

Image-guided Radiotherapy

a report by

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Inaccurate knowledge of a patient's anatomy and position during the course of therapy has always been a major source of concern in radiation therapy, potentially compromising the clinical results by insufficient dose coverage of the target volume and/or overdose of normal tissues. The management of target localisation emanates from the concept of treatment margins to cope with the uncertainty of the true location of the target volume during irradiation (gross target volume (GTV); clinical target volume (CTV); set-up margin (SM); internal margin (IM); planning target volume (PTV); and planning risk volume (PRV)).^{1,2} It is generally accepted that two classes of these so-called set-up uncertainties can be identified: systematic and random. Systematic errors exist because the imaging performed for treatment planning is typically a snapshot and the target position determined at that moment may differ from the average target position at treatment time, or if a certain procedure introduces an error that is repeated systematically over time. The random error is the day-to-day deviation from the average target position introduced with internal organ motion and the repeated treatment set-up that occurs in fractionated radiation therapy.

The systematic error is generally considered more important, because if uncorrected it would propagate throughout the treatment course and lead to a deleterious effect on local control. Day-to-day variations may be substantial and require safety margins that limit the maximum dose administered to the tumour volume due to possible toxicity to surrounding healthy tissue. With the introduction of image-guided radiation therapy (IGRT), clinical confidence has grown and it is possible to examine whether the traditional fractionated radiation therapy at 2Gy per fraction is still the optimum strategy. This introduces treatment schedules using fewer fractions (so-called hypo-fractionation),³ and the day-to-day variation in target localisation may no longer be statistically random. Finally, motion management becomes an issue as tumour

motion interacts with dose delivery, causing a dose spread along the path of motion in some delivery techniques.⁴

With the improved imaging modalities to define and delineate tumour volumes, identifying both morphological as well as functional and biologic information, and the introduction of treatment modalities that allow for shaped dose distributions (e.g. intensity-modulated radiation therapy (IMRT), stereotactic body radiotherapy (SBRT) and charged-particle beams), the radiotherapy community is now capable of creating dose distributions that match the tumour volume tightly.^{3,5} Conformal radiation therapy (CRT) aims at shaping the dose distribution to the delineated target volume, whereas conformal avoidance aims at avoiding critical structures. These advances have been driven by the dual goals of maximising radiation dose to tumour volume while minimising the dose to surrounding healthy tissue. Accurate knowledge of the patient's anatomy during the radiation process is of utmost importance, and it can be argued that novel technologies such as IMRT and shaped-beam radiosurgery are useless without proper image guidance.

The concept of image guidance is not new in radiotherapy. Aspects of image guidance have always existed, even with the first use of X-rays for cancer therapy, probably using the same radiation source for both imaging and treatment. The concept of IGRT has been introduced to define the accomplishment of tumour and soft tissue imaging in 'realtime' or 'near-realtime' for the correction of both systematic and random errors on a daily basis. It was born out of the need for both accurate target localisation in IMRT and SBRT and the delivery of boost doses to sub-volumes identified with functional and biological imaging. IGRT will be necessary to exploit the possible clinical benefits of the new treatment procedures. As the capabilities of IGRT improve, it will provide tools to better understand treatment uncertainties and allow a re-examination of the present practice regarding treatment margins. Conceptually, IGRT refers to in-room image guidance just before or during treatment and is based on the assumption that the tumour volume has been defined adequately. The imaging modalities applied for tumour identification and delineation, although they also help to 'guide the treatment', are not part of the IGRT concept in its current definition.

Image-guided Radiation Therapy Solutions

An ideal Image-guided radiotherapy (IGRT) system should have three essential elements: three-dimensional (3-D) and, if possible, motion (four-dimensional (4-D)) assessment of the target volume, preferably 3-D volumetric information of soft tissue, including tumour volume; efficient comparison of the image data with reference data; and an efficacious and fast process for clinically meaningful intervention (preferably fully automated). The clinical introduction of on-line electronic portal imaging devices (EPIDs) has led to an improved understanding of treatment



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uncertainties and a need for strategies to further reduce them.⁶ As early as the 1990s, strategies had been developed to use EPID for near-realtime patient set-up.^{7,8} Although the first requirement (3-D assessment) could be established by using multiple planar images, this procedure never became a mainstream solution as it was cumbersome to implement.⁶ This development did raise the awareness of the potential benefits of image guidance, and the concept of IGRT was born. IGRT solutions could be classified as follows: megavoltage (MV) imaging, kilovoltage (kV) imaging and solutions using non-ionising radiation.

