Image-guided adaptive radiation therapy (IGART) is an evolving approach to cancer treatment and represents the latest effort to fulfill a longstanding goal for radiation oncology: escalated therapeutic doses of ionizing radiation that are delivered precisely in time and anatomic space to tumor tissue while sparing healthy, nontarget tissues to maximize the therapeutic ratio. This article introduces and reviews the concepts, history, radiobiology, targeting, technological, planning, delivery, and plan-adaptation principles and approaches to IGART, with a focus on the increasingly important roles of functional imaging modalities in the IGART process.

Radiation therapy plays an important role in cancer treatment for many patients, but its curative potential has been constrained by dose-limiting toxicities that can follow irradiation of healthy, nontarget tissues, and insufficient dose delivery to tumor tissue. Many technological advances over recent decades have helped reduce the incidence and magnitude of these problems by better tailoring radiation delivery to target volumes and better sparing adjacent nontarget organs and tissues. One persistent challenge has been that tumors, nontarget tissues, and organs move during treatment, and their contours, positions, and sizes can change during the course of treatment. These changes can affect delivered radiation dose distributions in ways that cause significant deviations from treatment plans.

Image-guided adaptive radiation therapy (IGART) is a recent and evolving integrative approach to further minimize radiation toxicities by detecting and adapting treatment plans to compensate for sources of external-beam radiation therapy targeting variances. The goal of IGART is to adjust and improve the therapeutic ratio continually throughout a patient’s treatment course. It represents a synthesis of image-guided radiation therapy, which usually is confined to setup corrections, and adaptive radiation therapy, which refers to the technological capture of feedback data so that treatment plans can be modified to compensate for anatomic change. IGART also includes retrospectively reconstructed dose delivery history as feedback data in plan reoptimization.

Conventional radiation therapy relies on initial imaging for radiation...
therapy simulation and treatment planning, and follow-up imaging during patient setup before dose delivery to reduce targeting errors associated with incorrect patient positioning. In contrast, IGART involves follow-up imaging and dose-delivery assessments throughout a course of radiation therapy to correct for setup and anatomical sources of targeting errors and to determine whether treatment plan modification is required before each subsequent dose is delivered. These goals are achieved through imaging during and between dose deliveries. IGART is “the ongoing use of imaging to monitor, update, and adjust the treatment process,” and dynamic IGART is “the use of streams of imaging data to automatically control the dose delivery in real-time.” IGART can be described as “a closed-loop [radiation therapy] process in which treatment plans are modified using systematic feedback of measurements over time.”

The ongoing adjustment of radiation therapy planning volumes and margins allows radiation dose escalation without increased radiation toxicity to the patient.

Technologically, IGART is situated at the intersections of advanced imaging, gating, planning, and radiation delivery technologies and software systems, but it is not a new concept. Essentially, IGART represents a fulfillment of longstanding goals for radiation therapy: the conformal delivery of toxic levels of ionizing radiation to tumor tissue while largely sparing healthy, non-target tissue, and thereby maximizing the therapeutic ratio. These goals have driven radiation therapy-planning imaging for much of the past century. Emerging technological advances mean those goals now can be achieved better than ever before, accommodating both anatomic and tumor motion caused by physiologic processes, such as respiration, and slower changes in target and nontarget volumes associated with radiation therapy and other cancer treatments, either directly (tumor shrinkage or deformation caused by radiation therapy) or indirectly (a patient’s weight loss).

Imaging is central to this process. The role of imaging in radiation therapy was long restricted to the use of 2-D—and later, 3-D—diagnostic radiographic images acquired for treatment planning. However, volumetric imaging now is incorporated into radiation treatment planning and delivery, and multimodality imaging is integral to treatment planning, patient setup, and the delivery of radiation therapy. Computed tomography (CT), magnetic resonance (MR) imaging, and functional and other imaging modalities all have undergone technological advances over the past decade, helping to usher in an era of clinical IGART.

Functional positron emission tomography (PET)-CT imaging plays a role in IGART treatments employing modulated radiation therapy, intensity-modulated radiation therapy (IMRT) and volumetric modulated radiation therapy (VMAT). Although IGART will continue to evolve, it already is playing an increasing role in cancer treatment. IGART is not a single technology or a seamless, integrated set of technologies; instead, it is a paradigm or approach to radiation therapy that employs a collection of tools—planning, targeting, gating, delivery, and adaptation software and equipment—to address clinical challenges presented by a patient’s particular disease. This toolkit allows options and approaches for achieving the therapeutic goals of IGART: improved tumor control and patient safety with a reduced risk of acute or late radiotoxicities. However, components of IGART technologies, such as volumetric imaging, image registration, image data postprocessing, and rapid radiation therapy adaptation and replanning algorithms, are being integrated into commercially available radiation therapy systems, and IGART-ready systems will become less expensive and widely available in coming years.

IGART is “a generic term” encompassing several ways to use medical images to assist radiation therapy, and some of these technologies are being researched. Researchers have summarized several “fundamental aims” for IGART, including:

- Radiation therapy planning.
- Anatomic and functional target delineation.
- Identification of tumor biology and the molecular biology of adjacent tissues to inform modulated treatment planning.
- Patient positioning because the patient’s location relative to planned radiation beam paths can reduce delivery errors associated with interfraction changes in anatomic positioning and target volumes.
- Detection of intrafraction motion with the aim to compensate for it.
- Determination of how much radiation has been delivered to the target.
Radiation therapy outcomes monitoring (e.g., tumor deformation, shrinkage, or evidence of intrinsic or acquired radioresistance). PET imaging can detect interfraction gross tumor volume (GTV) changes sooner than CT imaging can. PET and PET-CT also play a clinical role in response assessment in many cancers.

In the future, clinical IGART practice likely will incorporate the use of numerous molecular and metabolic biomarkers of treatment response, in addition to anatomic measurements, to further and more rapidly inform radiation therapy plan reoptimization. Elements of this approach already are evident with the use of functional imaging such as PET in IGART treatment.

History

IGART has emerged because of innovations in radiation therapy delivery and medical imaging, particularly the availability of modulated treatment delivery, cone-beam CT (CBCT), and other onboard volumetric imaging capabilities. The technological demands of contemporary IGART required advances in computer processing speeds, imaging equipment design, and image data processing algorithms that emerged in the 1990s. The electronic portal image device (EPID) and standalone CT scanners offered early feedback systems for adaptive redelineation of tumor volumes, for example. Three-dimensional conformal radiation therapy (3-D CRT) was an early example of IGART because the beam portal could be adjusted based on feedback from online portal imaging. The emergence of IMRT, VMAT, stereotactic treatment methods, and real-time gating, motion-harmonized 4-D radiation therapy (using 4-D CT) to accommodate tumor movement caused by respiratory motion, allowed more precisely delivered radiation beams and smaller safety margins around irradiated volumes.

Although IGART is not a single technology, it developed and matured during the IMRT era of treatment delivery and sometimes is described as a historical outgrowth of— or complement to— IMRT, which also emerged in the 1990s. It uses imaging-data-informed algorithms to generate precise 3-D tumor-irradiation plans to deliver multiple external radiation beams of different shapes, orientations, and intensities, using adjustable leaf collimators and allowing steep radiation gradients across anatomy.

Radiation therapy planning volumes can be affected by small differences in patient position, organ motion, or changes in a patient’s body mass. Modulated treatment methods better achieve external-beam radiation therapy’s longstanding conformal goals for radiation dose delivery across anatomic volumes, and growing evidence suggests that it improves the therapeutic ratio. However, modulated treatment methods’ improved delivery of the correct dose to the correct place is not sufficient alone to meet the goals of radiation therapy because of the other intrafractional and interfractional sources of targeting error, such as organ motion and tumor change over time. These sources of targeting imprecision also must be taken into account for IMRT to maximize its therapeutic potential—a problem that first led to the formal proposal of adaptive radiation therapy in the late 1990s.

