Image-guided Radiotherapy Based on Kilovoltage Cone-beam Computed Tomography – A Review of Technology and Clinical Outcome

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Abstract

In this article an overview about the technology and clinical application of gantry-mounted kilovoltage cone-beam computed tomography (CBCT) systems for image-guided high-precision radiotherapy is provided. The emphasis will be on the body sites that are most frequently targeted in daily clinical routine (prostate, lung and head-and-neck region).

Keywords

Image-guided radiotherapy (IGRT), cone-beam computed tomography (CBCT), prostate, lung, head-and-neck region

Disclosure: The author has no conflicts of interest to declare.

Received: 9 February 2011 **Accepted:** 10 March 2011 **Citation:** *European Oncology & Haematology*, 2011;7(2):121–4 *DOI: 10.17925/EOH.2011.07.02.121*

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Support: The publication of this article was funded by Elekta. The views and opinions expressed are those of the author and not necessarily those of Elekta.

Rationale and Technology of Cone-beam Computed Tomography-based Image-guided Radiotherapy

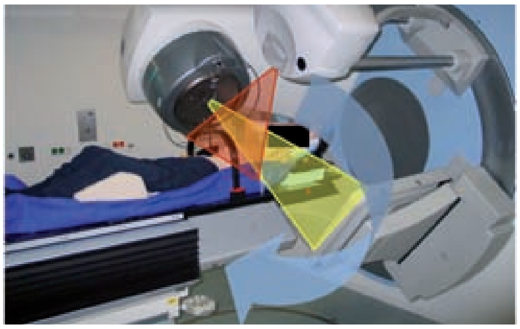
Variation of the target position is a major challenge in the clinical practice of external beam radiotherapy (EBRT). Variability of the tumour position from day to day is caused by breathing, changes of the filling of hollow organs and peristaltic or more complex changes of the anatomy of patients. If not corrected or compensated for, this variation of the target position may cause imprecise delivery of the irradiation dose with increased doses to the normal tissue and decreased doses to the tumour. Consequences are increased rates of toxicity and decreased tumour control probability. Traditionally, these uncertainties have been compensated for using safety margins around the tumour, which ensure dose coverage of the target volume despite these uncertainties.

However, application of large safety margins increases the delivery of radiation to healthy tissue: this increases the risk of toxicity and limits the total irradiation dose. Recently, image-guided radiotherapy (IGRT) became broadly available. IGRT aims to detect the tumour position immediately prior to treatment, and allows for the adaptation of RT in case the target position changes compared with the planned situation. This more precise delivery of radiation will decrease safety margins, reduce doses to normal tissue and decrease the risk of toxicity, and may allow a safe increase in the radiation dose to improve local tumour control and survival (improvement of the therapeutic ratio).

Kilovoltage cone-beam computed tomography (CBCT) is currently state-of-the-art technology for IGRT. The technology has been developed by David Jaffrey and was first commercialised by Elekta as X-ray volume imaging (XVI).[1,2] Major advantages of IGRT technology are high spatial resolution, sufficient soft-tissue contrast not requiring implanted markers, imaging in treatment position and low imaging doses. CBCT-based IGRT is currently in the process of replacing 2D IGRT methods and frame-based intracranial[3,4] and extracranial stereotactic treatments.[5–7] Of all IGRT solutions, CBCT is the technology is being installed at the fastest pace. The principles of CBCT-based IGRT are as follows: a flat-panel detector and a kilovolt radiation source are integrated into a linear accelerator. Via rotation of the linac gantry around the patient, multiple projection radiographs are acquired immediately before a RT fraction with acquisition times of 40 seconds to two minutes. The radiographs are reconstructed with a back-projection algorithm to a volumetric image. This CBCT verification image is registered to the reference planning CT data set, preferably by means of automatic image registration, for calculation of the target position relative to the planned reference position. Changes of the target position exceeding a pre-defined threshold are then corrected online prior to the start of RT. The positioning error is determined in six degrees of freedom while the possibility for correction of rotational errors in addition to translations depends on the specific treatment table.[8,9] Imaging, reconstruction and position correction requires about five minutes with the currently commercially available systems.[10] Additionally, more complex changes of the target and normal tissue such as weight loss and tumour regression are monitored in the verification images, allowing for adaptation of the treatment plan.