Megavoltage Imaging

The major advantage of MV-based imaging is the fact that the actual treatment beam is used for patient set-up (or verification). There is a direct alignment of the target and treatment beams, avoiding the need for additional calibration procedures of the IGRT system. As the treatment beam is used, it allows for verification of the beam-shaping and assessment of the transmission dose. The latter could be used for dose reconstruction strategies, allowing verification of the 'dose-of-the-day'.⁹⁻¹¹ The application of portal films (radiographic film) as a tool for treatment set-up verification could be considered as the first step in MV-based IGRT. This was a cumbersome method requiring off-line strategies based on population-based statistics to deduce clinically relevant treatment margins. EPIDs have been introduced to replace conventional film-cassette combinations.⁶ With the introduction of EPIDs, two classes of strategies have been introduced: the so-called 'off-line'^{6,12-14} and 'on-line' approaches.⁶⁻⁸ Off-line monitors the position of the individual patient during a limited number of fractions and adapts the safety margins and/or treatment plan accordingly. This approach does not allow for decreasing the treatment margins sufficiently for aggressive CRT and is based on the notion that the systematic component is more important than the random component. The approach should not be generalised, as an example of obese patients clearly illustrates that the random component can be more prominent.¹⁵ The on-line approach offers the possibility of reducing both systematic and random uncertainties, yet it was considered to be time-consuming and requiring automated control of the treatment couch to make it efficient in clinical routine.¹⁶⁻¹⁸ The use of EPIDs is limited in that it is a planar imaging technique requiring at least two images to assess 3-D information on patient set-up. The image quality from MV beams is inferior to that obtained from kV, and often surrogates such as bony structures or implanted radio-opaque markers are required to locate the target volume.⁶

The next step in the evolution process was the introduction of the cone beam MV computed tomography (MV-CBCT).¹⁰ The advantages to this were: volumetric imaging with sufficient image quality for soft-tissue contrast; no additional hardware needed as the same flat panel detector introduced for EPI could be used; and a stable and linear relationship between Hounsfield Units (HU) and electron density with a potential use for dose calculation, and no high-Z artefacts in the images. This allows for accurate target delineation and dose calculation in the presence of high-Z prostheses in patients. An important advantage of CT-based imaging is that it facilitates comparison between the CT-of-the-day volumetric image data set with the reference CT data set that has been acquired for treatment planning. It allows for 3-D localisation, as well as assessment of volumetric changes during the course of treatment, potentially enabling the adaptation of the treatment based on this information.

A completely novel approach is presented with helical TomoTherapy (Hi-Art®, TomoTherapy Inc.), which is the fusion of a linear accelerator (linac)

Figure 1: Patient in Prone Position for Treatment of Rectal Cancer on the Helical TomoTherapy System Hi-Art® (TomoTherapy Inc.) at the AZ-VUB



Note the use of a customised patient support (AIO Solution, Orfit Industries), emphasising the need for patient comfort to help maintain the same position, as the actual patient set-up will be performed based on the MV-CT scan prior to treatment.

