I. INTENDED USE OF TECHNOLOGY

An active arena for technological advancement in radiation oncology treatment delivery has focused on the motion inherent in target structures and normal organs in their proximity. These structures are subject to targeting uncertainty due to motion not adequately represented on planning computer tomography (CT) scans that may occur both during (intrafraction) and between (interfraction) daily treatments. To address some of these localization uncertainties, devices that may be implanted in the organ or volume of interest and tracked during and between treatments have been developed.

For example, several studies have suggested that the prostate gland is subject to significant intrafraction motion during radiotherapy\(^{(1-7)}\). Unlike respiration motion, this motion is neither periodic nor predictable, with patterns ranging from continuous target drift, to transient and persistent excursions, to high frequency motion\(^{(8)}\). A recent technology initially developed to address these issues, the Calypso 4D Localization System has made it possible to monitor intrafraction prostate motion on a real-time basis.

Additionally, with the advances over the last decade (and more so within the last few years), in Intensity Modulated Radiation Therapy (IMRT), both intra- and extra-cranial stereotactic radiosurgery (SRS)/radiotherapy(SRT) and stereotactic body radiotherapy (SBRT), and Image-Guided Radiation Therapy (IGRT), it has become critical to position patients in the treatment positions precisely and reproducibly. The use of noninvasive and nonionizing systems presents an attractive solution. The goal of this report is to provide a review of emerging nonionizing technologies designed to continuously localize the tumor, patient, or a surrogate, (> 4 Hz). Specifically, this report considers the Calypso 4D Localization System as well as the RadioCameras and the AlignRT system.

Some of the published studies utilize ‘in-house’ hardware and software designs with differing approaches to acquire both static and real-time patient positions. These studies have also confirmed that with these systems positioning errors can be reduced and verified in many treatment sites such as the pelvis, central nervous system, head/neck and breast/thorax. Similar to angiography where two images are subtracted from one another
to create a new image, the optical techniques include the utilization of difference imaging (video) in a two-dimensional coordinate frame\(^9\), three-dimensional (3-D) photogrammetry/optical stereoscopic scanning and laser interferometry evaluating surface morphologic changes\(^{11-16}\), and infrared optical 3-D tracking with/without tissue markers both as an independent alignment system or with x-ray alignment\(^{17-25}\) (e.g. Novalis Tx/ExacTrac X-ray). For the purposes of this discussion, only the completely independent (nonionizing) systems were evaluated. Systems integrated with stereoscopic X-rays will be evaluated in a subsequent report. Furthermore, systems utilizing optical tracking primarily as input information for motion management and not target localization (e.g., Varian Real-time Position Management (RPM) system, the Accuray Synchrony Respiratory and XSIGHT Lung Tracking Systems) will be addressed in a subsequent report. Presently, we are aware of only three innovative systems which are both FDA-approved and commercially available; the Calypso system, RadioCameras and AlignRT. This report summarizes these three systems and their current results.

II. DESCRIPTION OF THE CURRENTLY MARKETED DEVICES

A. Calypso 4-D Localization System

The major components of the Calypso 4D Localization System are: (1) a mobile AC electromagnetic console; (2) a receiver array; (3) three ceiling-mounted infrared optical cameras and a hub, all located in the treatment room; (4) wireless transponders (Beacons); and (5) a tracking station located in the control area (Fig. 1)\(^{26}\). The system uses an array of AC magnetic coils to generate a resonant response in implanted transponders that is subsequently detected using a separate array of receiver coils. The transponders are approximately eight mm in length and two mm in diameter (see Fig. 2), and are inserted within the prostate gland under ultrasound guidance in a manner analogous to a needle biopsy\(^{26}\). Typically, three beacons are implanted, though the system can use as few as two implanted beacons. The spatial coordinates of the beacons are identified on a treatment planning CT, and the offset between the beacons’ centroid and the intended (treatment planning) isocenter is reported at a frequency of 10 Hz (or every 0.1 second). The location of the array relative to the linac isocenter is defined
through a calibration procedure, and the array itself is tracked in the treatment room using the three ceiling mounted infrared cameras (see Fig. 1).

