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Literature Review

Image-guided radiation therapy using computed tomography in radiotherapy

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Abstract

The sharp dose gradients in intensity-modulated radiation therapy increase the treatment sensitivity to various inter- and intra-fractional uncertainties, in which a slight anatomical change may greatly alter the actual dose delivered. Image-guided radiotherapy refers to the use of advanced imaging techniques to precisely track and correct these patient-specific variations in routine treatment. It can also monitor organ changes during a radiotherapy course. Currently, image-guided radiotherapy using computed tomography has gained much popularity in radiotherapy verification as it provides volumetric images with soft-tissue contrast for on-line tracking of tumour. This article reviews four types of computed tomography-based image guidance systems and their working principles. The system characteristics and clinical applications of the helical, megavoltage, computed tomography, and kilovoltage, cone-beam, computed tomography systems are discussed, given that they are currently the most commonly used systems for radiotherapy verification. This article also focuses on the recent techniques of soft-tissue contrast enhancement, digital tomosynthesis, four-dimensional fluoroscopic image guidance, and kilovoltage/megavoltage, in-line cone-beam imaging. These evolving systems are expected to take over the conventional two-dimensional verification system in the near future and provide the basis for implementing adaptive radiotherapy.

Keywords

Image-guided RT; treatment verification; inter-fractional uncertainties; computed tomography

INTRODUCTION

The success of radiotherapy heavily depends on the accuracy of delivering the prescribed dose to the target volume while sparing normal tissues during all phases of treatment. However, this can be difficult, given the uncertainties during treatment. These uncertainties may result in discrepancies in dose distribution between treatment and planning and, therefore, cannot deliver the intended dose of radiation to the target. In general, treatment uncertainties can occur between or during treatments, that is, inter- and intra-fractional errors. The inter-fractional errors most commonly arise from external setup variation and patient motion, which can be present in all treatment sites. It may also be due to internal geometric and volumetric changes throughout the fractionated radiotherapy course. Many studies had proved that there was tumour or shrinkage of organs at

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risk (OARs) and body-weight loss in head and neck (HN) cancer patients, as well as tumour regression in lung-cancer patients.[1–3] For pelvic treatment, the daily uncertainties can be induced by the differential filling of bowel and bladder, therefore compassing the tumours and causing displacement and distortion,[4,5] whereas the intra-fractional breathing and cardiac motion will lead to organ or tumour movement in the chest and upper-abdomen region during treatment.[3,6] Clearly, the ability to correct inter- and intra-fractional errors is important to the accuracy of treatment in varies sites. Leaving the radiotherapy uncertainties uncorrected may result in discrepancies between the dose delivered and the dose planned, leading to insufficient dose to the tumour and/or overdose to adjacent OARs. Intensity-modulated radiation therapy (IMRT) provides highly conformal treatment with steep dose fall-off outside target volume. It allows radiation-dose escalation and increases the tumour-control rate. However, the sharp dose gradients at boundaries between target and surrounding OARs increase the treatment sensitivity to errors, in which a slight anatomical change may greatly alter the actual dose delivered. Conventionally, a generic margin has been added to the tumour to ensure adequate dose delivery to it, however, there is always the risk of many abutting normal tissues getting unnecessarily irradiated. Moreover, these treatment inaccuracies can be patient specific and may vary with different degree and combination in each individual case. All of these urged the development of advanced imaging guidance systems in radiotherapy.

According to Mackie et al.,[7] image-guided radiotherapy (IGRT) means continuous quality improvement, using images to better achieve the goals of radiation therapy. Image guidance technique allows more precise tracking and correction of patient-specific variations over the IMRT treatment course so that target margin can be significantly reduced. Tumour dose escalation can be carried out safely, and without risking the surrounding normal tissues, which ultimately minimises the normal tissue toxicity and maximises the local tumour control. Image guidance techniques also allow one to monitor the organ changes during the course of radiotherapy.

In-room (i.e. inside radiotherapy suite) image guidance can be achieved by several methods ranging from conventional portal imaging,[3] ultrasound localisation,[8] stereoscopic kilovoltage imaging,[9] computed tomography (CT) to some new, emerging techniques like electromagnetic marker-based localisation and tracking[10] and 3-dimensional (3D) body-surface imaging.[11] Among them, in-room CT imaging, which includes CT on rails, mega- and kilovoltage cone-beam (CB) CT, and helical megavoltage CT, has gained most popularity nowadays, as it provides volumetric images with soft-tissue contrast for on-line verification of tumour. This article reviews the principles of these CT-based image guidance systems and their recent developments. Among them, the system characteristics and clinical applications of the megavoltage CT and kilovoltage CBCT systems are discussed in greater depth because they are currently the more commonly used systems for radiotherapy verification.

