

Image-guided radiation therapy (IGRT): practical recommendations of Italian Association of Radiation Oncology (AIRO)

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Abstract The use of imaging to maximize precision and accuracy throughout the entire process of radiation therapy (RT) delivery has been called “Image-guided RT” (IGRT). RT has long been image guided: in fact, historically, the portal films and later electronic megavoltage images represented an early form of IGRT. A broad range of IGRT modalities is now available and adopted. The target location may be defined for each treatment fraction by several methods by localizing surrogates, including implanted fiducial markers, external surface markers or anatomical features (through planar imaging, fluoroscopy, KV or MV computed tomography, magnetic resonance imaging, ultrasound and X-ray imaging, electromagnetic localization, optical surface imaging, etc.). The aim of the present review is to define practical recommendations for IGRT.

Keywords Radiotherapy · Image-guided radiation therapy · Computed tomography · Magnetic resonance imaging

Introduction

The use of imaging to maximize precision and accuracy throughout the entire process of radiation therapy (RT) delivery has been called “Image-guided RT” (IGRT).

By comparing these images to those obtained during simulation, the patient’s position and/or the geometry of the radiation beams may be adjusted to more precisely address the radiation dose to the target.

RT has long been image guided: in fact, historically, the portal films or, later on, electronic megavoltage images (obtained with electronic portal imaging devices, EPID) represented an early form of IGRT. Portal films and EPID images are two-dimensional evaluations that, lacking 3-D visualization of soft tissue, provide limited information with a poor image quality. EPID images can reasonably well show the location of the isocenter and of the field margins relatively to the bony landmarks. However, the treated tumor is often a mobile soft tissue mass within the body, and patient repositioning based on bony landmarks alone is subject to error. Due to these uncertainties, it is inevitable to include a larger volume of normal tissue in the planning target volume (PTV) to ensure target coverage.

The advances in RT planning and delivery, producing much more conformal dose distributions with sharper dose gradients, need a greater accuracy and precision in treatment reproducibility. Modern IGRT techniques, improving soft tissue localization, coupled with frequent imaging/repositioning cycles (ideally, before each treatment session), reduce uncertainties, therefore, allowing margins

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reduction and possibly less toxic treatments. Thus, IGRT is particularly useful when high tumoricidal doses are prescribed with highly conformal treatment modalities, including 3-D conformal-RT (3D-CRT), intensity-modulated RT (IMRT), stereotactic body RT (SBRT) or stereotactic ablative RT (SABR), proton therapy [1–3].

A broad range of IGRT modalities is now available and adopted [4]. The target location may be determined by several methods for localization of surrogates, including implanted fiducial markers, external surface markers or of anatomical features [by planar imaging, fluoroscopy, KV or MV computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and X-ray imaging, electromagnetic localization or optical surface imaging]. This practice parameter addresses qualifications and responsibilities of personnel, clinical IGRT implementation, documentation, quality control and improvement, safety and patient education.

The aim of the present review is to define practical recommendations for IGRT.

IGRT system

The components of any IGRT system are the follows:

- An image acquisition system.
- A set of reference images for comparison.
- A software for the comparison match between reference images and CT planning.
- A protocol that defines the correction method.

Two kinds of procedures are used for the correction strategies: online and off-line method [5, 6].

The *online correction* strategies include the analysis of images' information immediately after the acquisition and, if necessary, the application of the correction before each RT session [5–7]. With this type of correction method, the systematic and random errors are effectively corrected. The disadvantage is that the process of analysis and correction needs to be fast, simple, and unambiguous.

With the *off-line correction* instead, the images' data were stored, and analyzed and corrected at a later time [7, 8]. The rationale for this type of approach is based on the consideration that the systematic error is the most common uncertainty with respect to random one. Usually, with this strategy, verification of sequential images in a sufficient number of initial fractions (usually 3–5 fractions) is performed: thus, the off-line protocols correct the average systematic error but not the daily error [5]. Statistical analysis of these data allows to calculate the mean value (M) and the relative standard deviation (SD) of the systematic

component of the setup error. It has been estimated (with biological and physical models) that the number of daily images needed to obtain a reliable systematic error evaluation is equal to about 10 % of the total number of sessions [9, 10].

In general, online strategies allow a greater reduction of the geometrical uncertainties with respect to off-line methods, but with an increased workload, treatment time and radiation dose.

An online approach is to be preferred especially when the high dose volume is close to anatomical structures critical for organ function, in the dose-escalation programs or for hypofractionated treatments. However, as reported recently, the off-line procedure seems to achieve similar efficacy. The radiation oncologist (RO) in charge of the patient should, therefore, define the preferred procedure for each individual case.