The Calypso 4D Localization System is used in the clinic as follows: (a) The patient is first localized using the skin marks and room lasers, (b) The Calypso system is subsequently used in localization mode by moving the couch in three dimensions until offsets (between the beacon-defined centroid and the treatment planning isocenter) read $0.0 \pm 0.5$ mm. This process establishes the patient’s initial treatment position and usually takes less than two minutes to perform. (c) During treatment, the Calypso system continuously monitors and reports the offset (in three dimensions) between the actual and the desired isocenter locations. Individual facilities may choose to use action criteria (tolerances) to re-localize the patient or interrupt treatment based on the observed intrafraction motion. For example, during the course of the initial clinical evaluation, various facilities chose different criteria. These criteria included: no action taken, regardless of motion observed or treatment interruption during delivery if the motion exceeded a specified threshold (e.g., a threshold of three mm for a duration of 30 seconds continuously).

Although pre-clinical studies using the Calypso System for breast and lung cancer applications have recently begun, this report will focus on the published literature as it applies to prostate localization since this represents the only currently FDA-approved indication.
1. Device Operation

When a patient is scheduled to undergo prostate radiation therapy using the Calypso 4D Localization System, the localization process begins when three transponders are permanently implanted into the prostate under transrectal ultrasound guidance. Approximately four to fourteen days later the patient undergoes thin-slice CT simulation. Target volumes are delineated and a radiation treatment plan is created. Transponder coordinates on the CT scan relative to the treatment plan isocenter are determined and entered into the Calypso system.
The Calypso system can be operated in either localization (interfraction monitoring) or tracking (intrafraction monitoring) mode. For localization, the patient is placed on a treatment table and aligned with skin marks and treatment room lasers. Either supine or prone patient positioning is possible, but immobilization devices (e.g., a belly board) can not contain carbon fiber as this interferes with the signal from the transponder. Next, the Calypso receiver coil array is placed over the patient and its position relative to the isocenter, as well as the transponder position relative to the array, is detected. Manufacturer-provided software sends an output of the transponder position relative to the isocenter (the offset) to the tracking station. Radiation therapists at the control panel can then align the patient to the machine isocenter within desired guidelines. After alignment is complete, real-time intrafraction tracking of the transponders can be performed by operating the system in tracking mode. If the target moves beyond pre-specified motion thresholds, the radiation therapist can take appropriate corrective action.

2. Installation and Calibration

Installation of the Calypso 4D Localization System is performed primarily by the Calypso engineers with assistance from a radiation physicist and typically requires approximately three to seven days. Three infrared cameras are permanently mounted in the treatment room using customized ceiling bolts and camera mounts and the cameras, console, and tracking station are connected to the system’s network hub\(^{26}\).

Commissioning of the system requires calibration and acceptance testing. A manufacturer-provided optical calibration procedure aligns the optical system to the treatment machine isocenter. Acceptance testing includes system safety tests as well as performance measurements. Performance testing involves several measurements with a localizer phantom embedded with three transponders at known distances to determine the ability of the system to accurately (and precisely) determine the absolute transponder positions and offsets. Other acceptance tests are performed to verify the functionality and accuracy of the optical localization system within the room.

Routine quality assurance (QA) of the Calypso system is performed on a daily and monthly basis. Daily QA is performed before the system is used for patient treatments. It entails verification of the positions of the transponders within a vendor provided phantom.
against their calibrated values. The daily QA test is estimated to take 5-15 minutes. Monthly QA (typically performed by a radiation physicist) is comprised of a camera calibration procedure and subsequently a measurement of the known transponder positions within a phantom. The purpose of the monthly QA is to ensure that the camera systems are able to localize the transponder array in the room coordinate system accurately, and that the array is able to detect the transponder positions within the patient coordinate system accurately. In one study, repeated monthly calibrations showed that the system stability was within one \( \text{mm} \)\(^{28}\). The monthly QA procedure requires approximately 30-45 minutes. Other tests, such as the positional stability of the transponders over time\(^{29}\), are also helpful in evaluating the accuracy of the system, and could provide an indication, if necessary, to acquire additional imaging\(^{30}\).

### B. RadioCameras

Wagner *et al* performed an excellent review of the RadioCameras system, commercially available with the trade name RadioCameras. The system is specifically designed for intracranial radiosurgery with high-precision patient positioning. The system includes two, two-dimensional charged couple device (CCD) cameras and a rigid array containing four infrared, passively reflective markers. The cameras are rigidly mounted in the ceiling of a treatment room and interfaced with a personal computer. The infrared markers fixed to the array are also connected with the patient by rigid attachment of the array to a maxillary bite-block. The CCD cameras intercept the infrared light reflected from the markers, thus localizing the positions of the markers at a frequency of \( \sim 15 \text{ Hz} \). The camera system must be able to identify at least three of the four markers to determine the array’s position with six degrees of freedom (translations and rotations). The software application will then display the vector displacement (with 0.1 mm precision) of the patient, along with the rotations (yaw, pitch, and roll with 0.1 degree precision).