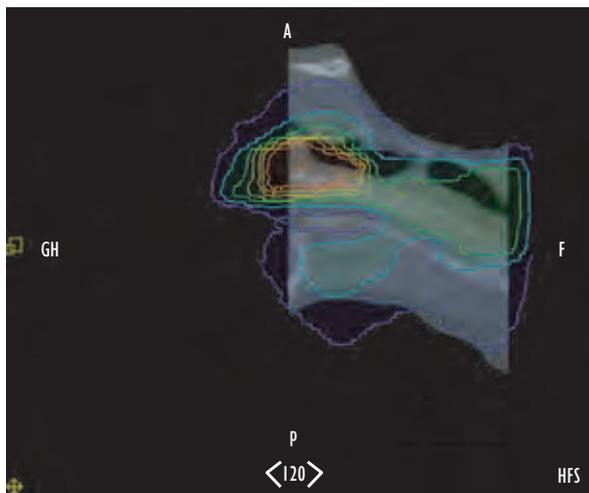
with a helical CT scanner (see Figure 1). This system uses a fan beam to acquire an MV-CT (the energy of the treatment beam is de-tuned from the initial 6MV to 3.5MV in imaging mode, with a lower dose rate of 11cGy/min, opposed to approximately 850cGy/min for treatment mode) of the patient prior to and, if necessary, during treatment.^{9,19} For treatment, a dedicated binary multileaf collimator (MLC) is used to modulate the fan beam to provide rotational IMRT.^{5,19} The beam rotation is synchronised with continuous longitudinal movement of the couch through the bore of the gantry, forming a helical beam pattern. When operating as a helical MV-CT system, the leaves are fully retracted to an open state. The on-board MV-CT option offers a number of verification processes. The MV-CT scan can be fused with the planning CT scan for automated target localisation and positioning prior to treatment. Verification of the automated fusion routine on an anthropomorphic phantom showed correct translations and rotations to an accuracy of less than 1mm or 1°. The set-up correction (involving rotations and translations) can be implemented either by moving the patient or, in principle, by modifying the IMRT delivery to account for the patient's actual geometric offset. It is possible to superpose the prescribed dose distribution on the 'CT-of-the-day' images to align the patient's anatomy with the dose (see Figure 2).

The CT detector system can be operated during treatment to compare the detector signal with the expected signal and, as such, detect deviations or, alternatively, reconstruct the dose delivered to the patient from exit dose measurements on the 'CT-of-the-day'. This reconstructed dose distribution represents the dose the patient actually received, representing a new form of *in vivo* dosimetry. A concern with MV-CT imaging is patient dose. Measurements from both MV-CBCT (approx. 20–90mSv per scan) and MV-CT (approx. 20mSv per scan) show patient doses comparable to other IGRT techniques based on kV or MV.¹⁰

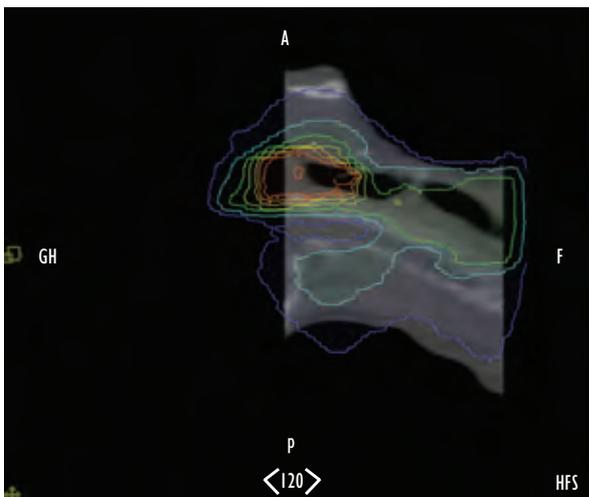
Kilovoltage Imaging

A solution to the inherent limitation of EPIDs on image quality has been offered with the introduction of stereoscopic kV imaging devices.^{17,20-23}

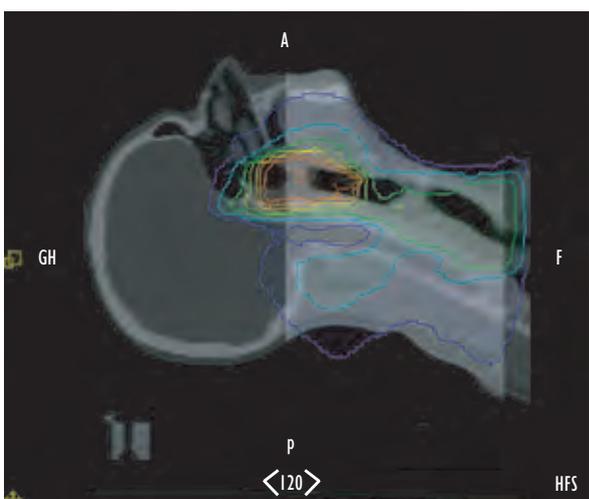
Figure 2: Illustration of Superposing the Prescribed Dose Distribution onto Megavoltage 'CT-of-the-day' Images



A high dose intersecting the patient's spinal cord (orange, green and dark blue represent 70.5, 50.0 and 20.0Gy, respectively).