Independent of the correction procedure method, a “tolerance margin” (TM, acceptable error range of the setup) should be determined for each disease and location of target, considering also the priority of PTV coverage, organ at risk (OAR) functional relevance, the extent of organ motion and the patient individual features.

The next step is the definition of “action levels”. Two possible procedures are possible in off-line correction protocols: “no action level” (NAL) and “shrinking action level”(SAL).

The NAL is the procedure more frequently used: the systematic error, calculated as the average of the errors identified in the first n fractions, is corrected systematically in all the subsequent sessions, without tolerance limits. In the “extended NAL” procedure (e-NAL), additional weekly checks are also performed. If the measured error is less than the TM, no further corrections are suggested; if TM is exceeded, the acquisition of more images to identify any residual systematic error is warranted.

In the SAL protocol, the correction is performed if the measured error exceeds the TM.

Direct comparisons between the SAL and NALs show that NAL protocol may be more cost effective in terms of number of images needed for the systematic error reduction [11], but both procedures may be used, depending on RO's clinical evaluation in the individual case.

IGRT modality

We refer the interested reader to a recently published comprehensive description of IGRT modalities, with the pertinent geometric uncertainties and basic technical features [12]. However, a short description of the main IGRT techniques follows.

Electronic portal image systems

Orthogonal portal images are produced by the source of the LINAC. The bone structures are evaluated.

Tomographic cone image systems with high (megavolt, MV) and low (kilovolt, KV) energy

Cone beam computed tomography (CBCT) is the most widespread three-dimensional IGRT system. It utilizes an X-ray tube source. The X-ray source and a flat panel detector are mounted on the gantry of the linear accelerator; it is not only possible to acquire planar images, but also multiple projections during a 360 rotation in about a minute resulting in a “cone-beam CT scan” used for a volume reconstruction in transversal, coronal and sagittal slices providing 3D bone and soft tissue image information. The images acquisition and the KV generator are controlled by a specific software for each commercial solution. In MV systems, the detector unit receives the beam directly from the accelerator source to acquire a series of 2D projections that are then 3D reconstructed. In terms of image quality, KV CBCT allows to obtain a higher contrast resolution with respect to the MV [13, 14].

Tomotherapy image systems

Helical tomography is an IGRT mode combining the properties of a linear accelerator for intensity-modulated RT (IMRT) and a conventional helical scanner.

Using the slip ring technology of diagnostic CT scanners, the unit is capable of continuous rotation around the patient while the couch is moving into the gantry, providing smooth helical delivery. A compact (~40 cm long) 6 MeV S-band (3 GHz) linear accelerator generating a 6 MV photon beam is mounted on the rotating gantry and attached to the slip ring. The beam from the accelerator is collimated by a multileaf collimator consisting of 64 leaves. Using a separate collimation (“jaws”) system above the multileaf collimators, the “slice thickness” can be varied between 0.5 and 5 cm. The on-board megavoltage CT detection system is from a conventional, commercial diagnostic scanner using xenon detectors. The CT detection system can be used for patient setup verification and repositioning, if necessary, verification of leaf positions during treatment, and reconstruction of the actual dose delivered to the patient with the possibility of making corrections in subsequent fractions.

CT-on rail

In this system, the linear accelerator and a CT scanner are connected through a rail system, with the treatment table common to both. The main advantage of this system is the excellent

quality of image definition; a possible disadvantage could be represented by the minimum setup errors in the passage of the treatment couch from the imaging to the treatment position.

Ultrasound images

The ultrasound probes are able to provide volumetric images using special software that allows the comparison between the current position and that of planning. This system is used mainly for IGRT in prostate cancer and breast cancer.

IGRT and dosimetric issues

Clinical-dosimetric evaluation of the additional dose delivered to the patient with the use of IGRT is a somewhat overemphasized issue. There are several studies reporting the additional dose derived from CBCT with discordant results and the dose delivered varies greatly based on the IGRT system and scan protocol used [15, 16].

However, considering an indicative value for each CBCT scan of about 3 mSv for the head–neck area and of 10 mSv for the chest, assuming daily CBCT and an average number of 30 sessions, an effective additional dose of 90–300 mSv has been calculated, to allow an evaluation of the potential risks of this exposure.

The small potential risk of sequelae should, however, be weighed against the benefits of a more accurate target definition, with the resulting sparing of healthy tissues due to margin reductions, and the RO should take it into account in the individual case (age of the patient, type of tissues involved, etc.).