#### 1. Device Operation
Clinically, the relationship between the markers on the array and the treatment isocenter of the patient is established using the treatment planning CT, where the treatment isocenter is determined and the coordinates of the infrared marker positions in relation to the treatment isocenter are fixed. It is generally assumed that the treatment isocenter is rigidly related to the positions of the markers. Therefore, the desired treatment position for a specific patient in the treatment room is linked to the desired positions of the infrared markers in the linac coordinate system. A calibration procedure is required for the RadioCameras system to transform the marker’s position in the camera coordinate system to the treatment machine’s coordinate system (with its origin at isocenter). When a patient with a bite-block is set up for treatment, the RadioCameras system applies a geometry pattern search algorithm to detect the position of the center of each marker and computes the necessary translation and rotational shifts to co-register the treatment planning isocenter with the machine isocenter. The system displays the detected marker positions and the calculated shifts approximately 15 times per second.

For frameless SRS/SBRT of head and neck (H & N) or central nervous system (CNS) treatments patient flow begins with an initial simulation where a custom bite-block is attached to the RadioCameras system’s passive IR array. Developing a relationship with a prosthodontist, who has experience making obturators and other devices to reconstruct palate and other surgical defects, can help with customization. The bite-block provided by Varian Medical Systems can then be modified for a very precise, immobile and patient specific fit. Generally, the patient needs to have the majority of their upper teeth, or very tight fitting dentures for the system to work. Edentulous patients can be problematic.

After the bite-block is created, the patient undergoes CT simulation. A thermoplastic mask is created and a hole is pulled open while the thermoplastic is still hot (if the entire head is to be immobilized). The custom bite-block is placed into the mouth prior to simulation. After the plan (FastPlan, Varian Medical Systems) is finished the data is sent to the RadioCameras system. The array balls are localized manually on the computer screen. Tolerances within 0.4 mm are usually achievable by experienced personnel; this again is dependent on voxel resolution achieved during acquisition of the CT dataset.

The patient is next brought to the linear accelerator, where he/she is registered in 3-D space using the passive infrared system. The entire RadioCameras system consists of a
ceiling mounted optical position sensor that senses infrared reflections from the optical reference array attached to the patient. The positions of these reflections are then input to a workstation that outputs information regarding the patient’s position. The system generates coordinate shifts: the couch is adjusted for the x, y and z coordinate offsets (and the stereotactic head-holder can adjust for tilt and spin). With a secure bite-block and a compliant patient, the system is robust and reproducible.\(^{(20)}\) If the patient moves his mouth or lips or grinds his/her teeth, the system will show an error and the patient will need to be repositioned. A noncompliant or difficult patient can add significant time to setup and treatment. During treatment, the patient is monitored continuously and if the patient moves, he/she needs to be repositioned. Additionally, for each couch move, the RadioCameras system position must be re-zeroed.

2. Installation and Calibration

A calibration procedure is necessary to transform the coordinates of the inherent RadioCameras system to the linear accelerator’s coordinate system. A calibration apparatus consisting of an array of infrared markers is placed at a defined location relative to the machine isocenter. The positioning of the calibration jig so that its center is precisely at the radiation isocenter is critical and challenging. The vendor provides a gantry-mounted and table-top calibration jig; in-house solutions are required to validate the jig’s positioning with respect to radiation isocenter if \(\leq 0.3\) mm positioning is desired. Once positioned, the passively reflective infrared markers of the calibration apparatus are optically detected by the camera system establishing the transformation between the camera and the machine coordinate system whose origin is at isocenter. An end-to-end test is recommended to verify the accuracy of the entire treatment procedure using the optical tracking system for treatment positioning. An effective end-to-end test includes imaging and planning treatment on a phantom, which contains a regularly shaped target (a sphere) at a known location. If the test target is radio-opaque, analysis of portal images of the radio-opaque target can be used to define the accuracy of treatment positioning.

Since the RadioCameras system utilizes the planning CT to establish the relationship between the positions of infrared markers and the patient specific treatment isocenter, a potential error is introduced, referred to as the “mean registration error”. It is the
difference between the CT defined geometry of the markers and the known geometry of the markers, mostly due to the finite CT voxel sizes. The mean registration error is approximately 0.3 mm in the phantom test, and less than 0.5 mm in most clinical situations.

