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Image Guided Radiation Therapy

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Abstract

With increasing emphasis on reducing the volume of radiation therapy fields while maintaining or improving precision of treatment and reducing radiation-related normal tissue toxicity, treatment position verification and correction before delivering radiotherapy had gained major importance. A variety of techniques have been developed that can accomplish this goal with aplomb, albeit each with its own set of limitations. The best method that eliminates uncertainties in treatment without a huge cost remains to be defined, but it is clear that carrying out "high precision radiotherapy" without periodic image guidance is as accurate as shooting in a dark room. This review discusses the concept of image guidance in radiotherapy, various techniques available along with expected benefits and pitfalls of these systems.

Keywords: Radiotherapy; IGRT systems; Electronic portal imaging devices

Introduction

Imaging is an integral component of modern day radiotherapy. 3D data acquired using volumetric CT, MR and angiographic studies are used for planning highly conformal radiotherapy with shaped beams in isocentric or non-isocentric geometry. Routine use of newer techniques such as intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) using a host of delivery methods, has enabled the reduction of safety margin around the target volumes thus allowing for reduced normal tissue doses without compromising delivery of tumoricidal doses. However, a great deal of uncertainty exists in accurately defining the position of radiotherapy targets during the process of fractionated radiotherapy, both during a given fraction and between consecutive fractions, thus highlighting the need to develop and implement strategies to measure, monitor and correct these uncertainties. This need has led to evolution of various in-room imaging technologies which help evaluate and correct the setup errors, anatomic changes related to weight loss or deformation or internal organ motion related to respiration, peristalsis or rectal/bladder filling. This review summarizes the concept of image guided radiation therapy (IGRT), the various existing techniques for IGRT delivery as well as the benefits and shortcomings thereof.

IGRT – The Concept

Unlike other forms of local therapy such as surgical resection where the target in question can be visualized and handled under direct guidance, traditional radiation therapy techniques are inherently fraught with the disadvantage of making quite a few assumptions. The 3D image dataset acquired at simulation is a single time snapshot of the tumor, its relation to normal structures and the patient shape and position, and this model is used for plan development and dose calculation. A lot of information is fed into the planning system including assumptions of microscopic spread around the visible tumor, expected range of internal organ motion and setup errors. We then proceed to treat the actual patient with the belief that nothing would have changed since the time of simulation and the patient anatomy on any given day would be in keeping with the original snapshot. However, the assumption that the calculated doses would actually match those delivered through each fraction or through the entire radiation therapy course is grossly in error. Wider margins are taken around the targets to assure that our assumptions do not compromise the dose delivered to the intended target, thus including a large volume of normal tissues in the irradiated volume as well. IGRT provides a method for capturing this information in the form of serial "snapshots" taken through the treatment course, and is a means of verifying accurate and precise radiation delivery. In simple terms, the IGRT process ensures that the delivered treatment matches the intended treatment in accurately targeting the tumor while minimizing 'collateral damage'. Changes to the composite delivered dose and their impact on disease control as well as toxicity may be minimized by use of appropriate localization devices and planning target volume (PTV) margins. Occasionally, re-planning may be required if gross deviations beyond predetermined tolerances are observed [1-3].

IGRT allows assessment of geometric accuracy of the 'patient model' during treatment delivery. It provides a method whereby deviations of anatomy from initial plan are determined and this information is used to update dosimetric assumptions. Correction strategies may include daily repositioning to register patient position in accordance with the base plan or recalculation of treatment delivery in real time to reflect the patient's presentation during a given fraction. This philosophy of re-evaluating treatment and accounting for the differences between actual patient anatomy on a given day and the snapshot of planned treatment is known as adaptive radiotherapy [4]. The eventual goal is to reevaluate and in certain situations redefine daily positioning for treatment to keep it on the same track as the intended treatment. Future applications may include dose titration for maximizing effect or mitigating side effects.

Errors and Margins

An error in radiotherapy delivery is defined as any deviation from intended or planned treatment. A great degree of uncertainty is inherent to radiotherapy practices and may be in the form of mechanical uncertainties related to treatment unit parameters such as couch and gantry motion, patient uncertainties related to ability to lie comfortably in a certain position and cooperate during the treatment time, geometric uncertainties related to position and motion of target, and dosimetric uncertainties. IGRT deals with the *geometric* uncertainties, which may be either intrafractional or interfractional [5,6].