Summary

- It is suggested to verify of the CBCT acquisition parameters by the manufacturer, optimizing image quality and the exposure dose based on patients' needs.
- The additional dose to the patient with a single scan of CBCT is inferior to that of portal images (by 2–10 times).
- Perform daily CBCT results in a slightly higher dose to the patient; therefore, based on the clinical assessment of the risk–benefit ratio, a specific CBCT protocol for specific diseases, type treatment, and each patient should be used.

IGRT and anatomical district

We refer the interested reader to the comprehensive description of IGRT of the British National Radiotherapy

Implementation Group (NRIG) that developed a strategy for the use of IGRT [17]. Thus, only a short description of site-specific recommendations for IGRT use follows; however, several general principles may be applied to all sites, including:

- a. Effective immobilization for reducing setup and systematic errors,
- b. Establishment of departmental PTV margins based on calculation of the systematic and random center-specific uncertainties.
- c. Univocal definition of volume(s) or the region of interest for volumetric imaging, to allow reliable automated matching.
- d. Continuous update of IGRT internal procedures, according to the literature, since IGRT is still an evolving area.

Excluding rare tumors, the most common anatomical districts to which IGRT procedures are applied are listed below.

Breast

EPID-based IGRT is commonly used to assess reproducibility for breast RT. When appropriate immobilization is used, systematic and random errors are approximately of 3–4 mm. However, an acceptable TM for setup error is 5 mm. If this value is exceeded, patient's setup re-imaging could be suggested and if the TM is still exceeded re-simulation/replanning should be advised.

In case of partial breast irradiation, sequential tumour bed boost or simultaneous integrated boost, 2D paired images or 3D imaging could be required, especially when tumour bed PTV margin is less than 5 mm.

When reduction of PTV margins is required, 2D imaging (with a non-opposed pair of images) and 3D volumetric imaging, resolving the displacements in all directions accurately, could be useful in selected cases [17].

Brain

Brain structures are not affected by large position variations, and image guidance is, therefore, based on imaging of bone structures. The estimated setup error is approximately equal to 3–5 mm using currently available masks. If the stereotactic frame is used, the estimated error is 1.3–2.5 mm [18].

It is important to determine the setup error of this patient population according to the immobilization system. The calculation and correction of systematic errors require, usually, the off-line imaging for the first three fractions with the application of the average error for the subsequent

fractions and subsequently another weekly imaging (e-NAL off-line protocol).

Head and neck

Level 1 evidence supports the use of IMRT or volumetric modulated arc therapy (VMAT)/helical tomotherapy (HT) for head and neck cancer patients. Volumetric imaging and matching allow to monitor the relationship between target and healthy tissues. IGRT is, therefore, strongly suggested for these patients, at least to define systematic errors [19, 20].

In head and neck cancer, there are several factors that affect the patients' setup, including the accuracy of immobilization systems, the anatomical changes, and the reduction in tumor volume. For example, it is well recognized that during treatment the parotid glands' volume decreases with the subsequent risk of receiving more than the planned dose [21]. Thus, CBCT, with direct visualization of anatomical changes during the entire course of treatment, could be very helpful also for assessing the timing of replanning [22–28].

Although the published literature relating to the suitable CTV-PTV expansion is limited, it is shown that, to ensure adequate coverage of the target without daily IGRT, CTV-PTV margins in the three directions should be of about 4–5 mm [29]. Thus, when margins are reduced to less than 5 mm, daily CBCT is strongly suggested [30].

Prostate cancer

Several IGRT systems are available for prostate localization: planar, volumetric images (KV or MV), electromagnetic or ultrasound systems.

The prostate gland can move inside the pelvis up to 2 cm, and its position is strongly influenced by the rectal and bladder filling, as well as by respiratory motion or by intestinal peristalsis. Such organ motion could produce an insufficient coverage of prostate volume and/or an increasing exposure of the surrounding healthy tissues, especially for IMRT treatment [31].

CTV-PTV margins of 10 mm in all spatial directions except posteriorly (5 mm) are usually applied to cover the prostate volume [32, 33]. The anterior–posterior margin is the most critical one because its extent depends on the different rectal filling. Obviously, increasing the frequency of verification, the residual error decreases and an online correction strategy allows to further reduce margins [34, 35]. Thus, daily execution of CBCT could be suggested [36]; other IGRT procedures may, however, be acceptable, also depending on the fractionation schedule adopted (hypofractionated regimens may require more sophisticated IGRT procedures).

Rectal/anal cancer

Considering the large treatment volumes needed for these diseases, some studies reported a reduction in toxicity using IMRT/VMAT with IGRT [37, 38]. The NCCN guidelines recommend IMRT for the treatment of anal canal cancer. Thus, the choice of the best IGRT approach depended on the technique utilized [39, 40].

