.

7.) Statistical Analysis:

- **Describe the statistical analysis you will use to analyze your data including sample size and associated power:** This is a pilot study. The choice of sample size is one of practicality.

- **Briefly outline the data analyses that are proposed and who will do the analysis:** Mean estimates and associated 95% confidence intervals will be attained for registration error and registration time for the mixed reality and standard of care methods and the paired difference of the two techniques. We will assess feasibility using a paired T-test. The hypothesis is that the mean paired differences across all measures of registration error and registration time are not significantly different than 3 mm and 5 minutes, respectively. The number of CBCTs collected as part of the registration process will be assessed subjectively since count data are not truly continuous. This analysis will be carried out by the study investigator and study statistician.

- **Describe your plan for conducting interim analysis. What stopping rules are in place?** N/A.

8.) Data Safety and Monitoring Plan:

- **Is there a Data Safety Monitoring Board (DSMB) or an oversight committee for this research project?** The UF Data Integrity & Safety Committee will provide oversight through annual monitoring.

- **Describe your plans for monitoring study conduct and subject safety:** The Principal Investigator will be responsible for monitoring.

- **Provide Information about the DSMB or committee including who is on the committee, how frequently will the committee meet, and when will you get information from the committee:** N/A

9.) Possible Discomforts and Risks:

- **Identify all discomforts and risks (physical, psychological, social, and/or economic) study participants may encounter, listing more common risks first and less common risks separately:** Based on prior study utilizing anthropomorphic phantoms, we anticipate that our patient alignment system will ultimately reduce setup time and the number of X-ray images used for alignment. We have yet to try this with patients, however, and there is a risk that it could marginally increase setup time, at least during the initial implementation.

  The study also involves an increased utilization of CT and CBCT in order to quantify the difference in registration accuracy when using the mixed-reality method. Patients who receive a verification CT will receive 1-2 additional CT scans. During MixRT guided patient setup, patients will receive at least 0-10 additional CBCT scans (depends on modality). While it is routine for breast 3DCRT to employ planar kV imaging weekly as opposed to CBCT, it is not uncommon to utilize daily CBCT for difficult cases. Daily CBCT is also used for all cases where an IMRT approach is utilized. The dose from CBCT imaging is orders of magnitude less than the dose received during treatment, (approx. 1-2 mGy vs 45 Gy). According to the linear-no threshold model, there is non-zero risk of developing a radiation induced malignancy from any level of ionizing radiation. We believe the marginal increase in risk incurred through participation in this study, however, is low based on the limited amount of radiation delivered during CT and CBCT acquisition and the fact that these patients are already receiving high levels of ionizing radiation as part of their cancer treatment.

  Only those Adverse Events related to the use of the HoloLens will be reported.

- **Identify potential financial risks study participants may incur:** None

- **Indicate any procedures, medications, tests, or therapies that study participants (or their insurer) will have to pay for. Are these considered standard therapies or are they specific to the research study?** None

- **Describe procedures to protect against or minimize potential discomforts and risks:** For individual cases, we will discontinue the use of the holographic alignment system if setup time is increased by more 30% during two consecutive sessions.

- **Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be gained:** We believe the marginal increase in risk of developing a radiation induced malignancy incurred through participation in this study is low. The immediate benefit to the study participants is that the additional CT and CBCT may improve the accuracy of their setups for instances in which these images are acquired. The long-term benefit for patients outside the study cohort will be the knowledge gained about the clinical use of mixed-reality for patient setup. We believe this method can improve the patient setup and alignment process and will eventually make the process faster and with the use of less ionizing radiation.

10.) Possible Benefits:

- **Describe the potential benefits to subjects or to others that may be reasonably expected to result from the research:** Based on prior study utilizing anthropomorphic phantoms, we anticipate that our patient alignment system will ultimately reduce setup time and the number of X-ray images used for alignment. By reducing setup time, we increase patient comfort and minimize the risk of patient movement during treatment. By reducing the number of X-ray images used, we reduce the amount of ionizing radiation the patient receives.

- **If there is no potential for direct benefits, you must state this in the Informed Consent Form:** Due to the fact that CBCT will be utilized for all study fractions, patients may benefit from a more accurate setup if CBCT was not standard of care for their treatment approach.

- **Will the research study benefit future populations?** Yes, possibly.

11.) Conflict of Interest:

- **Describe any real or potential conflict of interest you or any other investigators may have with regard to this research project:** The principal investigator has filed a provisional patent application in coordination with UF Innovate related to concept of aligning a patient via hologram.

- **When deciding whether a conflict may exist, consider the following:**

    - **Do you, the University of Florida, or any of the sub-investigators hold a patent or license for any material, object, or process used in this project?** No

    - **Is a patent or license pending or under consideration or is there any intention to file a patent application at a later date?** Yes.

    - **Do you, the University of Florida, or any of the sub-investigators own stock in the company sponsoring the project?** No

- **Do you or any of the sub-investigators give presentations for or serve as a consultant to the sponsoring company on their behalf?** No