Before IGART was implemented, the same treatment plan and initial patient-positioning simulation radiographs typically were used throughout a patient’s radiation therapy treatment course. This is still the case in many facilities. The emphasis was placed on attempts to replicate simulation-stage patient positioning and immobilization, rather than accommodating and correcting for this and other sources of targeting error. Xing et al described the differences between anatomes and planning volumes at simulation and subsequent deliveries of radiation dose treatment fractions as “one of the weakest links in the quality chain of the current radiation therapy practice.”

IGART can address this weakness. It allows modulated treatment methods and conformal delivery of radiation to accommodate anatomic and tumor contours at the time of initial treatment planning and simulation. It also allows radiation beam targeting to be adjusted repeatedly (reoptimized) throughout the course of treatment to accommodate anatomic and tumor changes over time, allowing better sparing of radiosensitive nontarget organs. Over the past decade, IGART began to replace a linear process of simulation, treatment planning, and delivery of a set treatment plan, with a model of iterated reoptimization of the initial treatment plan over time.
IGART software tools essentially are algorithms for reiterated evaluation of imaging feedback about tumor and anatomic changes over time, and the use of those feedback data for plan adjustment (ie, reoptimization of the treatment plan). Two overall categories of these software tools have been described by researchers:

- Adapting to changing geometry algorithms – quantify interfraction changes (tumor or organ deformation) immediately before each treatment fraction.
- Adapting to changing geometry and delivered dose algorithms – adapt or update treatment plans to accommodate anatomic deformations and cumulative radiation dose distributions for previous fractions.

IGART-related technologies and software are undergoing rapid development, refinement, and clinical testing. However, IGART still is far from achieving its full promise to precisely “personalize” radiation therapy treatments. The anticipated ability of IGART to render immobilization strategies and radiation therapy planning-volume safety margins largely unnecessary has not yet arrived. The field is evolving rapidly and the goals of IGART, including real-time, intrafractional plan adaptation, widely are considered feasible and achievable in the near future.10,11

**Radiobiology and IGART Concepts**

Reducing irradiation of nontarget tissues in conventional radiation therapy has relied on closely replicating patients’ positioning from initial simulation imaging in radiation treatments. In contrast, IGART involves imaging-based delineation of planning volumes, assessment of changes in those volumes, and plan reoptimization to accommodate detected changes on 3 distinct time scales: offline (between delivery of treatment fractions), online (right before a radiation fraction is delivered), and in real time during irradiation (dynamic IGART).6,8 Although the conventional approach relies on implementing the initial plan as precisely as possible, IGART involves using feedback data to reoptimize the treatment plan repeatedly. This is why adaptive radiation therapy has been described as a “feedback control strategy” that incorporates new information about potential sources of error during and between delivery of treatment fractions (see Figure 1).6,7

The repeated offline and online imaging examinations provide feedback data so radiation delivery can be adapted to changing conditions.27 It now also is possible to acquire volumetric feedback data online and dynamically to assess and reoptimize a patient’s radiation therapy model or plan repeatedly.1,6 Planning tumor volumes and margins can be adjusted between and during radiation dose-fraction delivery, and because delivered radiation doses also are calculated with imaging feedback data, plan adaptations can correct for past treatment fractions’ failure to deliver planned radiation doses.1 Simulation and planning are the first, rather than the final, word in IGART plan implementation, providing “an overall estimate of the treatment specifics and dosimetry” and

![Figure 1. Image-guided adaptive radiation therapy (IGART) process for each new treatment session or fraction. The radiation oncologist decides whether replanning and reoptimization are needed or whether treatment can be delivered as planned. If adjustments are needed, the previous steps are repeated until the physician is satisfied and instructs treatment delivery. © 2013 ASRT.](image-url)
geometric uncertainties in treatment setup and patient movement (see Figure 3). Because traditional, nonadaptive radiation therapy does not correct for setup errors, patient motion, or anatomic changes, PTV margins before IGART had to be fairly wide, causing unavoidable, dose-limiting irradiation of nontarget tissue around the tumor.

With advances in precision functional imaging of metabolic and molecular processes, anatomic delineations of treatment volumes increasingly will be informed by so-called biologic planning volumes. This is an important consideration because anatomic imaging modalities do not visualize tumor cells harbored in the seemingly healthy tissue surrounding a macroscopic tumor. Therefore, the true biologic extent of a tumor can be larger than is suggested by the visualized macroscopic tumor.
Only after functional imaging techniques are able to detect the microscopic extent of malignant cells around tumors will it be possible to minimize radiation therapy planning volume margins. Microscopic extent can be estimated using proxy measures from surgical biopsy samples or tumor staging and, more crudely and probabilistically, using clinical biomarkers such as prostate-specific antigen scores. These indirect indicators do not measure the actual locations or extent of microscopic tumor spread and seeding precisely, however, and are unreliable. Therefore, they cannot inform radiation therapy planning or reoptimization accurately.

Potential sources of radiation therapy targeting errors include patient setup errors, beam targeting errors, and anatomic motion or changes within irradiated volumes. The latter have been categorized as either anatomic motion caused during irradiation by patient physiology (eg, respiratory, cardiac, genitourinary, or gastrointestinal motion) or interfraction treatment-associated changes caused by tumor necrosis and shrinkage or deformation, continued tumor growth despite treatment, or disease-associated or treatment-associated changes in internal organs. These sources of error vary over time and anatomic space, so they cannot be addressed solely on pretreatment planning and imaging. Whereas respiratory or other intrafraction sources of motion traditionally were accommodated with wide additional PTV margins, contemporary approaches to intrafraction volume motion seek to reduce motion or, more often, to mitigate motion effects through temporal or spatial gating or image postprocessing.

Imaging examinations are performed for each step of the IGART process, including:

- Treatment simulation – the patient assumes radiation therapy treatment positioning for a CT scan for radiation dose-delivery calculations based on the CT tissue-density values encountered in target and nontarget volumes.
- Target volume delineations – 3-D volumetric imaging allows treatment volume delineation, an increasingly automated process. Multimodality imaging with CT, MR, and PET appears to improve GTV delineation compared with delineation that can be achieved using any of these imaging modalities alone.
- Pretreatment planning – radiation therapy planning traditionally is based on CT scan data acquired during treatment simulation. IGART treatment planning incorporates imaging data from treatment simulation and target volume delineation examinations from CT scans and other imaging modalities to plan external radiation beam pathways and shapes to optimize dose intensity. For example, IMRT targeting algorithms use inverse planning algorithms for target delineation and avoidance data regarding non-target tissue radiosensitivities to identify optimal beam configurations and intensities (see Figure 4). Hounsfield values from CT scans provide important tissue-density information relevant to radiation therapy dosimetric calculations, whereas other modalities provide additional valuable anatomic and functional-biological data for treatment planning.
- Patient setup – imaging the patient in position immediately before treatment helps identify setup errors. Consistent patient setup is crucial for treatment and to monitor accurately delivered radiation doses over time. This is a particular concern in hypofractionated radiation therapy, with longer irradiation times and fewer subsequent opportunities to correct for dosimetric deviations from treatment plans. Rigid immobilization and patient pain management might improve success rates, along with motion-tracking technologies. Imaging examinations are performed for each step of the IGART process, including:
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The rationale for radiation therapy fractionation is to limit short-term radiation exposures of nontarget tissue as a result of these sources of targeting error.\textsuperscript{5} As modulated treatments and IGART reduce the risk and frequency of nontarget tissue irradiation, radiation dose fractionation schedules will be reassessed, and “truly optimal” treatment regimens will be identified and validated in clinical studies.\textsuperscript{5}