Gynecological cancer

In the treatment of uterine carcinoma, 3D-CRT and IMRT/VMAT/HT guarantee a high conformity of the dose to the target and a simultaneous reduction of the undesired exposure to surrounding OARs: small intestine, bladder, rectum, bone marrow (and also kidneys and the spinal cord for extended para-aortic fields) [41, 42].

The displacement of the position of the organ can be caused both by the physiologic mobility of the uterus according to the different filling of the rectum and bladder in subsequent fractions (interfraction motion), and also by the tumor regression as a response to radiotherapy [43].

Several authors have shown that during RT, inter- and intra-fraction motion of intact uterus and cervix were in the range of 3–18 mm in every direction [44–46].

Thus, 3D-CRT may carry a risk of gastrointestinal side effects due to the generous safety margins that must be applied to compensate for organ motion [47–51]. This problem could be reduced by the application of IGRT procedures; in addition, the inhomogeneity of dose distribution with IMRT techniques suggests to verify the reproducibility of the daily setup with volumetric IGRT to avoid geographic miss, resulting in worse clinical results compared to those obtained with conventional techniques [50].

Lung cancer

Lung cancer is one of the most difficult neoplasms to be treated due to significant “intrafraction tumor motion”. Most lung cancers are subjected to respiratory excursions up to 3–4 cm, especially if they were near to the diaphragm and CBCT reduced both the systematic and random errors [52, 53].

If the role of 3D verification systems is undisputed, it is not so clear how often these checks should be performed. For example, Yeung et al. [54] retrospectively simulated several schedules of IGRT verification: no IGRT, weekly CBCT, CBCT in the first five fractions and subsequently every week, and CBCT every other day. Analysis of the results showed that the residual error is never null. This is due to the evidence that while the bias decreases with the increase of frequency of controls, the random error remains unchanged. The systematic error reduction, however, allows a significant reduction in margins with the increasing frequency of IGRT procedures.

Higgins et al. [55] conducted a similar study in which IGRT reduces the magnitude and frequency of the setup error: an error ≥ 5 mm in CC direction was evidenced in 21 % of cases in the absence of IGRT versus 2 % with CBCT. Thus, the execution of CBCT could be suggested.

Paraspinal lesions

In relation to the proximity to the spinal cord, RT with curative doses of paraspinal lesions, for primary cancer or oligometastatic patients, often requires the use of IMRT/VMAT/HT supported by IGRT techniques [56–58]. A study performed to assess setup uncertainties in 45 patients with paraspinal tumors treated with IMRT evidenced translation errors from 0.1 to 0.9 mm [59].

Re-irradiation

To date, due to increased clinical experience, radiobiological knowledge and to the improving technique and technology, including IMRT/VMAT/HT, re-irradiation is much more common in clinical practice [60].

In this context, the usefulness of IGRT systems is in relation to the necessity of sparing the OARs, such as the eye and the optic nerves in case of re-irradiation of craniofacial volumes, the spinal cord in case of re-irradiation of vertebral metastasis or, finally, the rectum and the bladder in the case of pelvic targets re-irradiation [61–63].

Pediatric cancer

The incidence of second radio-induced tumors is a relevant issue in RT in pediatric patients. The childhood cancer survivor study reported the results of 14,359 patients cured of a childhood cancer: 1402 of them developed a second neoplasm, with a cumulative incidence at 30 years of 20.5 % In a multivariate analysis, RT associated with age ($<$ or >15 years), the initial diagnosis, female sex and exposure to chemotherapy (platinum), appeared to be the major risk factors [64].

Thus, in these patients, it is theoretically important to assess carefully also the doses received with IGRT. Literature data are, however, very conflicting about the use of IGRT systems in this setting. In a recent review, the authors propose a reduction in the use of methods based on ionizing beams, and if it is not possible to realize a treatment without the use of volumetric IGRT, they recommend an assessment of some parameters: age, gender, anatomical site of the target, decreasing amperage, use of filters, use of protocols with lower exposure doses, using custom protocols for the frequency of IGRT and careful documentation of the dose received at the target and to all healthy tissues [65].

Conclusions

In summary, in the modern RT era, IGRT seems to be crucial in terms of increasing precision of therapeutic radiation delivery, to increase target coverage and maximize OARs sparing [66]. Specific protocols for the individual treatment sites and based on the available technology are needed to optimize IGRT use and RT department's logistical problems.

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Compliance with ethical standards

Ethical approval The manuscript does not contain clinical studies or patient data. This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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