IMAGE ACQUISITION AND REGISTRATION

CT on rails

The most straightforward way to obtain volumetric CT images for treatment verification is to install a conventional CT scanner in the treatment room. One of the commercially available models is the Siemens Primatom System (Erlangen, Germany). It consists of a Primus linear accelerator (LINAC) and a Somatom CT scanner with sliding gantry, with each unit located at one side of the patient couch. After positioning the patient appropriately, the couch is rotated 180° to the CT bore. Image acquisition begins when the CT scanner is driven on rails and travels across the stationary patient lying on the couch. After scanning, the CT gantry is retracted to its original position. The treatment couch is then rotated backward such that the patient is under the LINAC gantry for treatment delivery. The imaging parameters of the CT on rails generally resemble those of a conventional CT. The

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gantry can rotate up to 0.33 second per rotation and travel along the rails with the speed varying from 0.1 to 10 cm per second. The field-of-view (FOV) of the CT scanner is 50 cm in diameter.[12]

After image acquisition, the pre-treatment CT images are fused with the planning CT (PLCT) images using the image management software for treatment verification. Both image sets are displayed side by side on the computer screen and can be viewed in transverse, coronal and sagittal planes. The software allows automatic and manual alignment to evaluate the isocentre shift in translational (lateral, longitudinal, vertical) and rotational (yaw, pitch, roll) dimensions. However, the current practice allows only translations and yaw rotations. Therefore, rotational adjustments, except for yaw direction, are being disabled in the registration software during clinical use. In the mode of automatic landmark registration, reference points can be defined on those landmarks that are easily identified on both sets of images for alignment. For visual alignment mode, the two image sets are overlapped such that they can be aligned manually according to the anatomical structures location. Structure contours from the PLCT can also be displayed on the verification images to aid the alignment process.[12,13] Normally the time needed for scanning plus registration is about 7 to 8 minutes.[14] The offsets measured by the registration system are then corrected by precise couch motion before proceeding to treatment.

Megavoltage CBCT

Technical innovation in portal imaging system recently allows the acquisition of volumetric data, in addition to conventional 2-dimensional (2D) images. The megavoltage (MV) CBCT imaging utilises the radiation source of the LINAC and the electronic portal imaging device (EPID) for image acquisition. This provides a more compact system configuration when compared to the CT-on-rails system. During image acquisition, a series of portal images (projections) are captured by the EPID while the gantry rotates to place the patient under treatment position. These projection images are then reconstructed using the Feldkamp filtered back-projection algorithm[15] to give volumetric image set. The imaging energy ranges between 2 and 8 MV, depending on the output of the LINAC.[14] Typically, the gantry rotates at a speed of 6° per second, and one portal image is obtained in each degree. The FOV is 24 cm in diameter and 28 cm in longitudinal dimension.[16] Unlike conventional CT, partial gantry rotation (e.g. 180° with 180 projections) is possible for volumetric image reconstruction. The acquisition procedure plus the time for image read-out take about 1.5 to 3.0 minutes. The imaging dose is estimated by the product of total number of projections and the dose delivered by one image, which is approximately 1 to 15 cGy.[17,18]

The reconstructed MVCBCT image set is superimposed to that of the PLCT in the transverse, coronal and sagittal planes for registration. The MVCBCT is displayed in a different colour scheme with adjustable transparency level such that either one CT set or superimposed images of both CT sets are visualised. Matching can be carried out automatically by mutual information algorithm.[17,18] The anatomic landmarks can also be aligned manually, and the structure contours and isodose distribution can be displayed on the MVCBCT images for the fine-tuning of the registration result. Again, the LINAC couch motions allow only translational and yaw correction, in spite of the registration software's ability to quantify the errors in all six vectors.

Kilovoltage CBCT

Cone-beam reconstruction technique is also applicable with the use of kilovoltage x-ray source. Elekta Synergy (Crawley, United Kingdom) and Varian Trilogy (Palo Alto, USA) are the two common systems that are mounted on LINAC for pre-treatment kilovoltage (kV) CBCT imaging. Both systems consist of a kV x-ray tube and an amorphous silicon flat-panel detector which is attached to the LINAC, perpendicular to the radiation-beam direction. Other than volumetric imaging, these systems also allow 2D radiography and fluoroscopy. Similar to MVCBCT, the gantry with the

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x-ray tube is rotated once round the patient in treatment position for image acquisition. Image projections acquired by the detector are reconstructed to give CBCT images. Most of the imaging parameters for kVCBCT are variable. In general, the imaging energy is ranged from 40 to 130 kVp and 25 to 100 mA, and the rotation speed is 6° per second. The FOV is 50 cm in diameter and 25 cm in longitudinal dimension. The system requires 1 to 3 minutes for image acquisition. The imaging dose is 0.3 to 6.0 cGy, depending on the imaging parameters employed.[17,19,20] The image registration process and the software design are similar to those used in the MVCBCT system. Overlapped images in three orthogonal planes are displayed for automatic or manual fusion. After defining the setup errors, corresponding couch adjustments are then performed and patient is ready for treatment.