**Imaging**

Imaging plays a central role in IGART. Plan adaptation uses feedback from imaging data to delineate the residual tumor, tumor progression or regression, and even molecular-biological or physiological responses to treatment.\textsuperscript{7} Contemporary IGART involves a wide range of imaging modalities and techniques, including planar radiography, EPID, CBCT, MR, ultrasonography, optic

Figure 4. SCC of the right tonsil of a 65-year-old man. Axial CT image obtained for radiation therapy planning (A) and deformably coregistered axial T1-weighted magnetic resonance (MR) image (B) show GTVs generated independently from each image data set. Deformable coregistration of B with A was performed with the XD3 multimodality diagnostic software (Mirada Medical). C. Axial fludeoxyglucose positron emission tomography (FDG-PET) image shows a composite of the GTV that was contoured manually at image interpretation. Contour lines are color coded to show imaging modality data on which they are based, with green representing CT, blue representing MR, and orange representing functional PET imaging. Reprinted with permission from Bhatnagar P, Subesinghe M, Patel C, Prestwich R, Scarsbrook AF. Functional imaging for radiation treatment planning, response assessment, and adaptive therapy in head and neck cancer. Radiographics. 2013;33:1914.
imaging, and functional imaging with single-photon emission CT (SPECT), PET, and PET-CT. The role of functional imaging and the use of biomarkers in treatment planning is growing.

**Plan Adaptation**

Plan-adaptation imaging data can be acquired and registered for treatment reoptimization offline, online, or in real time. Each of these involves different time intervals between planning, treating, imaging, and plan adaptation (see Table 1). The specific approaches considered part of IGART vary among researchers, but broadly construed, IGART represents any approach to radiation therapy that involves repeated reassessment and replanning based on feedback in the form of imaging data during the course of treatment.

Offline plan adaptation refers to the acquisition of imaging feedback data separate from radiation therapy—typically a day or more removed from treatment. Offline imaging typically is performed with a conventional or in-room volumetric (helical or multidetector) CT scanner to assess tumor response between treatment fractions and changes in patient anatomy. With this data, GTV contours can be compared with previous imaging data to help recalculate GTV as part of plan adaptation. Significant changes frequently are evident between initial treatment planning and simulation images and midtreatment images. Those differences inform dosimetry calculations (monitoring delivered radiation) and radiation therapy adaptation for the subsequent treatment. Offline imaging and adaptation can be built into the IGART protocol, and it might be indicated when substantial clinical changes are observed in the patient, or if differences are noted between initial planning CT images and CBCT images acquired online or during pretreatment setup imaging.

Online image acquisition and plan adaptation are performed during treatment in the radiation therapy room and occur minutes or less before radiation therapy. Similar to offline imaging, online imaging most frequently involves CT scanning equipment.

Dynamic adaptation refers to near-simultaneous imaging and radiation therapy, and it is the newest component of IGART. The time interval between imaging, adaptation, and irradiation is a few seconds. Real-time adaptation is indicated when a target tumor occurs in the chest or abdomen and is affected by respiratory or other sources of intrafraction motion. Means of addressing intrafraction motion include conventional approaches (eg, patient breath-hold or compression of the abdomen), or IGART approaches (eg, respiratory gating or real-time image-based plan adaptation). Real-time IGART imaging and treatment adaptation still is a nascent field, but imaging components for dynamic IGART, which are undergoing research, development, and clinical testing, include volumetric MR, CT, x-ray, optical, and electromagnetic transponder systems. A CyberKnife robotic treatment system also is available for real-time tumor-motion adaptation.

Regardless of the time between imaging and treatment, image data must be compared with previously acquired images. This is the heart of IGART. Image registration and coregistration (fusion) of multimodality imaging examinations using algorithmic processes is required.

**Modalities**

Major contemporary imaging technologies have different and overlapping roles or applications in IGART, as well as particular strengths and weaknesses (see Tables 2 and 3). Two-dimensional digital radiography can be employed for patient positioning and tumor target localization for treatment planning, particularly if there are no issues with tumor or organ motion. However, volumetric imaging allows precise visualization of tumor or organ deformation or motion.

Volumetric CT plays central roles in offline simulation and planning and subsequent IGART imaging for plan

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**Table 1**

<table>
<thead>
<tr>
<th>Type</th>
<th>Time Interval Between Imaging and Irradiation</th>
<th>Typical Imaging Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offline</td>
<td>1 day or more</td>
<td>Conventional or in-room volumetric imaging</td>
</tr>
<tr>
<td>Online</td>
<td>Minutes or less</td>
<td>In-room volumetric imaging</td>
</tr>
<tr>
<td>Real-time</td>
<td>Seconds or less</td>
<td>4-D CT or other imaging modalities</td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>Technology</th>
<th>Clinical Applications</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereoscopic kilovolt (kV) x-ray</td>
<td>kV-pretreatment planar images</td>
<td>Appropriate when bony landmarks are used as surrogates</td>
<td>High radiation dose</td>
</tr>
<tr>
<td></td>
<td>Intrafraction imaging for motion management</td>
<td>Capable of real-time tracking</td>
<td>Blocked views at certain gantry angles</td>
</tr>
<tr>
<td></td>
<td>Implanted marker alignment</td>
<td>Compatible with other systems for hybrid guidance and motion management</td>
<td>Might only provide “snapshot” images for evaluation</td>
</tr>
<tr>
<td></td>
<td>6-D translational and rotational correction</td>
<td></td>
<td>Not capable of 3-D volumetric data acquisition</td>
</tr>
<tr>
<td>Megavoltage (MV) and kV cone-beam</td>
<td>3-D volumetric image acquisition, with 3-D matching to planning CT</td>
<td>Slow acquisition provides average position of internal anatomy for respiratory motion</td>
<td>kV has better contrast resolution than does MV</td>
</tr>
<tr>
<td>computed tomography (CBCT)</td>
<td>X-ray source/detector</td>
<td>Monitoring patient setup and anatomical changes during treatment</td>
<td>kV has more artifacts present on high-density materials</td>
</tr>
<tr>
<td></td>
<td>O-ring x-ray source rotation flat panel detector for imaging data collection</td>
<td>Ongoing monitoring of tumor response throughout treatment course</td>
<td>Degradation of image quality from patient scatter—especially for larger patients on kV imaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opportunity for online replanning</td>
<td>Radiation dose can be excessive with routine use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Same isocenter for MV CT and linear accelerator</td>
<td>No real-time organ motion information</td>
</tr>
<tr>
<td>In-room CT or CT-on-rails</td>
<td>Pretreatment volumetric imaging for setup and adaptive plan reoptimization</td>
<td>3-D, 4-D image information, or both</td>
<td>Excessive radiation dose if used routinely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Online replanning</td>
<td>No real-time organ motion-tracking information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnostic-quality CT images</td>
<td>Assumes fixed isocenter relationship between the independent CT scanner and linear accelerator</td>
</tr>
<tr>
<td>MV helical CT</td>
<td>Pretreatment volumetric imaging for setup and adaptive replanning</td>
<td>Ability to monitor ongoing treatment response</td>
<td>Excessive radiation dose if used routinely</td>
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<tr>
<td></td>
<td>Pretreatment MV projection imaging for patient setup</td>
<td>Widely applicable to anatomical sites</td>
<td>Soft-tissue discrimination inferior to kV CT</td>
</tr>
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</table>

*Not all equipment has the same applications and capabilities.