The error has been corrected and this information will be used to adjust the patient's position accordingly.



The reference kV-CT data set has been superposed on the MV-CT images, together with the dose distribution.

While the use of diagnostic X-rays for verifying treatment set-up is not new, it offers several advantages.²⁴ Image quality (a well-documented problem in EPIDs) is no longer an issue, especially in combination with amorphous silicon (AmSi) detectors.⁶ Patient dosage becomes less important compared with daily megavoltage images acquired with EPIDs. Dose measurements performed at the Academisch Ziekenhuis van de Vrije Universiteit Brussel (AZ-VUB) with an appropriate ionisation chamber resulted in 0.513mSv per image for a typical clinical setting using a ceiling-mounted, dual kV source-detector system (Novalis Body, BrainLAB).¹⁷ The combination with realtime monitoring of patient positioning, independent of linac gantry position, is not limited to target observation, but also offers the possibility of controlling the treatment beam based on that information for breathing synchronised irradiation.

In principle, two approaches exist. One uses image guidance to align the target volume with respect to the treatment beam using a remote couch control,^{4,18,25,26} while the other uses the imaging information to guide the treatment beam using a robotic linac (CyberKnife™, Accuray Oncology).^{20,21} The latter has the potential of true realtime tumour-tracking compared with the former; this can be used to gate the treatment in case of organ motion. An example of the gated treatment is given in Figure 3, using the Novalis Body system. Millimetre accuracy has been reported for both approaches.^{18,20} This ceiling-mounted, dual source-detector configuration has the advantage that it allows for realtime imaging during treatment, but it still requires a surrogate to identify the target (either bony structures or implanted radio-opaque markers). To overcome the two-dimensional (2-D) limitation of planar detection systems in assessing 3-D localisation problems, as with MV, the use of kV CT-scanning has been proposed. This allows the direct comparison of pre-treatment CT data with the planning CT data. kV-CBCT is based on an additional kV source-detector system that is mounted to the treatment machine perpendicular to the treatment beam and allows for volumetric imaging with soft-tissue contrast. The approach originally proposed by Jaffray et al. was to integrate a kV X-ray source and a large-area flat panel detector on a standard linac, allowing fluoroscopy, radiography and kV-CBCT.²⁷ The kV-CBCT allows a volumetric CT image to be reconstructed from data collected during a single gantry rotation. Image quality is generally considered to be superior to the MV solutions, but this is counterbalanced by the fact that the HU-electron density relationship is not straightforward. This hampers its use for dose-calculation purposes.

A final solution in this kV-based approach is the introduction of a state-of-the-art CT scanner in the treatment room. Court et al., reporting mechanical precision and alignment uncertainties for this integrated CT/linac system, give an illustration of the in-room CT system.²⁸ The system described integrates a high-speed CT scanner on rails and a linac. The couch top can be rotated to position the patient for either treatment or scanning, without having to move the patient from the treatment table to the CT couch. These kV-based solutions, as they are added to the treatment machine, require careful calibration to align the axis of the imaging system with the axis of the treatment beam. Both the MV-CT and kV-CT solutions can be used as an IGRT tool only prior to treatment (or near realtime), whereas the dual source-detector solutions can be used during treatment (realtime).