Additional sources of uncertainty can exist. Loss of reflectivity of the markers can result in the center-of-mass of the marker being inaccurately identified. Markers are attached to the array by metal posts, which when bent cause inaccurate localization of the array. The camera system’s accuracy diminishes as the radial distance of the array from isocenter increases. All of these uncertainties should be characterized for a given system and routine quality assurance of the array is appropriate. Periodic end-to-end testing, including applying known transformations to a phantom, is also appropriate to verify maintenance of sub-millimeter positional accuracy.

During patient setup and treatment, the RadioCamera system also displays overall vector misalignment (the root mean square of three translational misalignments). For intracranial stereotactic radiotherapy, 0.3 mm vector misalignment and 0.3 degrees of rotational misalignment about each axis have been accomplished.\textsuperscript{(31)} During treatment delivery, if the patient moves more than the threshold (<0.5 mm), the treatment can be interrupted until the patient’s position is corrected. This procedure can be repeated for each treatment field.

C. AlignRT

The AlignRT system consists of two imaging pods and analysis software running on a standard personal computer with a two-channel frame-grabber card. Each pod consists of two charge-coupled device (CCD) stereo cameras, a CCD texture camera, speckle flash with lens, a clear light flash without lens and a speckle projector as shown in Fig. 3. The two camera pods are mounted in the ceiling of the treatment room (or simulation room), and each covers approximately 120 degrees of axial body surface from the midline to posterior flank of the body. The stereo cameras acquire topological data of interest of the patient surface. The projected speckle supplies a unique pattern over the smooth patient surface, allowing a precise match of two stereo images. Data from both pods are merged to form an integrated surface model of the patient. The six cameras from the two pods are
calibrated relative to the linac coordinate system by a procedure using a special calibration plate with a printed grid. A reference surface can be obtained either during simulation or the first day of treatment while the patient position is confirmed with a radiographic technique (e.g., cone beam CT or portal images). If performed daily, this approach informs the user of the patient’s position relative to the one radiographically confirmed. Alternatively, the CT-based surface can be used as the reference surface, which requires transformation from the CT coordinates to the camera coordinates. This approach provides patient position information relative to that assumed when designing the treatment planning study. During treatment, the daily-acquired patient surface is registered to the reference surface using rigid body transformation, minimizing the distance between the surfaces, which include the user defined region of interest. The registration process yields treatment position adjustments in six degrees (translation and rotation) that maximize the congruence of the two surfaces. The AlignRT system assumes that the user defined surface is rigidly related geometrically to the treatment isocenter.

Fig. 3. The camera pod is shown at the top. The imaging system includes two camera pods directed towards the patient (shown middle bottom). The data from the two cameras are merged creating surface images (shown lower left bottom).
1. Device Operation

The system can be used in two principal modes, a single-frame mode and continuous mode. In the single-frame surface acquisition mode, two flashes are illuminated, one with the speckle pattern and one without speckle. The latter flash enables acquisition of textured images. In the continuous mode, the speckle pattern is projected continuously while acquiring image data at 6.5 frames per second. This mode allows for real-time monitoring of surface motion due to breathing, or for respiratory-gated image acquisition.

For accelerated partial breast irradiation (APBI) or conventional breast treatments, the patient flow begins with a standard CT-based simulation with immobilization on a breast board. The patient setup is initially determined by tattoos (and radio-opaque bb’s) marked at the time of CT simulation. This allows standard laser and portal film alignment of the patient to the isocenter on a daily basis. During the time of the first treatment session on the linac (or in the simulator room with a second imaging system) a reference surface model is acquired (or acquired from the CT data set). As mentioned above, the imaging system includes two camera pods suspended from the ceiling which triangulate a given position; see Fig. 4. The data from the two camera pods are then merged in a 3-D calculation process to form a single 3-D surface topographic image. An initial region of interest is chosen (10-12 cm over the tumor bed in APBI but can be as large as needed) to compare to daily 3-D images acquired after the patient is set up conventionally. The system then compares the reference to the daily image and provides couch offset values to align both images to within millimeter resolution.