Reoptimization, frequently using in-room or online CT scanners that can be positioned over the patient during radiation therapy or that are integrated with radiation therapy linear accelerators. Some radiographic imaging modalities used with IGART include stereoscopic kilovoltage (kV) x-ray imaging, in-room conventional volumetric CT, and online kV or megavoltage (MV) CBCT (MV CBCT) systems that have been integrated with beam-source equipment.

EPID images are projection images using the treatment beam and have long been preferred for ensuring patient setup accuracy between treatment fractions. EPID allows precise geometric concordance between visualization and treatment delivery. However, portal imaging and in-room planar radiography rely on bony anatomic landmarks or implanted fiducial markers and do not reliably detect soft-tissue deformations.

In-room CT was developed to visualize more sensitively soft tissues for patient setup, improving accuracy. CT also allows 3-D volumetric imaging and treatment dose calculation. Radiation shielding in radiation therapy rooms is sufficient for the addition of CT imaging.
Table 3

| Major Nonionizing Imaging and Feedback Techniques<sup>3,4</sup> |
|-----------------|-----------------|-----------------|-----------------|
| Technology      | Clinical Applications                        | Advantages                                           | Disadvantages                                      |
| Ultrasonography | Pretreatment volumetric imaging for setup    | Nonionizing alignment and tracking method, with visualization of nearby radiosensitive organs 4-D capabilities offer real-time intrafraction monitoring | Interuser variability Limited real-time target tracking Applicability to specific treatment sites, primarily prostate and lung |
| Optical surface imaging | Patient setup Real-time intrafraction motion monitoring Indicates anatomic changes | Nonionizing superficial alignment and tracking method Real-time monitoring and gating capabilities | No internal anatomic or target information Applications limited to specific anatomical surfaces; not ideal for flat surfaces |
| Electromagnetic transponders localization | Pretreatment setup and target localization Real-time intrafraction fiducial marker tracking | Nonionizing radiation High accuracy of tracking Temporospatial target information | No spatial information of nearby radiosensitive organs Invasive transponder implantation Limited applications in compatible anatomic sites and because of array capabilities Typically causes imaging artifacts on MR imaging |
| Magnetic resonance (MR) | Pretreatment volumetric imaging for setup Should be capable of adaptive plan reoptimization | Nonionizing alignment and visualization of nearby radiosensitive organs 3-D image information and online replanning Superior soft tissue information | Nonuniform magnetic field causes image distortions Susceptible to artifacts and motion |

<sup>3</sup> Not all equipment has the same applications and capabilities.

tumors, usually in the brain, that are not subject to significant intrafraction motion.\textsuperscript{10} Some experts anticipate helical tomotherapy being used for more complex radiation therapy treatments in the future.\textsuperscript{5}

Although CT imaging techniques play increasingly important roles in IGART, not all imaging modalities used in IGART involve radiation. Other modalities include transabdominal ultrasonography, MR, and optimal or electromagnetic target tracking.\textsuperscript{1,5} Volumetric ultrasonography sometimes is used in patient setup for prostate or breast radiation therapy, for example.\textsuperscript{1,20} Optical or infrared tracking systems sometimes are used to track intrafractional targeting and motion, and often are used in respiratory gating.\textsuperscript{1,10} However, external skin markers are not always reliable indicators of target or organ position or motion.\textsuperscript{5,12,20} Electromagnetic tracking beacons can be placed in the tumor to track its motion in 4-D prostate motion tracking.\textsuperscript{1,20} MR-guided radiation therapy also can allow intrafractional tracking but is prone to motion artifacts and artifacts associated with prosthetic metallic implants or pacemakers.\textsuperscript{1,5,12,20}

Ultrasonography is noninvasive, inexpensive, and does not involve ionizing radiation.\textsuperscript{5} However, it is less accurate than CT imaging and unlike Hounsfield units associated with CT, different tissues’ sound wave impedances are not predictive of radiation dose. Therefore, ultrasonography is not preferred for IGART, and its utility largely is limited to patient setup confirmation that can be achieved using bony anatomic landmarks, or target localization of prostate tumors.\textsuperscript{1} Interuser variation is a significant concern for ultrasonography, even in prostate tumor radiation therapy imaging.\textsuperscript{1,20} When ultrasonography is used, prostate-motion-reducing rectal balloons and full-bladder ultrasonography are recommended.\textsuperscript{2} Rectal balloons also help remove nontarget rectal tissue from target prostate volumes, serve as landmarks for ultrasonographic target localization, and might help reduce prostate motion caused by the ultrasound probe.\textsuperscript{4}

**Functional Imaging and Biomarkers**

Advances in the molecular-biological and genomic understanding of tumorigenesis, growth, heterogeneity, and disease progression have revolutionized oncology, from tumor staging to precision therapeutics like specific tumor-gene targeting agents.\textsuperscript{13} Similar emphasis now is being placed on molecular and metabolic imaging with functional imaging as part of IGART to help develop cancer treatment plans, identify planning volumes, assess tumor responses to treatment, and more quickly predict probable treatment outcomes.\textsuperscript{13} These biological-imaging approaches should allow more timely assessments of treatment responses and quicker and more effective plan adaptations in the future.\textsuperscript{13} In addition, these approaches will allow insights into tumors’ biological processes, intratumor heterogeneity, microscopic tumor extent, and responses to treatment (see Figure 5).\textsuperscript{13}

Anatomic imaging modalities, such as routine CT and MR (with or without contrast), lack functional and metabolic information. PET and other functional modalities poorly visualize anatomic structures but can display functional and metabolic information accurately such as specific cell-surface receptors, including prostate-specific antigen and epidermal growth

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**Figure 5. SCC of the epiglottis in a 67-year-old man.** Axial fused FDG PET-CT image visualizes tumor contours automatically generated with the XD3 multimodality diagnostic software program. Different degrees of tumor metabolic activity are represented here as percentages of maximum standardized uptake values (SUV). Reprinted with permission from Bhatnagar P, Subesinghe M, Patel C, Prestwich R, Scarsbrook AF. Functional imaging for radiation treatment planning, response assessment, and adaptive therapy in head and neck cancer. Radiographics. 2013;33:1912.
factor receptors (EGFRs). EGFRs can be targeted with cetuximab to increase radiation therapy effectiveness. Combining anatomic and functional imaging modalities to yield information-rich composite images therefore makes sense. Functional imaging with PET-CT uses different tracer agents, allowing the visualization of facets of tumor histology that can help guide treatment planning with targeted biologic agents. Functional imaging also allows sensitive visualization of molecular-biological processes involved in a tumor’s development of resistance to radiation, including tumor hypoxia, cell proliferation, and apoptosis (cell death) and could allow early detection of acquired radioresistance.

Fludeoxyglucose (FDG) is a radiolabeled form of glucose that is accumulated differentially in metabolically active cells. Once inside the cell, FDG is metabolized into FDG-6-phosphate, which cannot be further broken down and accumulates inside cells. Tumor cells accumulate greater concentrations of this form of FDG than do healthy cells because of their elevated glucose metabolic rate. FDG-PET and FDG PET-CT can demonstrate biological processes that allow tumors to escape the cytotoxic (cell-killing) effects of cancer treatment, including intrinsic (pretreatment) radioresistance and hypoxia.

However, other disease processes, such as pulmonary tuberculosis, also can cause differential accumulation of FDG, and FDG is therefore not a tumor-specific imaging marker. Functional imaging can identify hypoxia and metabolic activity associated with hastened cellular proliferation at baseline, before treatment, and throughout treatment to monitor the emergence of radioresistance and to inform treatment adaptation (ie, dose escalation or cessation of radiation therapy in favor of other treatment options).