Both inter- and intrafractional uncertainties may be a result of a combination of systematic and random errors.

A systematic error is essentially a treatment preparation error and is introduced into the chain during the process of positioning, simulation or target delineation. This error, if uncorrected, would affect all treatment fractions uniformly. A random error, on the other hand, is a treatment execution error, is unpredictable and varies with each fraction. Systematic errors shift the entire dose distribution away from the clinical target volume (CTV), while random errors blur this distribution around the CTV. Of the two, systematic error is more ominous since it would have a much larger impact on treatment accuracy and hence the therapeutic ratio.

Margins are added to the CTV to take these errors into account. These margins are geometric expansions around the CTV and may be non-uniform in all dimensions depending on the expected errors. These margins ensure that dosimetric planning goals are met despite the variations during and between fractions. ICRU 62 defines the expansion of PTV around the CTV as a composite of two factors – internal target motion (internal margin) and setup variations (setup margin) [7]. Depending on observed systematic and random errors in a given setup for a particular treatment site, a variety of recipes for calculating PTV margins exist in literature [8,9]. To enhance the therapeutic ratio, a host of correction strategies may be applied to reduce these margins and may include online or offline correction of interfraction errors or real-time correction of intrafraction motion. Tracking and correcting organ motion helps reduce internal margin while improved accuracy of positioning reduces setup margins, thus reducing the required PTV margin.

IGRT Technology Solutions

Depending on the imaging methods used, the IGRT systems may broadly be divided into radiation-based and non-radiation based systems [10,11].

Non-Radiation Based Systems

These may employ ultrasound, camera-based systems, electromagnetic tracking and magnetic resonance imaging systems integrated into the treatment room [12-18].

Ultrasound-based systems such as BAT, SonArray, and Clarity acquire 3D images that may help align targets to correct for interfractional errors. Geometric accuracy is 3-5 mm and the greatest advantage is lack of any ionizing radiation. Sites of common application include prostate, lung and breast radiotherapy.

Camera-based (infra-red) or optical tracking systems identify the patient reference set-up point positions in comparison to their location in the planning CT coordinate system, which aids in computing the treatment couch translation to align the treatment isocenter with plan isocenter. Optical tracking may also be used for intrafraction position monitoring for either gating (treatment delivery only at a certain position of target) or repositioning for correction. Tools such as AlignRT image the patient directly and track the skin surface to give real time feedback for necessary corrections. These systems have found application in treatment of prostate and breast cancer and for respiratory gating using external surrogates. Geometric accuracy is 1-2 mm, but application is limited only to situations where external surface may act as a sufficient surrogate for internal position or motion.

Electromagnetic tracking systems (Calypso) make use of electromagnetic transponders (beacons) embedded within the tumor, and motion of these beacons may be tracked in real time using a detector array system. Beacons need to be placed through a minimally invasive procedure, their presence may introduce artifacts in MR images and there are limitations to the patient size. This system has a geometric accuracy of <2 mm, but its use at present is limited to prostate radiotherapy.

MRI-guided IGRT (e.g., ViewRay) helps real time assessment of internal soft tissue anatomy and motion using continual soft-tissue imaging and allows for intrafractional corrections. Geometric accuracy is 1-2 mm, but the limitations applicable to MRI including distortions with non-uniform magnetic fields, motion artifacts and exclusion of patients with pacemakers or metallic implants who would be otherwise unsuitable for MRI. A wide application potential exists in treatment of prostate, liver, and brain as well as for brachytherapy.

Radiation-Based Systems

These include static as well as real-time tracking, using either kilovoltage (KV), megavoltage (MV) or hybrid methods.

Electronic portal imaging devices (EPID): EPID was developed as a replacement of film dosimetry for treatment field verification and is based on indirect detection active matrix flat panel imagers (AMFPIs). They are offered as standard equipment by nearly all linear accelerator (LINAC) vendors as both field verification and quality assurance (QA) tools. Image acquisition is 2D, with a geometric accuracy of 2 mm. Bony landmarks on planar images are used as surrogates for defining positional variations respective to the digital reconstructed radiographs (DRRs) developed from the planning CT dataset. Different systems may use either KV or MV X-rays for imaging, the image contrast being superior with KV images while there is lesser distortion from metallic implants (dental, hip prostheses) in MV images. System is unable to detect or quantify rotations. Average dose per image is 1-3 mGy for KV systems while it is as high as 30-70 mGy for MV systems [19-21].