Helical megavoltage CT

The helical megavoltage (MV) CT imaging is provided by the Tomotherapy HI-ART System (Madison, Wisconsin), which is an integration of a LINAC and a CT scanner. Inside the ring gantry, there is a short LINAC with a xenon detector positioned in the opposite side. The MVCT image acquisition process is similar to that of conventional CT scanner: patient in treatment position is continuously translated through the gantry, with x-ray fan beam rotating above the patient. In the imaging mode, the beam energy is detuned to 3.5 MV, and full-gantry rotation (i.e. 360°) is in a speed of about 6 second per rotation.[21] Depending on the length of the scan region, the total scan time requires 3 to 10 minutes (scan time = number of slices x gantry rotation speed).[7] The maximum FOV is 40 cm in diameter and 180 cm in longitudinal dimension. The imaging dose is approximately 1 to 3 cGy.[21,22]

Similarly, the MVCT images are superimposed onto the corresponding PLCT images and are displayed in a range of colours, and in three orthogonal planes, for automatic or manual alignment. According to the tomotherapy-treatment-couch specification, correction of the setup errors can only be carried out in the translational dimensions. The roll correction is addressed by modifying the initial gantry angle. The pitch and yaw adjustments, though available in the software, are not used as currently they can be corrected only by physically moving the patient. In practice, automatic registration will be carried out first, followed by manual fine-tuning. The registration result can be validated by matching the anatomical landmarks on the two image sets or by displaying the structure contours and isodose cloud on the MVCT image set, to ensure correct dose is delivered to the intended area. According to the registration result, the couch and the initial gantry angle are adjusted automatically before the start of treatment.

COMPARISON BETWEEN MVCT AND KVCBCT

An ideal image guidance system is able to generate high-quality images with low imaging dose, which can accurately detect and quantify the patient-positioning errors as well as internal organ displacement and deformation. Moreover, the system should allow fast and accurate correction of the errors detected. The system performances of MVCT and kVCBCT are compared in terms of hardware configurations and specifications, image quality, and imaging dose (Table 1).

Hardware configurations and specifications

MVCT images are in exact geometric coincidence with the treatment because same x-ray source is used for imaging and treatment. But for kVCBCT, which uses an isolated kV x-ray source, cross-isocentre calibration is needed.[23] The maximum longitudinal FOV of 180 cm makes MVCT suitable for verifying prolonged treatment area, whereas kVCBCT with a limited detector length (25 cm) may require two scans for a long treatment region. Nevertheless, kVCBCT has a faster image-acquisition time, as it images the whole volume with a single gantry rotation. The ring-gantry design allows a full unobstructed gantry rotation in MVCT, whereas the retraction and extraction of the CBCT detector arm involves the risk of

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Table 1. *Summary of the comparison between the system performances of MVCT and kVCBCT in terms of hardware configurations and specifications, image quality and imaging dose.*

		MVCT	kVCBCT
Hardware configurations and specification	Setup-error detection by software	3 translational + 3 rotational directions	
	Physical couch adjustments	3 translational directions	
	X-ray source	Same as treatment source	Separated from treatment source
	Longitudinal FOV	180 cm	25 cm
	Image acquisition time	3–10 minutes	1–3 minutes
	Collision risks	NA	Yes
	Images dimensions	3-dimensions (volumetric images)	
	Intra-scanning motion artifacts	Yes	
	Uniformity & spatial resolution	Comparable	
Image quality	Radiation interaction	Compton scattering	Photoelectric effect
	Contrast resolution	Relatively low	Relatively high
	Imaging of metallic implants	Clear images	Signal loss/Streaks in images
Imaging dose		1–3 cGy	0.3–6.0 cGy

collision. Moreover, for CBCT, when scanning laterally situated target, for example, breast and limbs, with patient positioned to one side on the couch, only partial gantry rotation is possible, which in turn may degrade the image quality.

MVCT and kVCBCT volumetric imaging allows detection of rotational errors that may be missed in the conventional orthogonal planar match. However, the physical restriction of the couch in yaw and/or pitch adjustment not only reduces the registration accuracy but also increase the setup errors in translational dimensions. A yaw offset without correction during fusion will increase the lateral shift, whereas uncorrected pitch errors will increase the vertical and longitudinal shifts.[24] Effort has been put in developing the pitch and yaw correction algorithm for tomotherapy couch in order to eliminate possible errors during the process of physical patient adjustment.[25] A hexapod robotic treatment couch, which allows pitch, roll and yaw correction up to 3°, is now available to complement CBCT.[26]

Image quality

The volumetric images provided by the MVCT and kVCBCT systems give superior soft-tissue visualisation over the conventional EPID verification.[18,27] This advantage allows direct measurement of organ–target variation instead of using bony structures as surrogates. Moreover, the 3D images are readily comparable to the PLCT images in a slice-by-slice fashion in different viewing planes. Errors in various directions and organ deformation can be easily detected.