Functional and anatomic image data sets are fused to create information-rich data sets and visualizations—a process that largely is automated now with integrated PET-CT and PET-MR systems. Such functional imaging approaches help to determine and track the biological extent of cancer over time and provide more precise and timely visualization of treatment effects. Serial functional imaging examinations at each step of the IGART process should allow more sensitive and detailed monitoring of treatment response and plan-adaptation needs than anatomic imaging alone. PET, SPECT, and functional MR spectroscopy might play increasing roles in defining target and nontarget volumes for CRT planning and IGART alongside anatomic imaging. FDG PET-CT already is used widely for the detection, diagnosis, and staging of tumors, and treatment monitoring. It also is employed for modulated treatment planning and target volume delineation because target delineation is crucial for modulated therapy’s steep radiation dose gradients. MR data sets can be interrogated with different algorithms to reveal numerous facets of a tumor’s physiology. MR spectroscopy allows sensitive visualization of cell metabolism and metabolic byproducts and is undergoing investigation as a possible way to differentiate malignant from benign tumors and the metabolic extent of tumors. However, this and other MR-based functional imaging approaches remain investigational and are not in widespread clinical use for adaptive radiation therapy. FDG PET-MR also is under investigation for metabolic volume delineations (see Figure 6).

The metabolic uptake of FDG in FDG-PET imaging might even have prognostic value, predicting tumor responses and patient outcomes, but this remains an area of controversy.\textsuperscript{22} Proponents of FDG as a prognostic biomarker point to evidence that tumor uptake of FDG reflects the tumor’s metabolic activity before and after irradiation and that the difference might be a proxy measure of tumor viability and aggressiveness.\textsuperscript{22} Preliminary studies of small numbers of patients suggest that lower tumor metabolic rate after radiation therapy, as assessed by FDG uptake, has been associated with superior rates of both local tumor control and patient survival.\textsuperscript{22}

In addition to FDG, other radiopharmaceuticals used in PET imaging are undergoing development for different clinical-imaging and treatment-planning applications.\textsuperscript{13} For example, fluorine-18 fluoromisonidazole and fluoroazomycin arabinoside accumulate in hypoxic tissues and are undergoing development for use with PET imaging to detect emerging regions of tumor hypoxia.\textsuperscript{13} 3′-deoxy-3′-fluorothymidine can visualize tumor cell proliferation and also is undergoing development for use with PET.\textsuperscript{13} The comparative effectiveness research is scant, and no consensus has been reached about which radiopharmaceuticals are best for visualizing hypoxia.\textsuperscript{3}

Ongoing research aims to identify other prognostic and predictive genomic biomarkers detected in blood tests or imaging examinations that might further personalize the molecular-biological basis of radiation therapy planning and adaptation by more precisely identifying tumor contours or margins and treatment effects, potentially allowing the precise assessment of radioresistant foci emerging within a given tumor.\textsuperscript{13,16,17} Ultimately, these imaging biomarkers could help detect tumor responses to treatment earlier and predict the risk of disease recurrence and late toxicities, which could inform patient survivorship care plans and post-treatment monitoring needs.\textsuperscript{13,16} PET, SPECT, or MR imaging biomarkers could help identify molecular or metabolic and cell-proliferation changes in tumor biology and intratumor responses to treatment, augmenting their already increasingly important role in IGART.\textsuperscript{13,16}

**Image Data Processing**

Repeated and multimodality imaging undertaken for IGART planning, setup, monitoring, and adaptation requires 4 types of image data set processing:

- Image segmentation.
- Image registration.
- Coregistration – fusion of data from different imaging examinations or multimodality examinations.
- Visualization.

Image segmentation identifies the surface contours and boundaries of tumors and nontarget anatomies, whereas image registration identifies their positions and shapes using landmarks and other factors to allow identification of those anatomies in different images.\textsuperscript{5} Image segmentation partitions image data into anatomic features, distinguishing anatomic boundaries or surfaces of interest from adjacent anatomy so the surface contours or internal features of soft tissues, bones, or vasculature can be visualized. Segmentation involves several algorithmic approaches and increasingly is performed automatically, with relatively little manual input from the radiologic technologist. Segmentation reduces the file sizes, decreasing processing time.

Image registration anatomically aligns overlapping image data from serial or multimodality imaging examinations to help detect changes in the shape, size, or orientation of anatomic structures, or to detect differences in scale between sequential image data sets.\textsuperscript{4,22} Many registration algorithms compare maps of image intensity over anatomic space, between image data sets.\textsuperscript{4}

Registration can be achieved using rigid or deformable registration algorithms to map anatomies between image data sets.\textsuperscript{4} Rigid registration uses landmarks to identify the patient’s positional differences between imaging examinations and uses this information to correct for the identification of anatomic positions.\textsuperscript{4} However, rigid registration poorly accommodates the anatomic changes that can occur within and around treatment volumes over the course of radiation therapy treatment.\textsuperscript{11} Deformable registration detects changes in specific anatomies relative to other anatomies to show physical changes that occur between imaging examinations.\textsuperscript{4} Typically, rigid image registration is used to correlate data sets from treatment planning images obtained from different types of imaging examinations, allowing image fusion to precisely quantify and locate tumor contours, cancer-involved regional lymph nodes, and nearby nontarget organs and tissues.\textsuperscript{3}

Deformable registration is used in planning images to assess the effect of respiratory or other sources of
physiologic motion on volumes or anatomies of interest and between delivered fractions of radiation treatment to identify anatomic changes resulting directly or indirectly from treatment.\(^1\) Deformable registration algorithms also allow more accurate tracking of delivered radiation doses throughout the treatment regimen.\(^1\) Several deformable-registration models have been developed, but clinical validation is ongoing and some challenges remain unresolved, including certain types of relative organ displacement, such as sliding and mass loss.\(^1\)\(^1\) Deformable registration should better track radiation dose distributions over time; volumetric CT scans between treatment fractions, for example, can be deformably registered to recalculate delivered doses from the baseline or planning CT images forward.\(^1\)\(^1\) This allows cumulative dose-distribution mapping of changing tumor and anatomic volumes over time and correction or compensation for deviations from the initial treatment plan and subsequent reoptimized treatment plans.\(^1\)\(^1\)

Segmentation and registration increasingly are performed automatically in near real time using software, but these tasks also can be completed manually in part.\(^5\) Nevertheless, automatic rigid registration of data from sequentially performed planning examinations largely has replaced manual registration between planning images using visual alignment of 2-D simulation and portal images.\(^5\)

Fusion, or multimodality data coregistration, aligns anatomic data from different imaging modalities to produce information-rich fusion images. For example, PET-CT images contain physiologic PET image data and anatomic CT image data.\(^5\) Visualization, of course, refers to the end result of segmentation, registration, fusion, and postprocessing of image data to generate clinically useful images.