Cone beam CT (CBCT) – KV or MV: These systems consist of retractable x-ray tube and amorphous silicon detectors mounted either orthogonal to (Elekta Synergy, Varian OBI) or along the treatment beam axis (Siemens Artiste). These have capability of 2D, fluoroscopic and CBCT imaging. Another system (Vero, BrainLAB) consists of a gimbaled x-ray treatment head mounted on an O-ring with 2 kV x-ray tubes, 2 flat panel detectors, and an EPID. The O-ring can be rotated 360 degrees around the isocenter and can be skewed 60 degrees around its vertical axis. Geometric accuracy is 1 mm or lesser with possibility of 2D and 3D matching with DRRs or X-ray volumetric images generated from planning CT data sets. Scanning is done

through a continuous partial or complete gantry rotation around the couch, acquiring the "average" position of organs with respiratory motion. Both interfraction setup changes and anatomical changes related to weight changes or organ filling (bladder, rectum) may be monitored. Repeat scans at the end of treatment may give an estimate of intrafractional changes. For tumors discernible separately from surrounding normal tissue, treatment response may also be monitored and these scans may be used for dose recalculation or treatment plan adaptation after necessary image processing. KV CT gives better contrast resolution compared to MV CT but may be limited by artifacts from prostheses and scatter from bulky patient anatomy. Average dose per image is 30-50 mGy [22-25].

Fan beam KV CT (CT-on-rails): This system has an in-room CT scanner and gantry that moves across the treatment couch/patient, which can be rotated either towards the scanner or the gantry for imaging and treatment, respectively. 3D images are taken with the patient immobilized on the couch, the difference from a diagnostic CT being a larger bore size (>80 cm diameter) to accommodate bulky immobilization devices, and a multislice detector. Accuracy and applications are similar to CBCT with average dose of 10-50 mGy per image [26].

Fan beam MV CT (TomoTherapy Hi ART II): This includes an on-board imaging system to obtain MV CT images of the patient in treatment position. The same LINAC is used to generate both the treatment (6 MV) and imaging beam (3.5 MV). A xenon detector located on the gantry opposite the LINAC collects exit data for generation of MV CT images. Patient dose from imaging varies with pitch setting, and is typically 10-30 mGy per scan [27].

Hybrid systems for real time 4D tracking

2D KV stereoscopic imaging (CyberKnife): The Accuray CyberKnife robotic radiosurgery system consists of a compact LINAC mounted on an industrial robotic manipulator arm, which directs the radiation beams to the desired target based on inputs from 2 orthogonal x-ray imaging systems mounted on the room ceiling with flat panel floor detectors on either side of couch, integrated to provide image guidance for the treatment process. Images are acquired throughout the treatment duration at periodic intervals ranging from 5-90 seconds, and the couch and robotic head movements are guided through an automatic process. Several tracking methods may be used depending upon the treatment site. Skull, skull base or brain tumors may be treated using 6D skull tracking, paravertebral tumors whose movements parallels that of spine may be treated with X-Sight spine tracking, and lung tumors that are surrounded by normal lung parenchyma may be tracked with X-Sight lung tracking. Lung tracking may employ automatic generation of internal target volume depending upon visibility of tumor through both, one or none of the X-ray imaging systems in the treatment position. For all other tumors (e.g., prostate, liver, neck nodes, abdominal masses etc.), internal surrogates or fiducial markers may need to be placed within or in direct contact with the tumor and the tumor motion is tracked and corrected for through monitoring the fiducial position including translations, rotations and deformation. Respiratory motion is also monitored and accounted for when correcting for target position and motion through a synchrony model generated in real time. The system also has a couch that has 6 degrees of freedom to correct for positional variations. Treatment may be limited by patient position and size, and posterior treatment beams cannot be used. A semi-invasive procedure may be required if fiducial markers are needed for tracking. This system can be employed both for cranial (frameless) and extracranial radiosurgery or stereotactic radiotherapy [28,29].

Real-time tumor-tracking (RTRT) system: This system is designed for real time tracking of tumors by imaging implanted fiducial and using this information for gating. It consists of 4 x-ray camera systems mounted on the floor, a ceiling-mounted image intensifier and a high-voltage x-ray generator. The LINAC is gated to irradiate the tumor only when the marker is within a given tolerance from its planned coordinates relative to the isocenter [30,31].