With the scan time of greater than 1 minute, both MVCT and kVCBCT are classified as slow CT systems. That means, whenever there is an intra-scanning motion, for example, breathing, there will be artefacts like blurring, doubling and distortion which degrade the image quality and affect target localisation accuracy. Nonetheless, both MVCT and kVCBCT images have been demonstrated to give sufficient details for setup verification and delineation of certain soft-tissue organs.[19,21]

A study by Meeks et al.[28] on MVCT imaging performance reported that the uniformity and spatial resolution of MVCT images were comparable to kVCT images, but not the ones with low-contrast resolution. This is due to the Compton scattering effect on MV energies, which results in poorer soft-tissue contrast. For kVCBCT, the dominant photoelectric (PE) radiation effect, which depends on atomic

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number, facilitates better soft-tissue visualisation in the images. However, kVCBCT may not be favourable for patients with metal implants, for example, dental filling and hip prosthesis. Due to the inherent PE effect on kV energies, beam-hardening and clipping artefacts are visible around the metallic objects, which results in signal loss or dramatic streaks. Conversely, Compton scattering allows MVCT to give better results under this circumstance: clear images showing the implants, and nearby bony and soft-tissue anatomy seen with only a slightly degraded image quality.

In kVCBCT, the imaging parameters are variable, depending on the image quality required and the dose to be delivered to the patient. In terms of patient's size and anatomical sites, a large or thick body region like pelvis has great x-ray attenuation and, therefore, requires higher energy for acceptable image quality. Image quality can be improved by using smaller FOV, as there are fewer chances of scatter; higher current for reduced noise; and greater range of gantry rotation, with slower rotation speed for more image projections. However, the increase in energy and beam-on time (to get more projections) inevitably gives higher imaging dose to patient, which requires critical consideration during the scanning process. Moreover, the imaging performance of kVCBCT is particularly affected by the use of flat-panel detector and the cone-beam geometry. Unlike conventional CT detector, the flat-panel detector has only limited dynamic range. The large variation of x-ray fluence passing through the body can overwhelm the detector-signal range at the periphery and can, in turn, cause signal saturation. This in turn leads to information loss during image acquisition and image artefacts due to truncation of anatomy.[17] The cone-beam geometry also generates severe scatter radiation in patient that reaches the detector. The scatter component increases with large FOV and irradiated volume, for example, pelvis region, and reduces the image contrast to noise ratio with distracting shading artefacts. The signal loss together with the scatter deteriorate the overall uniformity, low-contrast visibility and CT-number accuracy in kVCBCT images; therefore, the image quality of kVCBCT is inferior to that of conventional CT.

Imaging dose

In standard scanning condition, the dose per scan from MVCT and kVCBCT are 1 to 3 cGy and 0.3 to 6.0 cGy, respectively. This dosage is comparable to those using orthogonal MV radiographs for verifying setup.[20] However, for highly precise IGRT, daily imaging is performed and results in substantial accumulating dose, which may exceed 1 Gy in 30 fractions of treatment. Moreover, MVCT and kVCBCT irradiate a much larger volume than do MV radiographs. As a result, it is difficult to include the imaging dose in the treatment-dose regimen, as in the case of MV portal imaging.[19] The daily large-volume irradiation also results in significant dose delivery to adjacent normal tissues and increase the probability of causing secondary cancer to areas that were non-malignant before dose delivery.[20] For verifying laterally situated target, the contralateral tissues are unnecessarily being irradiated during full gantry rotation. kVCBCT imaging was found to contribute greater than 1 cGy peripheral dose per scan (i.e. dose outside the imaged volume),[29] and a similar result for MVCT is also likely. Therefore, the risk of secondary malignancies should be weighed against the potential clinical benefit of using these image guidance systems for setup verification. For kVCBCT, reducing the energy, number of projection, FOV and partial gantry rotation for a given scan can minimise in-field and peripheral dose. For MVCT, the imaging dose can be reduced by shortening the longitudinal FOV or lowering the machine output. If high dose is unavoidable, the extra imaging dose can be calculated and factored into the dose tolerance during treatment planning for critical organs such as the lens, or the other option would be to reduce the imaging frequency.

CLINICAL APPLICATIONS OF THE MVCT AND KVCBCT SYSTEMS

In the following, the clinical applications of the MVCT and kVCBCT imaging systems in the

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management of inter-fractional uncertainties are thoroughly reviewed. The two systems are discussed separately under their applications of three body regions, which are the head and neck (HN) region, thoracic and upper-abdomen region, and pelvic region.

Head and neck (HN) region

Basically, organ motion is not an issue for this region, and the setup uncertainties are relatively small due to a more rigid immobilisation system. The major challenge for IGRT here is to detect the tumour or adjacent organ shrinkage and body-weight loss that consequently lead to target/OARs dose discrepancies during the treatment course. Other than the tumour itself, the surrounding bony landmarks can also be used as reliable surrogates for treatment verification, owing to their more stable geographical relationship with the tumour.