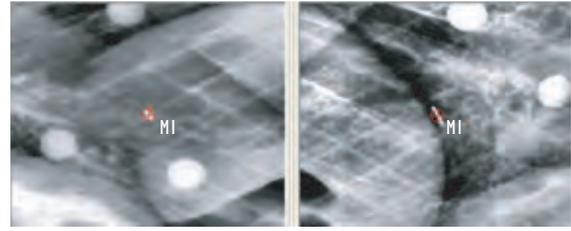
Alternative Solutions

A typical example of high-precision radiotherapy can be found in stereotactic radiosurgery of intra-cranial lesions, which uses an invasive frame that is attached to the patient's head and used as a reference

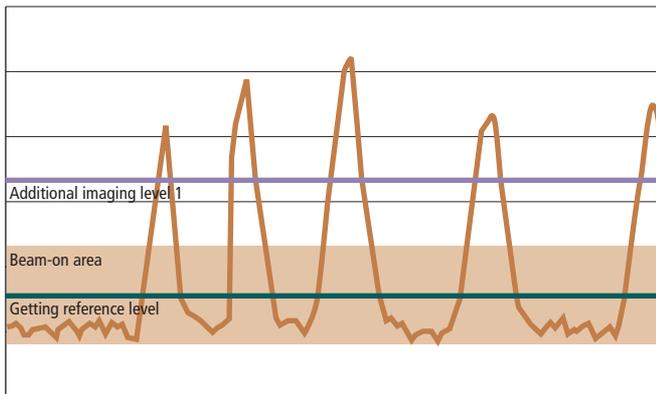
Figure 3: Gated Treatment Using the Novalis Body System (BrainLAB AG)



Room view of the Novalis Body system with six degrees of freedom robotic couch and breathing synchronisation, using a dual kV source-detector solution for IGRT. Note the X-ray tubes embedded into the floor and the flat panel detectors mounted to the ceiling.

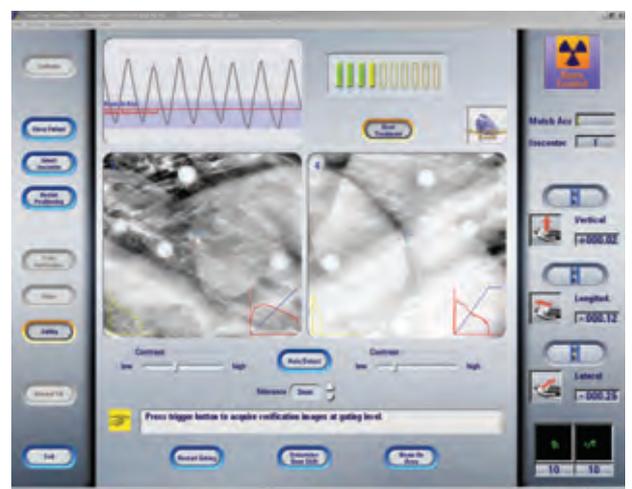
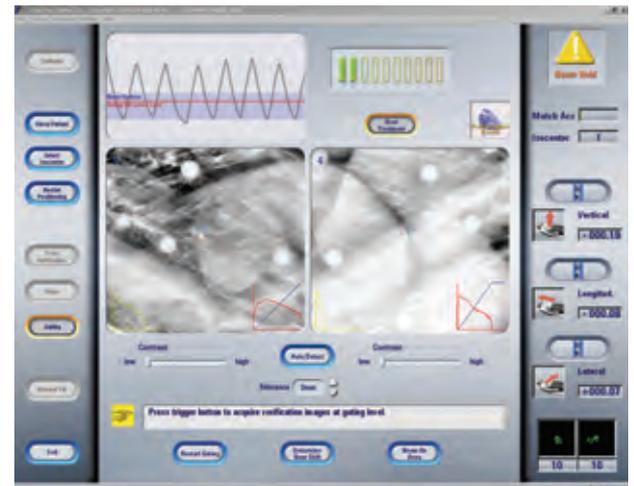


On the acquired images, the implanted radio-opaque marker that has previously been implanted into the tumour volume will be identified. This information will be used to guide the robotic couch to align the implanted marker with the axis of the treatment beam at that particular moment in the breathing cycle.