The AlignRT images are acquired quickly (~10 sec) and the calculation of displacement coordinates are rapid. A good immobilization device (especially in regards to arm positions) may be necessary to obtain reproducible breast surface topography. Variability can be introduced if regions of the patient’s anatomy are visible by only one of the two cameras (i.e., areas of the breast and supraclavicular region).
2. Installation and Calibration

Aligned by the projected light field from the linac, the calibration plate is positioned on the treatment couch at five specific couch and gantry positions. At each position and for each camera, four specific points in the grid plate image are identified by the user to specify the plate origin relative to the machine isocenter. After completion of this calibration procedure, the calibration software provided by the vendor establishes a correlation of the system’s camera coordinate system to the linac coordinates. After initial system calibration, the system is verified daily by a verification procedure that is similar to the initial system calibration except only one of the four plate positions is checked. The time required for full system calibration and daily verification is about 10, and three minutes, respectively. The calibration verification could fail if the adjustable threshold at the match-line from two stereo images exceeds one mm (personal communications). The approximate time for registration to generate new couch
coordinates is less than 30 seconds, based on initial clinical experience in alignment of 26 breast treatment setup procedures.

Bert et al.\(^{(11)}\) conducted a comprehensive evaluation of the AlignRT system. They reported that the system stability over a period of 57 hours was better than 0.5 mm. Compared to known couch shifts of a phantom, the maximum standard deviation was 0.75 mm for the three translational degrees of freedom and less than 0.1° for each rotation. Using the CT-derived surface as a reference surface model, the tested root-mean-square (rms) of the distance between the surfaces was 0.65 mm. With the known motion trajectory, the motion trajectories measured by the system were compared to another established system (Varian Medical System’s RPM™ system). The standard deviations of the differences to the known trajectory were 0.15 mm and 0.04 mm for the AlignRT system and the RPM system, respectively. Because of low frame acquisition rate of 6.5 Hz, rapid motion trajectories can be under sampled. These reported accuracy and precision values are based on measurements of a rigid phantom. Caution should be exercised when the alignment region involves great soft tissue deformation because it may not be approximated with the rigid body assumption.

III. DESCRIPTION OF PATIENTS POTENTIALLY BENEFITING FROM USE OF TECHNOLOGY

It seems intuitive that the use of “continuous localization technologies” would be implemented hand-in-hand with the use of advanced radiotherapy planning and delivery techniques (eg., IMRT, SBRT, SRS, etc.). The ability to conform the radiation dose distribution to the target(s) of interest while sparing surrounding normal tissues has the potential to reduce the margin for error with respect to localization uncertainty. The inability to localize appropriately may result in a geographic miss of the intended target tissues. The use of continuous localization technologies also has the potential to reduce normal tissue side effects as well as improve outcome due to the inaccurate utilization of advanced delivery techniques.

Tumors located in the pelvis, abdomen and thorax are subject to motion during treatment caused by respiration, inherent bowel mobility and peristalsis, and cardiac motion. This motion is often accounted for by applying a margin to the target of interest
to encompass the target’s spatial variability. However, treatment of this margin results in the delivery of unwanted dose to normal tissues when the target is not occupying a given position. The use of real-time tracking techniques may allow for a reduction in this margin and thus has the potential to reduce the morbidity associated with unnecessary dose to surrounding normal tissues. There is potential for all patients undergoing radiotherapy to the aforementioned body sites to benefit from real-time tracking techniques.

IV. EVALUATION/SUMMARY OF RESULTS OF EXISTING STUDIES

A. Calypso 4D Localization System

There have been several articles published on the use of the Calypso system both in phantom studies as well as in patients. These clinical studies have focused primarily on prostate cancer. In phantom measurements, Balter et al. (26) observed sub-millimeter localization and tracking capabilities of the Calypso system, with values that remained stable over prolonged periods of time. These results have been updated recently by Litzenberg et al. (29). Willoughby et al. (30), in reporting on the first human use of the system, evaluated the localization accuracy of the Calypso system relative to radiographic localization, and assessed its ability to track prostate motion in real-time. Their findings indicated significant intrafraction prostate motion (greater than 10 mm) in 2 of 11 patients (30). However, the Calypso system demonstrated comparable (within 1 mm) isocenter localization accuracy as compared to X-ray localization procedures (30). Kupelian et al. (6) reported on Calypso-based localization and continuous real-time monitoring of the prostate gland on a multi-institutional trial consisting of 41 patients treated at five institutions. They found differences between skin marks versus Calypso alignment to be greater than 5 mm in vector length in more than 75 percent of all fractions (6). They also observed that individual patients exhibited displacements of 5 mm or more, lasting at least 30 seconds, in 56 percent of all fractions (6). Using the criterion that 90 percent of patients receive 95 percent of the prescribed dose within the PTV,
Litzenberg et al.\(^{(32)}\) showed that margins required to accommodate intrafraction motion were approximately 2 mm in all directions, assuming that Calypso-based localization was performed for each fraction prior to the start of treatment. In the absence of Calypso-based localization these margins are approximately 10 mm, indicating that a substantial reduction in margins is possible when daily alignment is performed using the Calypso system\(^{(32)}\). A recent study on dosimetric consequences of intrafraction prostate motion, showed that significant reductions in treatment planning margins are possible without compromising target dose coverage, attributed primarily to the significant reduction in the setup uncertainty (and hence setup margin) when Calypso is used for daily localization\(^{(33)}\).