MVCT allows good contrast between bone, soft tissues and air cavities in the HN region, which makes image fusion easier in this region than is possible in other anatomical sites. Although images are more grainy compared to kVCBCT, the tumour volume is clearly visible, especially for those situated in air-filled sinus. However, for brain tumours that are surrounded by the normal brain tissues, the tumour boundaries are more difficult to differentiate; therefore, skull bone is used as surrogate. The translation and roll errors were less than 2.6 mm and 1.2°, respectively, in Schubert et al.'s study.[24] In particular, the small degree of rotational errors in this region can be easily detected by CT images, but not by 2D planar images, which in turn emphasises the advantage of applying volumetric imaging in precise radiotherapy treatment.

Daily MVCT has been used to quantify the parotid shrinkage during HN treatment. The parotid glands showed a median-volume shrinkage of 21% and migrated towards the patient centre at a rate of −0.22 mm/day.[30] In Han et al.,[31] the average parotid volume had decreased by 36%, which led to a 75% increase in median dose at the end of treatment. Lee et al.[32] also reported a 15% difference in daily mean parotid dose, with the total mean dose increasing from 29.7 Gy to 32.7 Gy. These results were comparable to studies using other image guidance systems,[1,2] and this implied that the parotid-dose increment was related to their migration into the high-dose region. Moreover, the maximum dose delivery to spinal cord had increased to 7.6% in average and in the absence of IGRT performed to verify its position.[31]

Regardless of the occasional metal artefacts arising due to implants, for example, dental amalgam, kVCBCT also demonstrates good definition of bone, air and soft-tissue interfaces in the case of HN, yielding superior results compared to the 2D EPIs.[19] Similar to that observed in MVCT, the tumour is barely visible in the cranial region, and registration is performed on the basis of parameters related to bony anatomy. Wang et al.'s study[33] showed a setup error of less than 3 mm in NPC case, which increased significantly when patients lost more than 5% of their body weight. With kVCBCT, Ding et al.[34] presented significant changes in patient's skin contours and planning target volume (PTV) contours throughout a treatment course. More pronounced organ shrinkage and displacement had been seen in patients with advanced tumours and in the later fractions.[35]

Thoracic and upper-abdomen regions

The treatment uncertainties in these regions are mainly due to target or organ movement induced by cardiac and respiratory motion. The performance of the IGRT systems is assessed by their ability to visualise these errors. As the tumour position is sometimes independent of the bony anatomy, the tumour itself should become the surrogate instead of the neighbouring bony structures.

Clearly, volumetric imaging with soft-tissue visualisation is a more effective approach than 2D planar imaging for verifying the tumour location in these regions and owing to the lack of reliable bony reference. Nevertheless, the MVCT and kVCBCT image quality is suboptimal due to their slow CT imaging feature. The

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tumour is usually blurred or distorted because it is visualised during motion. Although the patient's breathing induced blurring of organ boundaries in images, accurate discrimination remains possible in kVCBCT images, especially for lungs, kidneys, liver and spinal cord.[19] Nonetheless, it is difficult to separate the blurred tumour from the thoracic wall, mediastinum or the diaphragm if the tumour is situated close to them.[36] The inter-fractional error in pulmonary case was 7.7 mm ± 1.3 mm.[37] In the case of breast region, using partial gantry rotation during kVCBCT also gives acceptable images of chest wall, heart and lungs for setup correction.[19]

When using MVCT, the errors in the case of visualising lungs were found to be less than 6.1 mm in translation and less than 1° in roll rotation,[24] but could be as high as 17 mm in the antero-posterior (AP) direction.[38] Compared to these organs, however, it was liver that was shown to have the largest of displacements and shape changes in the supero-inferior (SI) and AP directions.[38] However, MVCT significantly reduced setup error in oesophageal tumour; as a result, a smaller PTV margin could be applied with the possibility of lesser irradiation of the lungs.[39] Furthermore, some studies have demonstrated the ability of daily MVCT to monitor the tumour regression in the lungs. The average regression rate was shown to be 1.2% per day[40] with the dose received by 95% gross tumour volume (GTV) and an average increase in radiation by 0.1% per day.

The relatively slower MVCT and kVCBCT scan reflects the motion-encoded tumour position rather than the snap-shot position as in the case of PLCT. The different presentation makes registration between the two image sets inappropriate and results in large patient-to-patient variation in translational errors. The organ movement can be corrected using respiration-correlated 4DCT to define the motion-encompassing CTV and PTV. The contoured 4DCT is then used for treatment planning and subsequent daily setup verification with MVCT and kVCBCT. This method proved to be adequate and allowed setup-error reduction from 5.2 mm to less than 2.0 mm.[41] Another option would be to overlay the contours from the 4DCT on the normal PLCT and use them for planning and registration. In this approach, for adequate dose delivery to the tumour, one should ensure that the blurred tumour lies entirely within the motion-encompassing PTV.