frame for imaging, localisation and treatment. Following this idea, one might argue that this approach could be extrapolated to high-precision radiotherapy for extra-cranial locations.³ This brings us to the concept of immobilisation. Opposed to intra-cranial locations, where tumour motion with respect to the skull can be assumed to be negligible, this assumption no longer holds for the extra-cranial situation. Wulf et al. investigated the use of stereotactic body frames, observing deviations of up to 12mm (with a safety margin of 5mm) where 12–16% of the target might be partially missed.^{29–31} These investigators concluded that, even with the use of immobilisation techniques, IGRT should be applied for safe margin reduction. It can be argued that patient comfort is to be preferred in combination with IGRT, as opposed to forcing a patient into an uncomfortable position (using immobilisation devices) to maintain a reproducible position during treatment. This is illustrated in *Figure 1*, where a customised combination of positioning aids (AIO Solution, Orfit Industries) is used to help the patient maintain a stable position during MV-CT scanning, positioning and treatment on the helical TomoTherapy machine at the AZ-VUB.

As most IGRT techniques currently used in a clinical set-up are based on ionising radiation (either kV or MV), one might challenge this approach in view of the 'as low as reasonably achievable' (ALARA) principle. Using daily imaging for 38 treatment fractions, patient doses of approximately 2340mSv, 1950mSv, 780mSv, 1950mSv and 40mSv will be obtained from MV EPID, MV-CBCT, MV-CT, kV-CBCT and a ceiling-



Finally, a gating window is defined (blue area), triggering the treatment beam to be 'on' when the breathing signal intersects with this period in the breathing cycle and switching the beam 'off' whenever the breathing signal is not in this area (indicating that the tumour will not be aligned with the treatment beam), as illustrated above. Note also the dotted circle representing a tolerance level of 3mm – if the implanted marker is not inside this tolerance area at acquisition of verification images during treatment (triggered at the reference level in the breathing cycle), this indicates that the correlation between external breathing signal and internal tumour motion is no longer maintained and a new correlation should be established.

mounted dual kV source-detector system, respectively.^{10,17,27} Some alternative solutions are currently being investigated, avoiding the use of ionising radiation in patient set-up. Ultrasound-based solutions are aimed at visualising soft tissue and, in particular, the target volume prior to treatment. The device is typically a portable system situated adjacent to the treatment couch. The import of patient-specific CT structures is required, as well as the isocentre localisation from the treatment planning system, prior to target volume alignment. A system to track the ultrasound probe position in space is introduced (i.e. a mechanical arm or an optical tracking such as infrared (IR) light-emitting devices (LEDs) or IR reflectors that are monitored by stereoscopically mounted IR cameras).^{25,32,33} Initial studies reported that ultrasound realtime positioning of the prostate showed promising results.²⁵ Recent studies comparing these initial ultrasound devices with EPIDs, in combination with implanted radio-opaque markers or daily CT scans, revealed some drawbacks for prostate localisation.^{32,33} The ultrasound-based alignments were systematically different from the marker-based alignments in some directions (depending on the study) and the remaining random variability of the prostate position, after the ultrasound-based alignment, was similar to the initial variability without the use of any alignment other than room lasers. A promising solution is the introduction of magnetic resonance imaging (MRI) in the treatment room, such as the combination linac-MRI that is being investigated at the Universitair Medisch Centrum (UMC) Utrecht in The Netherlands or three rotating sources in combination with a 0.5 Tesla MRI scanner (Viewray Inc).³⁴