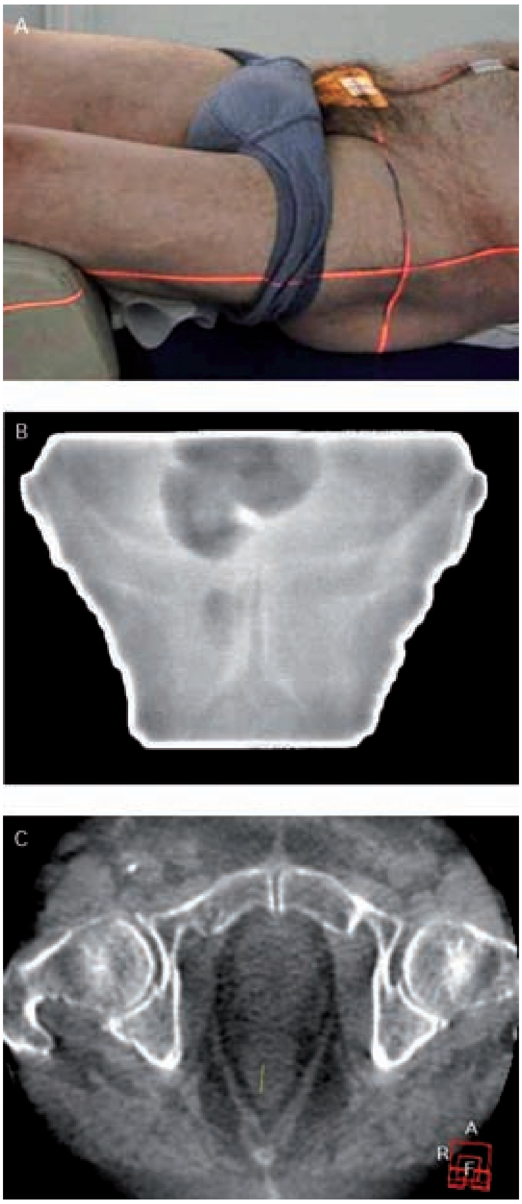
In this article, an overview about clinical applications of kilovoltage CBCT-based IGRT is provided, with emphasis on the tumour sites that are most frequently targeted in daily clinical routine (prostate, lung and head-and neck region) (see *Figure 1*).

Figure 1: Elekta Synergy S System with Integrated Kilovoltage Cone-beam Computer Tomography Technology



The X-ray source (red) is installed orthogonal to the therapeutic MV beam (yellow) and a cone-beam computed tomography is acquired via rotation of the gantry around the patient.

Figure 2: Patient Set-up in External Beam Radiotherapy for Prostate Cancer



A: Traditional patient set-up using alignment of skin marks (external markers) and room lasers; B: Image guidance using megavoltage portal imaging: patient set-up is based on the pelvic bones because of limited soft tissue contrast; C: Kilovotage cone-beam computed tomography with sufficient soft-tissue contrast for visualisation and precise targeting of the prostate.

Image Guidance for Prostate Cancer

Rationale for Image-guided Radiotherapy

Prostate cancer is one of the few cancer sites where clinical studies have clearly demonstrated the deleterious effects of systematic target displacements during RT treatment. Subgroup analyses of two randomised dose escalation trials studies reported biochemical control rates that decreased by 30 and 20% for patients with a distended rectum on planning CT,[11,12] a situation that is not representative of the treatment course, resulting in a systematic posterior displacement of the prostate and anterior rectal wall. Decreased doses to both the target and the organ at risk were the consequence, as no IGRT was performed to correct this systematic error.