Pelvic region

The most prominent factor that limits the accuracy of treatment delivery in pelvic region is the organ deformation and displacement between fractions. Unlike periodic respiratory motion, these changes are more unpredictable and may alter the body-surface contour. This reduces the accuracy of treatment setup using external skin marks. An effective IGRT system for this region should provide high image contrast to differentiate various organs and visualise their changes. Due to the independent movement relative to bony structures, soft-tissue tumour and surrounding OARs should be used as the surrogate for precise verification.

Due to the rectum- and bladder-volume changes, there is substantial movement of the prostate, cervical and endometrial tumours between fractions. Santanam et al.[42] presented the setup error of 1.3 to 4.8 mm for gynaecologic malignancies. In Schubert et al.'s study[24] that dealt with prostate tomotherapy, the errors detected were less than 7.2 mm in translation and 0.5° in roll rotation, with a particularly large error in the vertical direction. This was due to the sagging of couch when it was largely extended into the gantry bore. As the effect of couch sag increases with body weight,[43] image guidance is of great benefit for heavier patient to correct this setup uncertainty. In prostate cancer, MVCT registration was mainly based on the tumour and detectable bladder.[24] However, it was shown that the volume change in bladder could be as large as 50%.[38] Moreover, because the primary goal is to track the prostate position and deliver adequate dose to it, the dosages to the bladder and the rectum are frequently in variance with the treatment plan, particularly due to their random daily filling.[44] Dose-guidance radiotherapy would be needed to monitor these OARs doses. In some cases,

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due to the inferior soft-tissue contrast provided by MVCT, the prostate and bladder may fuse together in image. Using implanted marker as surrogate could be a way to improve the verification accuracy and reduce inter-observer variance.[45] With daily MVCT, Fiorino et al.[46] also illustrated that the excellent effect of rectum emptying drastically reduced prostate motion, reflected by only 5% of fraction that required $\geq$3 mm shifting.

Moseley et al.[47] showed that the accuracy levels demonstrated by kVCBCT for prostate radiotherapy setup correction are comparable to that demonstrated by MV portal images. The ability of kVCBCT to visualise soft-tissue organs was an advantage, but the boundaries of prostate, bladder and rectum were only partially differentiable.[19] These uncertainties in the kVCBCT images increased again the inter-observer errors during the registration process. Similar to MVCT, implanted prostate markers could be used to facilitate the alignment process and help increase the verification accuracy. In marker-based IGRT using kVCBCT, the prostate displacement of $\geq$3 mm was shown in 82 out of 96 fractions and mostly in the postero-inferior direction.[48] Moreover, the prostate could be deformed to in varying degrees. Thus, shifting and deformation were highly correlated with the rectal state, but not much with bladder.[38,48] The result implied that there was indeed benefit in emptying the rectum before PLCT and treatment so that the prostate movement could be minimised.

Many factors can affect the image quality of kVCBCT in pelvic region. Basically, better soft-tissue contrast is gained with smaller patient size, full bladder and gas-filled rectum (air–tissue interface). It is shown that the bladder dome was easier to distinguish than the bladder base or prostate apex, and a clear boundary could be seen at the prostate–rectum interface. In general, images in the sagittal and coronal planes are more differentiable. Specifically, confident tumour localisation in bladder- and rectal-cancer patient could be achieved using kVCBCT, but it is not possible in the case of prostate because of the unclear presentation of the prostate apex and base in images.[19] As the prostate displacement cannot be accurately quantified, reduction of PTV margin should be performed with caution.

RECENT DEVELOPMENT

Though CT-based IGRT has enhanced the capability of verification in radiotherapy, there is still scope for improvement, which is further discussed in the following sections.

Soft-tissue contrast

One prerequisite for implementing IGRT is the provision of adequate anatomical information for accurate patient alignment. The CT-on-rails provides the best image contrast among the four types of in-room CT-imaging techniques discussed here. Developments related to conventional CT scanner, such as high-resolution CT, have been reported in some studies.[49,50] For the CBCT and MVCT systems, the soft-tissue visualisation is inferior, and the blurring of soft-tissue boundaries, regardless of organ motion, can mislead therapists in their clinical judgments and, in turn, result in inaccurate shifting of patients' position. If uncertainties are present in defining the target during treatment, it is a potential hazard, rather than merit, to reduce the margin through the use of image guidance systems because this conversely increases the risk of target missing. In some treatment regions, implanted markers continue to be used to assist the verification process, but they carry the risk of infection and are not effective in assessing organ rotation and deformation. Therefore, improvement of the image contrast in these two verification modalities is needed.