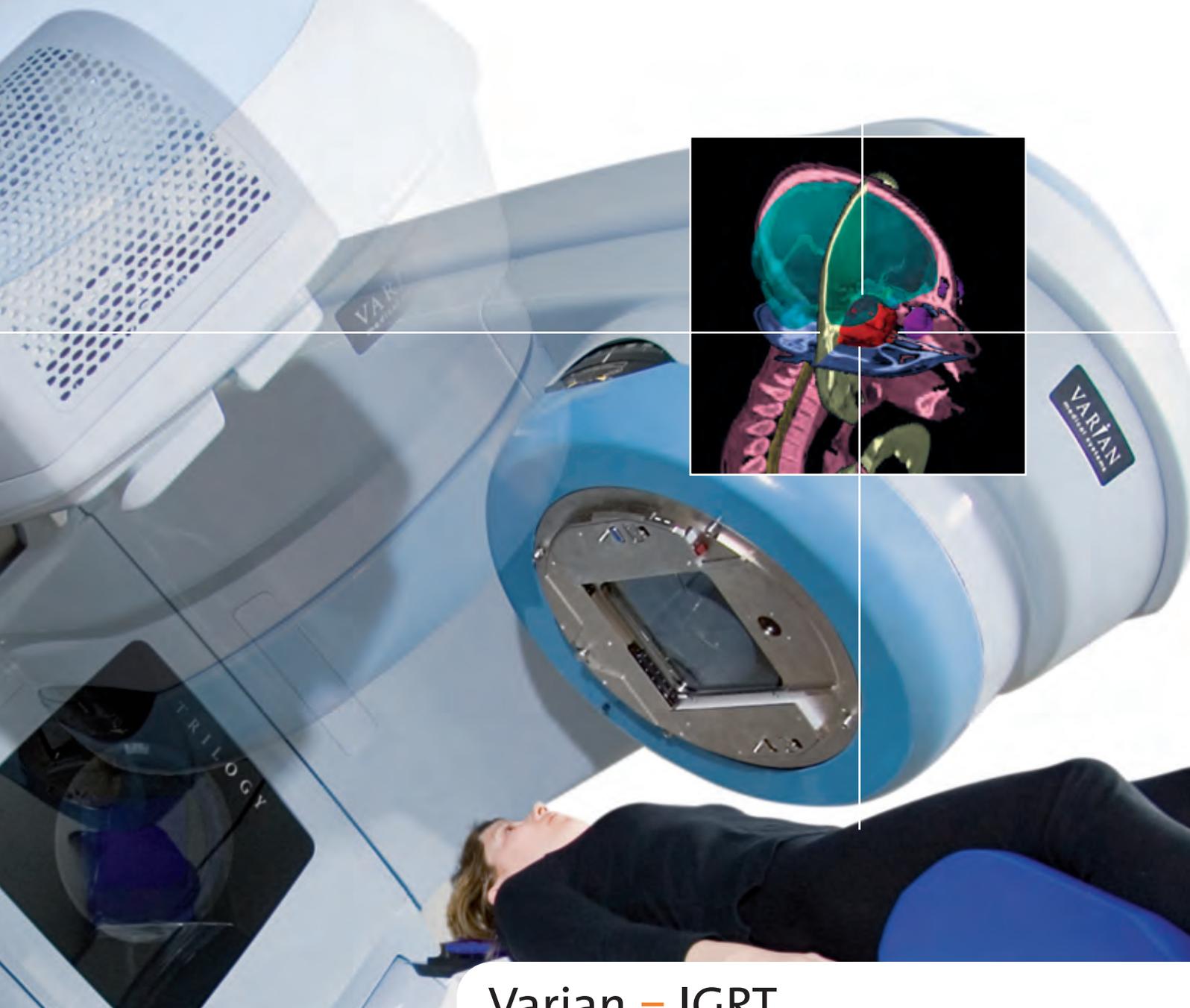
Conclusion

Radiation therapy has gone through a series of (r)evolutions in the last few decades and it is now possible to produce highly conformal dose distributions. This improved dose conformity, together with its sharp dose gradients, have necessitated enhanced beam-targeting techniques for radiotherapy treatments. Components affecting the reproducibility of target position during and between subsequent treatment fractions include displacement of internal organs between fractions and internal organ motion within a fraction. IGRT uses advanced imaging technology to better localise the target volume during treatment or for treatment set-up, and is the key to reducing and ultimately eliminating the uncertainties. Volumetric IGRT solutions allow for assessment of changes in the tumour volume in time and, as such, the potential of adaptive radiotherapy. In this review, some of the clinically implemented developments have been discussed; however, as technology is evolving, many new solutions are being developed and there is always the danger that some developments have been neglected here. A consequence of these fast-moving developments and emerging technologies will be the challenge of deciding which technology is optimal or clinically relevant for treatment objectives. An important logistical question needs to be asked, "Who is going to take the final decision as to whether to correct and then implement the intervention in (near) realtime?" ■

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