Several randomised trials have confirmed increased rates of biochemical control if irradiation doses were increased from 64 to β to 74 to 79.2Gy.[13–16] All of the studies used conventional or 3D-conformal RT (3D-CRT) treatment planning techniques and patient set-up was performed according to skin marks and portal imaging, which required rather large safety margins (~10mm). Consequences of large target volumes and suboptimal conformal dose distributions were increased rates of toxicity, especially late rectal toxicity,[17] providing the rationale for the efforts to increase the accuracy of RT.

Precise patient set-up has been reported to be more difficult in obese patients. IGRT-based patient shifts were larger than 10mm in a left-to-right direction in 1 and 21% of normal weight and severely obese patients, respectively.[18] This observation of less precise RT could explain reports about decreased biochemical control in obese patients in some,[19,20] although not all,[21] clinical series, which suggests the particular need for IGRT in this patient cohort.

Clinical Results of Image-guided Radiotherapy

There are no high-evidence-level data showing that IGRT improves outcome in EBRT for prostate cancer; however, promising studies have been reported by several groups. The deleterious effect of a distended rectum in EBRT without IGRT has been described above and two studies demonstrated that IGRT eliminated this 'risk-factor'.[22,23]

Retrospective single-institution studies reported decreased rates of toxicity when IGRT was added to RT,[24,25] and multiple studies reported low rates of toxicity when IGRT and intensity-modulated radiation therapy (IMRT) were practised in dose-escalated RT (see *Figure 2*).[26]

Image Guidance for Lung Cancer

Rationale for Image-guided Radiotherapy

Although RT is accepted as the treatment of choice for early-stage non-small-cell lung cancer (NSCLC) in medically inoperable patients, the rates of local tumour control have been disappointing with conventional RT techniques and conventional fractionation (see *Figure 3*). Local failure has been reported in 6–70% of the patients with stage I/II disease,[27] which is substantially higher than the gold standard in medically operable patients using open or video-assisted lobectomy.[28] As a result of the well-established volume effect,[29] local control is even worse in advanced NSCLC. After simultaneous radiochemotherapy with irradiation doses of 60–66Gy, local tumour control is expected in only one-third of patients.[30–32]

Achieving local tumour control is important even in advanced stages of disease with a high risk of systematic progression. Simultaneous treatment increased locoregional control by an absolute 6%, which transferred into an absolute survival benefit of 6% compared with sequential radiochemotherapy.[33] No difference in systemic progression was observed, indicating that an increase in local control transfers directly to increased overall survival (OS).

Escalation of the irradiation dose beyond 70Gy has been shown to increase local control in both early and advanced-stage NSCLC.[34,35] However, large safety margins associated with conventional RT planning and delivery techniques do not allow for the safe delivery of such escalated irradiation doses in a substantial proportion of the patients. Improving the accuracy of RT with smaller safety margins is consequently considered to be a safe approach to dose escalation with the potential to increase OS.[36]

Clinical Results of Image-guided Radiotherapy

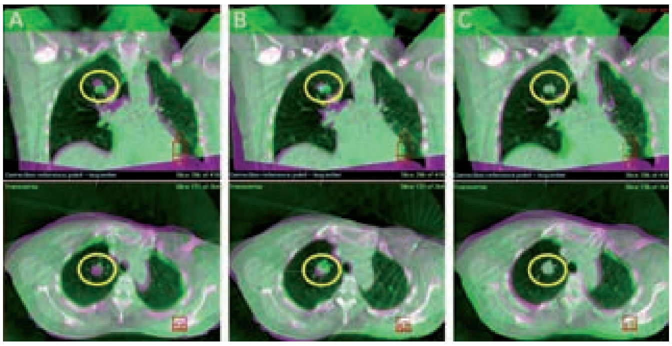
Clinical results of image-guided stereotactic body radiotherapy (SBRT) for stage I NSCLC are highly consistent. A multi-institutional analysis of over 400 patients treated with CBCT-based SBRT reported a local control rate of 92% at two years; local tumour control was even higher, at 95%, if the biological equitant planned target volume (PTV) prescription dose (BED_{10}) was >106Gy.[37] These excellent local control rates in SBRT are achieved with minimal toxicity due to high accuracy of treatment planning and delivery, which allows small safety margins and confinement of the hypo-fractionated high-doses to small volumes. OS approaching best surgical results are achievable if SBRT is practised in operable patients, who refuse surgery.[38] There are few data on practice and results of IGRT in advanced-stage NSCLC. Liao et al. performed a retrospective analysis in 496 patients treated with either 3D-CRT (n=318) or 4D-CT imaging and IMRT planning (n=91).[39] The authors reported significantly decreased rates of severe radiation-induced pneumonitis in the group treated with modern advanced technologies and OS survival was also significantly improved. This can be seen as a proof of principle that more accurate RT improves outcome; however, more and especially prospective data are required to better define the role of IGRT and adaptive RT in advanced-stage NSCLC.