The efficacy of Calypso localization among patients receiving androgen ablation therapy is not well-defined. One small comparative study of 41 patients in which 14 received neoadjuvant and concurrent androgen suppression found that the implanted electromagnetic markers maintained a stable geometry within the prostate gland over time, both in patients treated with androgen deprivation and in patients treated with radiation therapy alone\(^{(34)}\).

The impact of the electromagnetic detector array on the quality of radiation beams and portal images is of potential concern, as the array is placed several centimeters above the patients during treatment to detect signals from the transponders. Preliminary research demonstrated that the increase in skin dose attributable to the array was “within acceptable clinical limits\(^{(35)}\)” though this was not quantified. Additionally, researchers found that attenuation of the beams was less than 0.5 percent for radiation incident normal to the array; no comment was made regarding oblique or tangential beams\(^{(35)}\). Finally, the researchers stated that “portal image quality due to presence of the array in the beam path was similar to that of patient support devices, such as nylon-strung tennis racquet table inserts\(^{(35)}\).”

Another technical challenge is that of MRI compatibility with the transponder beacons. Calypso Medical Technologies tested the transponders according to ASTM F2503-05, and found them to be MRI safe\(^{(36)}\). ASTM F2503-05 [American Society for Testing and Materials: Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment] defines "MRI Safe" as "an item that
poses no known hazards in all MR environments." The Instructions for Use\(^{(36)}\) includes a precaution for planned magnetic resonance imaging (MRI) of the prostate after the beacon transponders are implanted. The statement reads as follows: "Beacon transponders are MR safe; however, when imaged with MRI, a local image artifact will occur in tissue adjacent to the implanted transponders\(^{(36)}\)." This radiographic artifact can extend up to 2 cm from the transponder\(^{(36)}\). An example is shown in Fig. 5, where a local but pronounced radiographic artifact surrounding the transponders is apparent.

![Artifact from transponders](image.jpg)

**Fig. 5.** Fast spin echo (FSE) T2-weighted MRI of patient with Calypso transponders implanted in the prostate. Provided by Mark K Buuyounouski, MD, MS, Fox Chase Cancer Center.

Researchers have also performed introductory studies analyzing possible application of the Calypso localization system to head and neck cancer patients. In one such study, a dental prosthesis was cast from a volunteer and some of the teeth were filled with dental amalgam. The prosthesis was placed under the detection array, adjacent to three transponders, and the resultant measurements were compared to those taken without the presence of the dental prosthesis. Despite the presence of the amalgam, the system could localize the transponders up to 20 cm from the array\(^{(37)}\). Placement of the transponders within a mouthpiece does not increase backscatter dose to overlying oral mucosa\(^{(38)}\).
B. RadioCameras

An optical (infrared) guided bite-plate system was initially developed at the University of Florida in the 1990s\(^{(18)}\). This system decouples the immobilization and localization functions and has been shown to provide high accuracy. The system has been utilized mainly for H & N and CNS malignancies and is shown in Fig. 6 and 7. With active light emitting diodes coupled to an ultrasound transducer, this infrared localization system has also been utilized for extra-cranial stereotactic localization\(^{(39)}\).

The initial clinical study of this technology focused on stereotactic radiosurgery for CNS malignancies at University of Florida\(^{(40)}\). Sixty patients (both with benign (e.g., meningiomas) and malignant (e.g., PNET tumors) received a total of 1426 treatments using this frameless SRS system. At 11 months follow-up, three patients were found to have recurrence of their malignant disease and minimal side effects from the treatment. All low-grade astrocytoma patients had marked involution of the tumor and, of the 36 percent which had post-treatment edema, all had eventual resolution of the edema. The system proved to be robust with a misalignment vector error of 0.18mm; the tolerance limit of 0.3mm and 0.3 degrees was achieved in every case (and accomplished within 15 minutes for a daily patient treatment). This accuracy was determined to rival frame-based systems. Two follow-up studies have further evaluated this technology\(^{(31, 41)}\). The most recent study followed 64 patients who received frameless stereotactic radiosurgery for intracranial metastatic disease. Some of the patients were treated upfront and others for progressive disease after initial resection or whole brain radiotherapy. Tumor and dose characteristics for these treatments confirmed a median of two metastatic sites with two isocenters and a median dose of 17.5 Gy. With a median actuarial follow-up of 8.2 months, ultimate local control was 88 percent. Median time to progression and overall survival was 8.1 months and 8.7 months, respectively. The authors noted that these
results were similar to outcomes with frame-based techniques. No patient had a serious (Grade 3 or higher) complication.