VERO: This system has 2 x-ray tubes and corresponding flat panel detectors, and uses a combination of initial couch motion and a pair of radiographs for patient alignment. The couch is capable of 3D alignment for initial coarse setup and then the on-board imaging subsystem helps fine-tuning. A pair of radiographs is acquired and registered with prior DRRs using bony landmarks to evaluate the translational and rotational shifts. The system can also compensate for organ motion [32].

Combination alignment systems: optical imaging and 2-D kV orthogonal imaging

ExacTrac x-ray 6-D stereotactic IGRT system: It uses a combination of optical positioning and kV radiographic imaging for online positioning corrections. There are 2 main subsystems: an infrared-based system for initial patient setup and precise control of couch movement using a robotic couch, and a radiographic KV x-ray imaging system for position verification and readjustment based on internal anatomy or implanted markers. Infrared system may also be used for respiratory monitoring and signaling to LINAC for beam tracking and gating. Novalis Tx combines this system with an additional on-board imaging system (MV, KV x-rays, and KV CBCT) on a multiphoton/electron beam LINAC [33,34].

Guidelines for Medical Personnel and Implementation

American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO) jointly developed guidelines for IGRT that define the qualifications and responsibilities of personnel including radiation oncologists, medical physicists, dosimetrists and radiation therapists, QA standards, clinical implementation and suggested documentation. Similar guidelines have also been proposed by European agencies. [35-37] A summary of the key points is given below:

Qualifications

Appropriate certification with specific training in IGRT before performing any stereotactic procedures.

Responsibilities

Radiation Oncologist

Conduct of disease-specific treatment, staging, evaluation of comorbid conditions and prior treatments, exploration of all available treatments including discussion of pros and cons of IGRT, treatment and subsequent follow up.

Determination of the most appropriate patient positioning method, recommendation of the appropriate approach to manage organ motion, supervision of simulation paying particular attention to

positioning, immobilization and appropriate motion management, determination and delineation of target volumes and relevant normal critical structures using available imaging techniques, communication of expected goals and constraints and collaboration with the physicist in the iterative process of plan development to achieve the desired goals, supervision of treatment delivery and determination of acceptable day-to-day setup variations, and participation in the QA process and subsequent approval.

Medical Physicist

Acceptance testing and commissioning, assuring mechanical, software, and geometric precision and accuracy, as well as image quality verification and documentation in a given IGRT system.

Implementation and management of a QA program:

Development and implementation of standard operating procedures (SOPs) for IGRT use, in collaboration with the radiation oncologist.

Dosimetrist

Normal structure delineation under the guidance of radiation oncologist

Management of volumetric patient image data (CT and other fused data sets) on radiation treatment planning (RTP) system

Generation of a treatment plan under oncologist's and physicist's guidance

Generation of all technical documentation for IGRT plan implementation

Assisting with treatment verification

Radiation Therapist

Understanding and appropriate use of immobilization/ repositioning systems

Performance of simulation and generation of imaging data for planning, implementation of treatment plan, acquisition of periodic verification images under supervision and periodic evaluation of stability and reproducibility of the immobilization/repositioning system and reporting inconsistencies immediately.

IGRT Implementation

Fiducial Markers: These serve as surrogates to soft tissue targets when they are difficult to visualize and their alignment cannot be related to bony anatomy. These may be tracked in real time to obtain 3D coordinates of the target for subsequent corrections.

Moving Targets and Delineation: Intrafraction target motion or interfraction displacement, deformation, or alteration of targets and other tissues should be accounted for during determination of planning target volumes. Appropriate motion management methods should be chosen depending on available expertise, and degree and type of motion. This process starts at the time of simulation and continues through to the end of therapy.

Patient Positioning: Ensure accuracy of patient position and its reproducibility for fractionated treatments relative to the chosen IGRT device as well as treatment unit.

Image Acquisition: Calibration of the IGRT system to ensure high imaging quality with attention to slice thickness uniformity, image contrast, spatial resolution, isocenter alignment between imaging and treatment planning and delivery systems, accuracy of software used for identification and correction of couch misalignments. Relevant QA procedures should ensure reliability and reproducibility of the entire process.

Treatment Verification: Image review by radiation oncologist at the first fraction and then periodically is necessary to ensure treatment accuracy and reproducibility. Each department should determine its own threshold of couch positioning changes that would necessitate setup review or change before treatment delivery.