Image Guidance for Intracranial and Head-and-neck Target Volumes

Rationale for Image-guided Radiotherapy

Frame-based stereotactic patient set-up for the treatment of intracranial lesions has been considered to be the most precise technique in RT. This accuracy allowed the application of high doses in a radiosurgical fashion, which achieved excellent clinical result in multiple benign and malignant intra-cranical tumours. However, fractionated treatment is not possible with invasive frame-based systems and treatment planning and delivery have to be performed within one day limiting the possibility of multimodality imaging. Non-invasive approaches using mask or bite-block systems allow fractionated treatment regimens but the accuracy of patient set-up is decreased compared with the invasive stereotactic approach. In RT of head-and-neck tumours, where patient set-up and immobilisation is usually performed with relocatable mask systems, there are no data clearly demonstrating that RT without IGRT negatively affects outcome. Nevertheless, more precise patient set-up and adaptation of the treatment to systematic changes during the fractionated treatment course may allow a reduction of safety margins with improved sparing of organs at risk.

Figure 3: Image Guidance in Stereotactic Body Radiotherapy for Early-stage Non-small-cell Lung Cancer



A: Misalignment of pulmonary tumour and bony structures after frame-based stereotactic patient positioning; B: Image registration based on the spine with misalignment of the pulmonary tumour due to a baseline shift; C: Image registration based on the pulmonary tumour with misalignment of the spine.

Clinical Results of Image-guided Radiotherapy

There are limited data on outcomes after image-guided stereotactic RT/radiosurgery. Breneman et al. reported a one-year local control rate of 80% after frameless image-guided radiosurgery of brain metastases, which is similar to results using the frame-based approach.[40] For head-and-neck cancer, IGRT without IMRT has the potential to reduce safety margins. In a prospective study, Den et al.[41] found that daily CBCT for head-and-neck cancer enabled a reduction in the CTV-to-PTV margins by about 50% (except for mobile targets such as the tongue), which could facilitate future studies of dose escalation and/or improved toxicity reduction.

By contrast, IMRT without IGRT is not recommended because the sharp dose gradients in IMRT planning require precise patient set-up. Consequently, most studies now combine conformal IMRT planning techniques with precise patient set-up using IGRT and preliminary clinical results e.g. in the re-irradiation situation are promising.[42]

Conclusion

CBCT volume imaging has streamlined and facilitated precision RT. Required imaging time is short, its percentage compared with currently quickly shortening beam-on times is, however, increasing, requiring further acceleration of the procedure. In many clinical situations, matching of planning CT and CBCT can be performed automatically based on the bony anatomy with a pre-set alignment clip box while manual matching by physicians or radiotherapists is still the procedure of choice for several situations, encouraging the assessment of not only target position but also OAR geometry. CBCT in combination with large-bore planning CT and good-quality digital radiographies obviates conventional simulation and also frame/fiducial-based stereotaxy. It will likely be the basis for all precision radiotherapy, such as IMRT/VMAT, ablative hypofractionated RT and proton therapy. ■

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