The authors also noted some advantages and disadvantages of the system\(^{(41)}\). The advantages included: no pain or discomfort to patient, ability to perform treatment planning and treatment delivery on different days, minimal monitoring of staff with the ability to leave facility during treatment delivery and reduction of resource utilization, personnel, cost and complexity of the stereotactic procedure. The main disadvantage of the technique was noted to involve the potential for lengthy treatment times. Because of the use of conventional linac-based machines, treatment times were about 15 minutes/isocenter. Patients requiring more than four isocenters were found to be technically challenging and otherwise not good candidates because of patient fatigue during the lengthy treatment times. Highly irregular volumes and patients with poor Karnofsky Performance Scores also prevented optimal use of the system.

A final publication utilized this optically-based methodology in 10 patients with advanced head and neck cancers at the University of Wisconsin\(^{(42)}\). These patients were prospectively enrolled to determine the potential impact of traditional daily setup variations with laser alignment and immobilization mask markings. The passive fiducial arrays were mounted to the maxillary bite-tray and acted as the ‘gold-standard’. They found an average composite mean vector error of 6.97 mm +/- 3.63 mm with conventional methods. Based on these findings, the authors noted that the GTV and PTV were under-dosed and critical normal structures like the parotid or globe were overdosed utilizing IMRT with conventional daily patient alignment. They concluded that more rigorous immobilization techniques are required and that routine daily assessment of patient setup and tracking are important for delivery of high quality IMRT for head and neck cancer patients.
19. Fig. 6. The patient has an (partial) immobilization mask with the RadioCamera maxillary-bite plate mounted as shown. A) Coordinates of each marker identified on the CT scan, relative to treatment isocenter, are determined from CT. (reprinted from Ryken et al.\textsuperscript{(31)}, with permission). B) In the treatment room a workstation coupled to a ceiling mounted optical position sensor computes and display’s the transformation required to reproduce the setup from CT. (re-printed from Hong TS \textit{et al.}\textsuperscript{(42)}, with permission).
Fig. 7. A close-up view of the RadioCameras device showing the passive IR array. The optical reference array has six fiducials that can be localized in a CT scan. Four of these fiducials have a reflective surface that can be used for optical tracking. The reference array is attached to a biteplate. The custom biteplate is fabricated by placing dental impression material in an acrylic dental tray and allowing the impression material to form on the patient’s maxillary dentition. (re-printed from Ryken, et al. (31) with permission).

C. AlignRT

AlignRT, as mentioned above, uses two ceiling mounted 3-D camera units to acquire 3-D surface images (photogrammetry) and is shown in Fig. 3. During each treatment fraction the current patient position (+/- respiratory gated) is acquired repeatedly at the same point in space (and respiratory cycle) and compared to a reference image providing
new couch position coordinates. Most of the data for this system have been provided during talks or supplemental abstracts and has primarily been related to the setup of breast cancer patients (11, 43-55).

One clinical publication from Massachusetts General Hospital (MGH) used the system to assess its utility in patient setup for accelerated partial breast irradiation (APBI)(44). The accuracy of the system (in nine patients) was compared to traditional laser and portal image patient setup. Mean 3-D displacements were 7.3 +/- 4.4 mm and 7.6 +/- 4.2 mm for laser and portal image setup, respectively, as compared to 1.0 +/- 1.2 mm for AlignRT. Breathing motion data at isocenter was 1.9 +/- 1.1 mm. As a comparison, the system was used to evaluate the surface motion of the abdomen and 5.7 +/- 1.3 mm of displacement was noted. Other sites explored in abstracts noted increased accuracy in positioning the head for use in stereotactic radiosurgery guidance(47, 51).