The problem of metal artefacts in kVCBCT images can now be reduced by modifying the projection data using metal artefact-suppressing algorithm. Reconstructed kVCBCT images of more advanced systems have improved soft-tissue visibility near the metal object.[51] The large amount of scatters at the imaging can be reduced by some physical modifications, for example, separating the region into two scans (i.e. decrease FOV) or optimising the source-to-detector distance.[52] Adding anti-scatter grids

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can not only improve contrast but also increase the noise.[53] Recently, a scatter-noise-suppression algorithm to correct scatter during image reconstruction has been reported.[54] Specifically, x-ray-intensity-shaping filters (bowtie filters) have been used in CT scanners for years, and its usage is now extended to the kVCBCT system. Bowtie filter flattens the beam profile across the detector by maximising the primary beam to the thicker body centre while reducing it to the thinner peripheral body part. Reduction in primary beam at periphery reduces scatter at the detector. The primary beam reduction also prevents detector saturation by cutting out excessive signals. Phantom studies demonstrated the bowtie filter had good performance on kVCBCT images, with spatial non-uniformity decreased from 9.8% to 2.1% and almost 100% CT-number recovery at periphery.[55,56] The overall image quality and CT-number accuracy (±21HU) were improved owing to the reduction of scatters and beam hardening. The patient dose was reduced by 26 to 43%. The bowtie filter has already been implemented to the kVCBCT system in some centres. However, like CT imaging, the influence of the filter selection, patient size and patient centring in the scan field on kVCBCT image contrast and dose should be quantified to maximise its usage in future.[57]

Like kVCBCT, MVCBCT images also suffer from image noise and x-ray scatter produced by cone-beam reconstruction technique. Moreover, the fact of low-quantum efficiency of EPID and the Compton scattering effect on MV energies also hinder its soft-tissue sensitivity. In order to achieve image quality similar to that of kVCT, a prohibitively large dose, for example, 50 to 200 cGy have to be applied if MVCBCT is used. Recently, efforts have been made to modify the imaging detector with new scintillation materials in order to increase its efficiency and dynamic range[58–60] for better soft-tissue visualisation while maintaining the dose at 4 to 16 cGy. There are also clinical data showing the feasibility of using lower dose (1.8 cGy) MV cone-beam images for treatment verification.[16] Besides, there are ongoing studies on using diamond and graphite instead of tungsten as target material for x-ray-beam generation during MVCBCT. [61,62] In lower energies (4 MV) and without using the flattening filter, the spatial resolution was greatly improved with the use of these alternatives, especially with the diamond target. Last but not the least, the tomotherapy system provides the post-processing function of 'TomoImage Filter', which helps reduce noise and subsequently improves the image quality.

Contrast agent is also being suggested to increase low-contrast delectability in kV CBCT. It shows benefit over implant markers which will be present in the follow-up examinations such as MRI or CT after the radiotherapy course. Intravenous contrast helps visualise the hepatic vessels and tumours, which allows higher setup accuracy on liver IGRT.[63] Currently, a contrast-enhanced biodegradable surgical marker which can be imaged with CBCT, MVCT and EPID is under investigation.[64] For MVCT, contrast enhancement may be given by a low-density agent such as air-rectal balloon.[17] Before widely applied, more studies should be carried out on the types of contrast agents used and development of safety protocols according to injection time, patient's site and condition.

Digital tomosynthesis (DTS)

A new imaging technique, digital tomosynthesis (DTS), has recently been introduced in the kVCBCT system. It reconstructs the volumetric images with substantially fewer image projections acquired through limited gantry rotation (e.g. 40°), while maintaining good image quality for treatment verification. In brief, initial image projections are acquired with gantry rotation centred at AP or lateral direction, yielding stacks of 3D DTS slices in coronal or sagittal planes, respectively. Due to the finite scan angle, high-quality axial DTS slices cannot be obtained. Similar to kVCBCT, the 3D DTS images are reconstructed using the Feldkamp filtered back-projection algorithm. The reference DTS images are generated from the PLCT data and are registered to the treatment DTS images for setup verification. In contrast to kVCBCT, the DTS only requires narrow scan angle and, therefore, can be used in

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patients with peripheral target, for example, breast, to solve the problem of geometrical clearance needed for full gantry rotation. Smaller arc also means lower imaging dose delivered to patients during image guidance process. Furthermore, the DTS scan can be completed in a shorter time, less than 5 seconds. This feature is desirable for imaging tumours in chest and abdominal regions, which are prone to organ movement.[65]

Several studies have been conducted to quantify the advantages of DTS technique. Godfrey et al.[66] studied the DTS performance on HN, liver and prostate case and presented similar image appearance between DTS and kVCBCT. In particular, DTS images showed clearly the bladder, prostate and rectum boundaries enabling target localisation. With breath holding, the DTS image is good at visualising the liver. Without breath holding, the DTS images still provide better visibility over free-breathing kVCBCT due to the shorter scan time. Wu et al.[67] and Zhang et al.[68] presented that the DTS position accuracy was only 1 to 3 mm different from kVCBCT, which was regarded as satisfactory. Dose reduction was shown in all the studies mentioned previously under this section. Nevertheless, Zhang et al. experienced difficulties in identifying the breast-tumour bed in DTS images and emphasised that there was insufficient information of DTS images for monitoring tumour-volume changes.