**ALARA and Imaging Dose Management**

Imaging data is central to all steps of the IGART process, and much research has been done on methods that do not use ionizing radiation for guidance and tracking to help limit patient dose. Because speed, accuracy, and objectivity are so important, IGART relies heavily on automated processes.\(^5\) In addition, IGART involves monitoring and management of the ionizing radiation dose associated with radiation therapy and the associated radiographic imaging.\(^1\)\(^4\) One challenge for IGART is the effect of repeated radiographic imaging on radiation dose distributions over time. Radiation doses associated with imaging long have been assumed not to approach those associated with radiation therapy. However, as radiation therapy doses to nontarget tissues continue to decline, radiographic imaging will become a more significant source of patients’ radiation doses, and it warrants consideration.\(^1\) This is particularly true for repeated CT scan acquisitions. For example, CBCT scans associated with patient setup can deliver radiation doses as high as 10 cGy per treatment day.\(^1\) Furthermore, the as low as reasonably achievable (ALARA) concept is observed to minimize the probability of stochastic radiation risks, such as DNA damage or lifetime cancer risk.\(^1\) ALARA applies to radiographic radiation dose in IGART just as it does in other settings. Quantifying cumulative radiation doses associated with

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Dose from kV CBCT(^24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Head</td>
</tr>
<tr>
<td>Maximum skin dose (mGy)</td>
<td>100.5</td>
</tr>
<tr>
<td>Mean skin dose (mGy)</td>
<td>68.5</td>
</tr>
<tr>
<td>Effective dose (mSv)</td>
<td>10.9</td>
</tr>
<tr>
<td>Conversion factor (mSv/mGy cm(^2))</td>
<td>6.0 x 10(^{-5})</td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th>Table 5</th>
<th>Dose from the Elekta kV CBCT(^24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Head</td>
</tr>
<tr>
<td>Mean dose at center (mGy)</td>
<td>29</td>
</tr>
<tr>
<td>Mean skin dose (mGy)</td>
<td>30</td>
</tr>
<tr>
<td>Effective dose (mSv)</td>
<td>3.0</td>
</tr>
<tr>
<td>Conversion factor (mSv/mGy cm(^2))</td>
<td>6.0 x 10(^{-5})</td>
</tr>
</tbody>
</table>

Simulation, Treatment Volume Delineation, and Treatment Planning

Simulation, an imaging procedure that helps to identify a patient’s optimal position for treatment, provides baseline index or reference setup images of that optimal treatment position. The resulting images are used as references for patient positioning immediately before each treatment fraction. The differences represent one form of imaging feedback in IGART. Simulation has long been a separate procedure from treatment-planning imaging. However, beam’s-eye-view digitally reconstructed radiographs allow simulation reference CT image data to be acquired during treatment planning rather than as a separate examination. This ensures excellent concordance between the patient’s treatment planning position and simulation positioning for treatment setup.

Internal target volume was formalized as a planning volume in part to accommodate tumor motion. Target volume delineations require the acquisition of image series representing the full range of physiological sources of motion, rather than a single planning image. Options include fluoroscopy, slow CT scans, 4-D CT, and MR, all of which include inhalation-phase and exhalation-phase breath-hold images.

PET radiopharmaceuticals offer sensitive differentiation of malignant and healthy tissues for accurate delineation of tumor contours. Although scant evidence supports that automatic volume delineations outperform visual interpretation by experienced operators, adjustments to the PET standardized-uptake values scale can change the visualization of tumor volume significantly—a potential cause of inconsistent assessments between observers. A lack of consensus about the best target-contouring methods remains.

Table 6

Dose Points for Various Phantoms and Imaging Systems

<table>
<thead>
<tr>
<th>Dose Point</th>
<th>Head Phantom Varian OBI</th>
<th>Head Phantom Elekta XVI</th>
<th>Pelvis Phantom Varian OBI</th>
<th>Pelvis Phantom Elekta XVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral dose range (cGy)</td>
<td>0.26-0.66</td>
<td>0.16-0.30</td>
<td>2.36-2.90</td>
<td>0.83-1.06</td>
</tr>
<tr>
<td>Isocenter (CAX) dose (cGy)</td>
<td>0.48</td>
<td>0.21</td>
<td>1.96</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Abbreviations: CAX, central axis; cGy, centigray.
Patient discomfort or pain can compromise a patient's ability to achieve or hold a particular position; pain should be assessed throughout the treatment process and addressed with appropriate pain management when it is an issue. Dynamic dose-optimization techniques have been developed for specific radiation therapy modalities, such as IMRT. Use of PET-CT imaging in the planning process allows plan-adaptation feedback with both anatomic deformation and biological data. These data offer complementary but overlapping information about tumor changes over time; tumor deformation and positional changes between fractions can markedly change GTVs, in ways that can appear different in PET and CT image series.

**Dynamic Adaptation**

Conventional radiation therapy maneuvers for respiratory motion control include:
- Shallow breathing.
- Voluntary, coached patient breath-hold at a specified part of the respiratory cycle.

Some authors argue that hybrid PET-CT should be preferred, or even mandatory, for planning volume delineation and treatment planning, citing evidence that PET-CT imaging results in changes to treatment plans in 10% to 50% of cases (see Figure 7). Precise coregistration is crucial for multimodality planning images; integrated PET-CT scanners offer automatic rigid and deformable coregistration of PET and CT images.

In IGART, the initial treatment plan is adapted throughout the treatment course using imaging feedback for reoptimization of every fraction. This enables discovery of patient setup errors and detection and accommodation of interfractional changes in tumor and patient anatomy, as well as intrafractional motion—sources of dosimetric errors. For IGART, treatment planning is not the first step in a linear process but a continuous, iterative process of replanning throughout treatment. However, implementation currently is patchy and sometimes incomplete.

Planning images should be acquired in as close a manner as possible to patient position during treatment delivery, including use of positioning limb supports, comparable degrees of bladder filling, and patient coaching to help achieve regular respiration rates. Patient discomfort or pain can compromise a patient's ability to achieve or hold a particular position; pain should be assessed throughout the treatment process and addressed with appropriate pain management when it is an issue.

**Figure 7.** Adaptive radiation therapy planning in a 68-year-old man with supraglottic SCC treated with chemotherapy and radiation therapy (70 Gy in 35 fractions over 7 weeks, with cisplatin chemotherapy). A. Axial coregistered PET-CT image obtained before the start of therapy shows marked metabolic activity in the tumor (arrowhead). B. Axial fused PET-CT image from before the 12th radiation treatment fraction shows reductions in both tumor size and metabolic activity. C. Axial fused PET-CT image obtained after the 21st fraction of radiation therapy shows continued reductions in tumor size and metabolic activity. Reprinted with permission from Bhatnagar P, Subesinghe M, Patel C, Prestwich R, Scarsbrook AF. Functional imaging for radiation treatment planning, response assessment, and adaptive therapy in head and neck cancer. Radiographics. 2013;33:1915.
- Deep-inspiration breath-hold.
- Forced breath hold employing assisting devices monitored by spirometry, such as an occlusion valve in the spirometer.
- External immobilization or abdominal compression, such as that used with stereotactic body radiation therapy.

In contrast, dynamic IGART involves the use of feedback data during treatment to adapt radiation delivery to tumor motion in near real time. Dynamic IGART techniques might be necessary to treat tumors at anatomic locations where respiratory or other physiological sources of motion cannot be managed adequately with breath-control procedures (e.g., tumors of the lungs, breasts, liver, pancreas, and kidneys).10

The most commonly encountered source of motion is respiration. Many thoracic and abdominal organs—even the prostate—are affected by respiratory motion.10 Therefore, much of the early research into managing the effects of intrafractional motion on radiation therapy focused on respiratory movement. However, other physiological processes, including bladder and rectum filling, also can cause organ motion.10

The ability to provide highly automated, real-time online imaging feedback and treatment plan reoptimization is a central, although incompletely realized, goal of IGART. Dynamic IGART is the most rapid and complex form of plan reoptimization, requiring precise image registration and tracking of tumor motion that can approach speeds of several centimeters per second.4 One category of dynamic adaptation in clinical use is the calculation of tumor position using indirect surrogate markers, such as spirometric lung volume or optically tracked visual markers on skin.4 Optical tracking systems are commercially available. However, not all patients’ respiration patterns are regular enough for this approach to be reliable.5 Electromagnetic tracking of implanted fiducial markers is undergoing clinical testing.5

Recent advances in computing speed have placed additional technological avenues toward dynamic adaptation within clinical reach.6 Several approaches or strategies for accommodating tumor motion during treatment exist. All require rapid and accurate target detection and tracking, and most involve complex planning algorithms.6,10 Although some still are experimental, such as moving the couch instead of the beam, a few are in clinical use, including beam gating and 4-D CT, and beam tracking.6,10