Quality assurance and documentation: A documentation of all the necessary QA procedures throughout the course of simulation, treatment and periodic verification should be maintained. These would help determine departmental thresholds for action as well as serve as guides for modification of the processes involved following review of findings.

IGRT – Clinical Benefits

Use of the IGRT process has improved our awareness and understanding of daily inter- and intrafractional set-up variations and motion. Real time tracking has helped quantify interpatient and intrapatient variations in lung and liver tumor motion related to breathing and complexities of such motion have become clearer. We now understand that even when breath-holds are repeated, the relative position of soft tissue and skeletal structures may vary, rendering use of bony landmarks useless for such endeavors. Changes in prostate position (translation, rotation as well as shape) have been quantified and we can better correct for these errors as well as tailor PTV margins to these findings, thus allowing more accurate targeting. Understanding of the various IGRT techniques, their applicability, limitations, additional radiation hazards help the radiation oncologist take an educated decision on the method best suited to a particular clinical situation for maximizing benefit from radiation therapy. Changes in parotid position relative to the tumor in head and neck cases, change in body contour due to weight loss, seroma or body fluid collections, change in prostate position relative to bladder or rectal filling and effect of bowel gas, reduction of tumor size during treatment and changes in spinal position during spinal or head and neck radiotherapy are situations which were never even considered of significance in the pre-IGRT era and their respective roles and solutions are being developed as we are understanding their role during treatment. With better geometric precision, volume of irradiated healthy normal tissue can be significantly reduced with reduction in toxicity risks. Adaptation to reduction in tumor volume may lead to additional gains in normal tissue toxicity reduction.

Results from ongoing and future trials will hopefully demonstrate the net gain in therapeutic ratio from application of IGRT technologies and the onus lies on the radiation oncology community to take up the challenge of demonstrating the benefit of these potentially expensive approaches.

IGRT is most likely to benefit clinical situations where the tumor is in close proximity to sensitive healthy tissues, when doses required for

disease control exceed the tolerance levels of adjacent normal tissues, or when large organ motion and setup errors may result in severe consequences of positional errors. All patients treated with conformal radiotherapy, IMRT, and SBRT should, in theory, benefit from IGRT. Thoracic and upper abdominal targets with significant respiratory motion, obese patients, head and neck cancers, paraspinal and retroperitoneal sarcomas, and prostate cancer are situations that are expected to derive maximum benefit with some clinical experience forthcoming. Clinical situations where even low dose irradiation produces excellent local control, palliative radiotherapy delivered using large fields and superficial tumors that are amenable to direct visual inspection are likely to derive least benefit from IGRT.

Concerns with IGRT

Limited availability of experienced trained staff is a major hurdle in wide application of the technique despite its demonstrable benefits, even with the simplest approaches. Other factors that need consideration include quality control, algorithms that define the decisions whether to change a plan or continue with original plan, and need for commercial development of software as well as hardware to match clinical needs and demands. Another major concern regarding frequent on-treatment imaging is the radiation dose to normal tissues. Although the doses from IGRT appear insignificant, only long tem follow up will define any potential risk of second malignancies from low dose exposure. Thus, there is an ongoing debate on the necessary frequency of verification imaging especially when using ionizing radiation. Recent developments in MR-LINACs have tried to address these concerns while allowing daily imaging for treatment verification. Another concern is that of treatment safety since the technologies available in the clinic require integration of hardware and software from different vendors. Clinical use of any system should be preceded by proper acceptance testing, commissioning, and routine QA used to assure accurate regular functionality. Education of all users (oncologists, physicists, technologists) on safe use and clinical utility is mandatory, along with knowledge of additional dose and possible risks associated with use. No single technology is ideal in every scenario and no single institution can manage to integrate all or most technologies in one place, hence it remains to be seen which of these methods gain wider popularity and acceptance.

Clinical Applications – Current and Future

Use of IGRT systems is essential to treatment of any site where setup deviations and organ motion are anticipated. Additional gains are monitoring of treatment response, weight changes and organ filling on day-to-day basis. With improved precision of planning systems, use of stereotactic radiosurgery or radiotherapy and high dose hypofractionated regimens, the chances of small deviations leading to significant errors in treatment delivery are much higher, and the use of IGRT is far more critical in these situations. Integration of LINACs with MR-based soft tissue imaging and PET-based biological imaging may help even further improve targeting accuracy in the future [38,39]. However, use of such technology and its integration into routine use would mandate that proper QA and training be put in place before undertaking such procedures.

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