The above-mentioned advantages of the DTS system indicate that it is a potential alternative to kVCBCT imaging, but studies are still limited in this area. Extensive investigations involving more samples in various treatment sites on quantification of dose reduction and optimisation of imaging parameters should be carried out to aid its full implementation in IGRT.

4D and fluoroscopic imaging with IGRT system

The impact of intra-fractional errors is not discussed in details in this article but should not be neglected. It is well known that the organ motion due to breathing limits the delivery accuracy. Respiration-correlated 4D CBCT, similar to 4DCT, is introduced to verify the position, shape and trajectory of the moving tumour and enables safe delivery of gated IMRT.[69–71] Active breathing control (ABC) is also integrated to the kVCBCT system for breath-hold radiotherapy.[72] Zhang et al.[73] suggested a new 4D tomotherapy technique that utilises dynamic 4DCT data for treatment plan optimisation. In addition, 4D MVCT data can be acquired and sorted on the basis of respiration phase which allows offline review of target motion.[74,75]

Real-time tracking of tumour motion and position using IGRT system also become a popular topic, as it allows monitoring of unpredictable infra-fractional organ movement like prostate motion. Such monitoring technique is beneficial to prolonged hypofractionated treatments where high dose per fraction is prescribed. The fluoroscopy function could also be integrated with gating technique to obtain 4D images during gated IMRT treatment. The technology of kV fluoroscopic imaging during MV therapy, given by the kVCBCT system, is continuously evolving. There were clinical evidences on its feasibility in assessing the infra-fractional displacement of prostate[76] and real-time tracking of moving fiducial markers.[77] However, this technique suffers from MV-beam scatter on the kV images[78] and its lack of ability to visualise the beam's eye view (BEV). The treatment source itself can be used for fluoroscopic imaging. Utilising the high-energy treatment beam allows noise reduction and low-contrast enhancement during image generation. In addition, the modality does not require extra time and dose for treatment verification. However, this technique has some inherent problems. The constantly changing fluence and multiLeaf collimator (MLC) pattern during IMRT treatment induces difficulties in acquiring acceptable images. Also, the anatomical information given by the image may be inadequate for verification, owing to the fact that the treatment beam only target to the tumour for therapeutic purpose. Nevertheless, the MV fluoroscopy has been successfully used to evaluate the stability of liver position during

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ABC treatment.[79] Investigation has also been carried out on collecting MVCT image during tomotherapy treatment.[80] The real-time CT data that reflect immediate organ position in 3D aspect would be more useful for treatment verification.

kV/MV in-line CBCT system

Recently, Siemens has introduced the ARTISTE system, which integrates the kVCBCT system to the LINAC using an 'in-line' approach. This implies that the x-ray tube is mounted in a retractable arm adjacent to the EPID while the flat-panel detector is placed beneath the MLC system at the gantry head. The imaging beam and the treatment beam are, therefore, opposite to each other, with their central axes aligned and sharing the same isocentre. This setting potentially provides kV or MV to 2D, 3D cone beam, 4D, as well as real-time image acquisition. Optimal modalities can be selected according to the treatment site's characteristics and treatment technique used. During monitor unit calculation, a factor must be applied to account for the presence the kV image detector between the therapy beam and the patient.[81] Other than this, there is no impact of the detector on the dose distribution profile. This kV/MV in-line CBCT system presents several advantages. It is less bulky than those currently used in most centres (refer to previous descriptions of this article). With the unique geometry, wide field image can be captured in line within the BEV (i.e. rotated 180°) during kV fluoroscopy, which facilitates the motion verification of target or OARs during treatment.

CLINICAL IMPACTS AND CONCLUSION

Compared to EPIDs, which can only produce 2D images, in-room CT IGRT systems definitely show advances in providing target visualisation and real-time tracking function which allow more precise radiotherapy treatment. Furthermore, the implementation of these systems contributes to the advancements in the field of radiotherapy. The vast data on geometrical errors acquired by the IGRT systems provide the basis to review the reproducibility of certain immobilisation systems and make improvement. Close monitoring in organ size and shape provides opportunities to analyse the radiation response that expands the radiobiologic knowledge. Today, great strides have been made from IGRT to adaptive radiotherapy (ART). By projecting the planned beam fluence to the CT data acquired by the IGRT systems, dose distribution on a specific treatment day can be calculated for dose verification. Treatment plan can then be revised according to the dose changes, and hence, to restore the planned dose to both the tumour and OARs. Practically, there are still many obstacles, such as increased workload, related overheads, system maintenance and manpower arrangement that hinder a comprehensive implementation of the IGRT systems. After all, these IGRT systems are constantly evolving in terms of robustness and efficiency in acquisition, registration and dose calculation process, and moving towards providing customised solutions for each and every patient. It is expected that the 3D CT-based IGRT system will take over the conventional 2D imaging in future. Besides, IGRT should be examined with systematic study to give concrete data on their long-term clinical outcomes, including tumour control or normal tissue complications. Practical strategies and workflow should also be established.

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