With beam gating and 4-D CT, beam-on is triggered by the tumor’s arrival at a specified anatomic location.6,10 Beam gating frequently is used for lung and liver tumor radiation therapy.10 Internal gating systems use internal landmarks or surrogate markers, such as fiducial implants, whereas external gating uses surface-motion markers and optical imaging systems.10 Four-dimensional CT is employed widely in treatment planning for gated radiation therapy. These planning scans involve acquisition of up to 20 different images from throughout the respiratory cycle. Of these images, phase-specific images most relevant to internal target volume delineation are selected to develop a 4-D CT gated treatment plan, and these images are postprocessed, typically using maximum-intensity projection image postprocessing.10 These 4-D CT methods assume that a patient’s breathing patterns are regular and reproducible, so coaching is sometimes necessary.10

With beam tracking, the radiation beam source can be dynamically realigned to track and follow tumor motion.6,10 Beam tracking has been used in robotic radiosurgery such as the Synchrony Respiratory Tracking System used with the CyberKnife robotic linear accelerator. These systems use implanted gold fiducial markers and employ radiographic planning images to calculate respiratory motion parameters.

Target detection and tracking provides real-time feedback for treatment delivery adaptation. Open-loop beam alignment responses can be achieved via gating, beam-collimation change, or electromagnetic “steering” of the beam. In reality, even these direct tracking strategies include millisecond processing lag times that necessitate calculation of the near-future position of the tumor.6,10 Onboard CBCT imaging and kV fluoroscopy allows real-time observation of the tumor during treatment.5 The CyberKnife system employs pairs of kV x-ray sources and detectors to allow orthogonal visualization of the patient in radiographic mode.5

Clinical Applications

Modulated radiation therapy treatments, such as IMRT and volumetric modulated arc therapy (VMAT), are the most commonly used treatments for head and neck, lung, and breast cancers. Not every cancer patient
requires or is likely to benefit from the use of IGART instead of conventional nonadaptive approaches to radiation therapy. Many tumors are treated using other radiation therapy approaches, and not all tumor types respond rapidly enough to radiation treatments for interfraction deformation to be a significant issue. Other cancer types, such as head and neck tumors, tend to exhibit marked deformation during the course of radiation therapy, including tumor shrinkage. Particularly with modulated treatment plans, these changes can degrade the conformal accuracy of initial radiation therapy plans, necessitating some degree of plan adaptation.\(^1,12\) Modulated treatment plans appear to be more sensitive to interfraction anatomic changes than other radiation therapy techniques, and non-IGART modulated treatment plans based on a single initial or baseline imaging examination likely increase the risk of marginal beam misses of target volumes and, therefore, the risk of adverse radiotoxicities for patients and underdosing the target.\(^1,12\) Therefore, the need for image guidance and plan adaptation varies depending on tumor location, size, and stage.\(^1\) Exactly how IGART is approached also varies between patients and cancer types. For example, organ motion and the need for dynamic intrafractional imaging and adaptation is usually less of an issue for patients with oropharyngeal tumors than for those being treated for lung, liver, or bladder tumors.\(^3,10\) Nevertheless, IGART is well-suited for head and neck, breast, and lung cancers.

**Head and Neck Cancer**

Modulated treatment delivery is the most common approach for patients with head and neck tumors.\(^27\) It is well suited for complex tumor contours and close anatomic association with radiosensitive nontarget tissues seen in head and neck cancers. Initial target volumes are predictive of the rate of tumor volume change between fractions of radiation therapy, which can help identify patients who are most likely to benefit from IGART.\(^27\)

Head and neck GTV represents the volumes with the highest tumor cell density, and therefore, the highest prescribed radiation dose.\(^27\) GTV contouring can employ CT images, MR images, or both and involves FDG-PET or PET-CT imaging.\(^3,27\) Modulated treatment delivery for head and neck cancer includes simultaneous integrated boost, which concurrently delivers different radiation intensities to several targets. Nontarget tissue contouring is undertaken for avoidance calculation—a crucial component of modulated treatment planning for head and neck cancers, in which nontarget tissue irradiation can lead to xerostomia (impaired saliva production), aspiration problems, and dysphagia, with serious effects on a patient’s quality of life. Nontarget parotid salivary gland shrinkage is common among patients undergoing head and neck tumor radiation therapy. This can be monitored between treatment fractions using pretreatment in-room CT or helical tomotherapy. Modulated treatment methods can reduce the incidence and severity of xerostomia, probably through sparing of salivary glands.\(^27\)

Setup errors for head and neck radiation therapy treatments are common, particularly regarding the larynx.\(^26,27\) However, intrafraction motion rarely is an issue in head and neck tumor radiation therapy because patients are immobilized with head rest supports, masks, and mouthpiece stents. Nevertheless, sporadic swallowing can be a source of intrafraction target and nontarget anatomy motion, and patients should be coached on this problem. Efforts are underway to capture swallowing effects in PTV delineation.\(^27\)

Interfraction changes in GTV and GTV position are assessed using pretreatment in-room CT or offline PET-CT between treatment fractions.\(^1,27\) IGART modulated treatment plan adaptation involves precisely registered treatment-target delineations and avoidance anatomy delineations for inverse planning. Deformable image registration has been validated for use with head and neck tumor modulated treatment delivery; its use with automated algorithms is replacing time-consuming manual contouring, which is prone to interobserver inconsistencies. Using deformable registration-based daily dose distribution mapping, cumulative dose distributions also can be assessed between fractions for modulated treatment plan adaptation to better spare salivary glands, for example.\(^27\)

In the future, functional imaging-delineated details of biological processes within tumors likely will allow more precise dose escalations, such as in FDG-PET and PET-CT-guided hypoxia-guided radiation therapy plan adaptations.\(^27\)

**Lung Cancer**

Lung cancer is a leading cause of cancer deaths, and radiation therapy is a key component of treatment for...
Coached breathing, deep-inhalation breath-hold, and respiratory gating are options for minimizing intrafraction motion during breast radiation therapy. Simulation 4-D CT as part of pretreatment planning can identify whether respiratory gating can help spare heart tissues during treatment. Surgical clips can be used as markers or fiducial markers can be implanted during breast-conserving surgery to help define the lumpectomy site’s target margins for subsequent radiation therapy. However, fiducial markers tend to migrate.

Modulated treatment delivery offers homogenous radiation doses but does not spare heart tissue as readily as does 3-D CRT with cardiac blocking. Whole-breast irradiation (45-50.4 Gy) sometimes is accompanied by a boost dose of 10 Gy to 16 Gy at the tumor bed to increase the cumulative radiation dose in the tissues most likely to harbor remnant tumor cells.

Interfraction changes and patient setup errors can be detected for IGART using CT-on-rails, helical tomotherapy, kV CBCT, or MV CBCT. Three-dimensional ultrasonography also can be used for planning (fused with planning CT images) and subsequent daily pretreatment target location and setup. MV and kV volumetric CT imaging is used for interfraction plan adaptations and delivered-dose distribution calculation.

Conclusion
Conformal radiation therapy has been limited in clinical practice by patient setup variations, changes in tumor and patient-organ size, volumetric contours, and relative positions, and by tumor and organ motion during treatment. The ultimate goal of IGART is to use feedback data from imaging examinations to reoptimize radiation therapy plans and beam parameters repeatedly throughout treatment. Technological advances in computing power, imaging, image-processing, and plan-adapting software, are hastening the day when IGART will be employed routinely in cancer treatment for selected patient populations. Automated replanning algorithm development and validation are crucial to progress IGART’s clinical implementation because of the time-consuming nature of repeated manual recontouring.