In theory the system can be used for patient positioning regardless of treatment site (i.e., extremity for sarcoma/skin treatments). Good correlation has been noted between surface and bony anatomy(45). The practical utility of the system may be limited by skin-to-tumor positional correlation, which was investigated in one abstract for the case of APBI(48) where the registration of lumpectomy-site clip-based imaging (‘gold standard’) was compared to the skin alignment assessed by AlignRT. Both agreed within 1 mm suggesting that the surface of the breast may be a reasonable surrogate for the treatment volume.

V. IDENTIFICATION, ANALYSIS AND EVALUATION OF CONSEQUENCES OF NON-USE

The inability to localize appropriately when using advanced radiation delivery techniques may result in a geographic miss of the intended target tissues resulting in uncertainties with respect to tumor control. Additionally, a geographic miss of the target(s) generally results in the unintended delivery of high dose to healthy tissues and has the potential to result in undo morbidity.
The use of real-time tracking techniques has the potential to limit morbidity by decreasing dose to normal structures through the reduction of target margins utilized for spatial uncertainty. Not employing tracking techniques makes it imperative that these margins be applied in order to maintain treatment outcomes gained to date.

Previous localization and tracking techniques typically utilize ionizing radiation. A notable exception is the use of ultrasound although to date this usage is limited to a few tumor sites. None of the technologies evaluated in this study involve the use of ionizing radiation.

VI. FUTURE PREDICTION BASED ON TECHNOLOGY DEVELOPMENT

Given the growing popularity of dose escalation, hypofractionation, and respiratory gating and the potential improvement of clinical outcomes from each, it can be postulated that the use of real-time tracking techniques will also gain favor in the radiation oncology community. Through further research and clinical trials the Calypso system is being expanded to use in body sites outside the pelvis, which may lead to its use on a routine basis for a larger population of patients.

The use of technologies that allow the registration of patient topography with planning data for use with respiratory gating will in all likelihood flourish. Current gating systems suffer from the uncertainty of correlation of external markers with internal structure movement. It may be that the increase in the number of registration points (the body surface) will decrease these uncertainties.

There are two main areas of clinical outcomes improvement that may be expected as a result of more accurate real-time localization using these technologies. The first involves target localization, in which the treatment fields are centered on a per-fraction basis on the center of mass of the target volume itself, as opposed to stable but unrelated
bony or other anatomical landmarks. Use of unrelated landmarks requires the use of wider margins around the target volume, as described in this report, and these margins must be particularly large in the case of very mobile targets, including tumors located in the thorax and abdomen. These same tumors generally have poor outcomes overall, and this is in part due to the inability to escalate dose to large volumes of the surrounding normal tissues. Therefore the use of real-time continuous localization techniques may allow for significant reduction in margins, which will then allow for reduced normal tissue dose-volumes and subsequently dose escalation to the target volume that may indeed lead to improved tumor control. These are the next phase of clinical trials which need to be conducted to verify outcomes following the implementation of continuous localization technologies.

The second important area of potential improvement in clinical outcomes involves the reduction of normal tissue dose-volumes, which will decrease toxicity. Radiation toxicity to normal tissue is directly related to the volume of the normal tissue that receives any given percentage of the prescribed dose. This outcome is important for all treatment sites, even in the case of tumors that do not exhibit a lot of inherent motion. For example, in prostate or breast cancer, in which the tumor motion is generally less extreme than for tumors in the thorax, and in which dose escalation either is already feasible (prostate) or not indicated (breast), it is still important to minimize the dose to critical normal tissues that surround the target volumes in order to reduce acute and especially long term toxicity. Many patients with prostate and breast cancer will enjoy normal life spans after treatment, therefore the avoidance of late toxicities to the bowel,
bladder, lung and heart will contribute to quality of life and reduce the cost of post-treatment care. In addition, the feasibility of hypofractionation depends upon the ability to very accurately localize the target volume with minimal margins, as treatment of large volumes of the surrounding normal tissues would result in a higher likelihood of developing late toxicities due to the large dose per fraction used in these regimens. Hypofractionation therefore is highly dependent upon technologies that allow precise and real-time target localization, in order to reduce normal tissue dose volumes. While the demonstration of reduced late toxicity may take many years to demonstrate in clinical trials, these outcomes should also be examined. In the interim, patients may well benefit from the use of continuous localization techniques as a component of image guided radiotherapy, and their use should be considered one method for achieving greater accuracy and precision.

REFERENCES


36. Instruction Manual: Beacon Care Package for Prostate, Calypso Medical Technologies, Inc. LBL0002-001.