Functional imaging is improving target delineation and the identification of targeted dose escalation.

Breast Cancer
Breast-conserving surgery with adjuvant radiation therapy to kill residual tumor cells is a standard treatment for early-stage breast cancer. Breast radiation therapy is plagued by tumor and nontarget anatomic motion during treatment and changes between treatment fractions.

Treatment volumes can include the lumpectomy cavity or the entire breast. CT imaging is used in treatment planning to detect and delineate glandular breast tissue as part of clinical target volume. Breast PTV margin reduction requires respiratory motion adaptation, management, or both. Four-dimensional CT gated radiation therapy reduces radiation doses to the heart, at least among patients undergoing treatment for left-breast tumors, and can be included in baseline planning imaging examinations. FDG PET-CT is undertaken to delineate planning volumes, including lymph nodes, and to track tumor metabolic treatment responses between treatment fractions.

most patients. Lung tumors are subject to considerable intrafraction motion associated with respiration, and irradiation of adjacent nontarget lung tissue can cause pneumonitis and other serious, dose-limiting acute radiotoxocities. Controlled patient respiration, 4-D CT, and beam gating all have been employed to reduce radiation therapy errors caused by respiratory motion in lung cancer treatment.

Interfraction tumor shrinkage and deformation can be significant, with volume reductions of 1.2% per day, on average, between day 1 of radiation therapy and 60 days later. Adaptation usually is undertaken offline, using data from CT, helical tomotherapy, or PET-CT. The information value of PET-CT is illustrated by average midtreatment-regimen lung tumor volume reductions of 26% as assessed by CT and 44% as assessed by PET, in one study. PET data can be used to inform targeted radiation boost plan adaptations. MR and SPECT also have been used to assess interfraction tumor volume and position changes, and if the use of these modalities in interfraction IGART is foreseen, they should be included in the baseline planning imaging examinations carried out before a treatment regimen is initiated.

The clinical rationale for IGART for lung cancer seems strong, but little empirical evidence exists showing that it improves patient outcomes when compared with other radiation therapy techniques.

Breast Cancer
Breast-conserving surgery with adjuvant radiation therapy to kill residual tumor cells is a standard treatment for early-stage breast cancer. Breast radiation therapy is plagued by tumor and nontarget anatomic motion during treatment and changes between treatment fractions.

Treatment volumes can include the lumpectomy cavity or the entire breast. CT imaging is used in treatment planning to detect and delineate glandular breast tissue as part of clinical target volume. Breast PTV margin reduction requires respiratory motion adaptation, management, or both. Four-dimensional CT gated radiation therapy reduces radiation doses to the heart, at least among patients undergoing treatment for left-breast tumors, and can be included in baseline planning imaging examinations. FDG PET-CT is undertaken to delineate planning volumes, including lymph nodes, and to track tumor metabolic treatment responses between treatment fractions.
Detailed biological imaging and the use of biomarkers could allow even more timely and precise radiation therapy plan adaptation in the future. Hypoxic tumor regions identified with FDG-PET and PET-CT are candidate targets for integrated boosts or so-called hypoxia-guided radiation therapy. Some researchers in the field anticipate that IGART will become standard practice in radiation oncology in the years to come.

Although the radiobiological rationale for IGART is sound, empirical confirmation of the tumor-control and survival benefits of IGART for patients will have to await completion of large, well-designed, prospective clinical trials.

Once IGART becomes more widely used, it likely will spark a reconsideration of fundamental issues in radiation therapy, such as fractionation of treatment regimens, which have been devised as a way to limit radiation doses to healthy nontarget tissues and organs. Modulated treatment delivery has allowed hypofractionated radiation therapy that delivers total therapeutic radiation doses in fewer treatments. As IGART more precisely contours radiation doses to tumor tissue over time and across anatomic space, fractionation schedules likely will be reconsidered.

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References


1. Image-guided adaptive radiation therapy (IGART) is the ongoing use of imaging to monitor, update, and adjust the treatment process.
   a. true
   b. false

2. Which of the following are among IGART’s “fundamental aims,” according to researchers?
   1. anatomic and functional target delineation
   2. intrafraction motion detection and compensation
   3. determination of delivered radiation dose
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

3. _______ can detect interfraction gross tumor volume changes sooner than computed tomography (CT) can.
   a. Magnetic resonance (MR)
   b. Positron emission tomography (PET)
   c. Radiography
   d. Ultrasonography

4. IGART developed and matured during the _______ era of treatment delivery.
   a. intensity-modulated radiation therapy (IMRT)
   b. 3-D conformal radiation therapy (CRT)
   c. helical tomotherapy
   d. beam-gated

5. _______ target volume margins before IGART had to be fairly wide.
   a. Clinical
   b. Gross
   c. Planning
   d. Internal

6. Which of the following can detect the microscopic extent of malignant cells?
   a. CT
   b. functional imaging
   c. MR
   d. ultrasonography
Directed Reading Quiz

7. Values obtained from which medical imaging modality provide important tissue-density information relevant to radiation therapy dosimetric calculations?
   a. CT
   b. functional imaging
   c. radiographs
   d. ultrasonography

8. Which of the following are characteristics of random errors?
   1. They are unique to a particular dose-fraction.
   2. They are difficult to predict.
   3. They have a smaller overall effect on the therapeutic ratio and treatment efficacy.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

9. Online image acquisition and plan adaptation are performed during treatment in the radiation therapy room and occur ______ before radiation therapy.
   a. minutes or less
   b. 2 hours
   c. a day or more
   d. 1 week

10. Which of the following is a disadvantage of cone-beam CT (CBCT), in-room CT, and megavoltage (MV) helical CT?
    a. applicability to limited disease sites
    b. blocked views at certain gantry angles
    c. excessive radiation dose if used routinely
    d. no spatial information of nearby radiosensitive organs

11. When compared with MV CBCT, ______ offers superior image contrast and signal-to-noise ratio for soft-tissue imaging.
    a. kV CBCT
    b. helical tomotherapy
    c. fan-beam CT
    d. PET-CT

12. According to the article, which of the following might play increasing roles in defining target and nontarget volumes for CRT planning and IGART alongside anatomic imaging?
    1. PET
    2. single-photon emission CT
    3. functional MR spectroscopy
    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

13. Which of the following is true about deformable registration?
    a. It cannot detect changes in specific anatomies to show physical changes that occur between imaging examinations.
    b. It is used in planning images to identify anatomic changes resulting directly or indirectly from treatment.
    c. It will not be able to track radiation dose distributions over time.
    d. Initial challenges in deformable registration have been resolved, including certain types of organ displacement.

14. CBCT scans associated with patient setup can deliver radiation doses per treatment as high as:
    a. 10 cGy
    b. 3 mSv
    c. 10.9 mSv
    d. 16 mGy

continued on next page
15. Four-dimensional CT planning scans involve acquisition of up to ______ different images from throughout the respiratory cycle.
   a. 5  
   b. 10  
   c. 15  
   d. 20

16. Adverse effects experienced by patients undergoing modulated treatment planning for head and neck cancers include all of the following except:
   a. aspiration problems.  
   b. xerostomia.  
   c. lymphedema.  
   d. dysphagia.

17. Interfraction tumor shrinkage and deformation can be significant, with volume reductions of 1.2% per day, on average, between day 1 of radiation therapy and 60 days later in which type of cancer?
   a. breast  
   b. head  
   c. lung  
   d. neck

18. Modulated treatment delivery offers homogenous radiation doses in breast cancer treatment but does not spare heart tissue as readily as:
   a. MV CBCT.  
   b. kV CBCT.  
   c. 4-D CT.  
   d. 3-D CRT with cardiac blocking.