Setup Uncertainty of Head and Neck Cancer (HNC) patients treated with Image Guided Intensity Modulated Radiotherapy (IG-IMRT)

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Abstract: Advances in radiotherapy technology has made it possible to deliver highly conformal beams such as Intensity Modulated Radiotherapy (IMRT). The treatment is often guided by on-board cone-beam CT (CBCT) imaging system known as Image Guided Radiotherapy (IGRT). This retrospective study investigates the reproducibility of treatment setup for 25 head and neck cancer (HNC) patients underwent IMRT treatment at a new centre using kiloVoltage CBCT based-IGRT. All patients were immobilised using the HeadSTEP^{TM} iFRAME. The planning target volume (PTV) margin was set to 4 mm for all directions during treatment planning. The pre-treatment CBCT imaging was acquired after patient setup. The treatment setup was corrected using online correction protocol for any errors ≥ 3 mm. 231 pre-treatment CBCT scans were acquired and setup errors were recorded in left-right (LR), anterior-posterior (AP) and superior-inferior (SI) directions. The treatment setup error of ≥ 3 mm occurred in 2.2% of measurements in LR direction, 1.7% in AP direction and 6.5% in SI direction. A PTV margin of 2.96 mm, 2.55 mm and 3.30 mm in LR, AP and SI directions, respectively was calculated using Van Herk formula, when no online corrections were performed. After online correction protocol, there were no more setup errors ≥3 mm in all three directions. The PTV margin was reduced to 2.53 mm (LR), 2.39 mm (AP) and 2.81 mm (SI). Therefore, CBCT-based online correction improves the accuracy of IMRT for HNC and reduces irradiated margin by reducing both systematic and random errors.

Keywords: *cone-beam CT, immobilisation, setup uncertainty*

1. Introduction

Advances in intensity modulated radiotherapy (IMRT) creates more complex treatment that can potentially deliver higher dose to target volumes and reduce toxicities to normal tissues.[1,2] The highly conformal dose distributions are more sensitive to misalignments of the target with respect to the planned dose. The variations in patient setup and organ motion are often become the limiting factors to achieve the precision and accuracy of radiation delivery in IMRT.[3] Though organ motion during radiotherapy delivery in head and neck cancer (HNC) is not significant; the setup errors however should not be underestimated. The term 'set-up error' describes the discrepancy between intended and actual treatment position which comprises of systematic and random error component. These errors might arise due to immobilisation and setup uncertainty during patient positioning.

ICRU reports 50 ad 62 introduced the concept of planning margins that takes systematic and random errors into consideration.[4,5] The planning margins refers to margin expansion of clinical tumour volume (CTV) to planning target volume (PTV) is designed to compensate for any variability of day-to-day setup errors and intrafractional errors. The calculation of CTV-to-PTV margin is determined using Van Herk formula based on the measured systematic and random error. The formula ensures 90% of patients receive a minimum cumulative CTV dose of at least 95% of the prescribed dose.[6] This helps to ensure adequate dose coverage to the target within the PTV margin.

The development of image-guided intensity modulated radiotherapy (IG-IMRT) techniques allow clinician to image the tumour and patient setup immediately before IMRT is delivered. The images provide the setup errors of each patient and can be used to calculate the systematic and random error of the setup, and subsequently the PTV margin for patients with similar treatment setup. IG-IMRT may reduce the PTV margin which allow possible dose escalation to tumour volume and enables surrounding healthy tissue to be spared.[1,2,7] IGRT also helps in reducing systematic and random errors which might occur before and during treatment delivery. For example, if a patient is positioned incorrectly on the couch, a suitable corrections were made to the couch position such that the patient can be treated according to the setup during treatment planning. However, if improper corrections were applied, there is a risk of missing the target volume. Missing the target during radiotherapy will under dose the tumour which eventually will compromise tumour control and potentially increasing the dose to surrounding normal tissues and organ at risks. Previous study done by Guckenberg *et al.* in HNC patients found that the setup error could be ≥3 mm.[8]

One of the IGRT protocols is the online correction. The online correction protocol compares the reference images from CT simulation with images from IGRT system taken in treatment delivery room. The protocol measures the difference as setup error and enables correction of the setup error for that treatment if it exceeds a designated threshold. This requires imaging, analysis and set-up correction before each fraction. The study done by Wang *et al*. showed that online correction was effective at 2 mm threshold level.[9]

In this paper, the setup error of HNC patients in Advanced Medical Dental Institute (AMDI), Malaysia treated with IMRT was measured using an onboard kiloVoltage CBCT imaging system (Elekta, Stockholm, Sweden). The patients were treated with IG-IMRT with a PTV margin of 4 mm. The setup error was corrected using an online correction for any errors ≥3 mm. The setup error for each fraction was also measured and analysed to assess the error distribution of patient setup during IMRT treatment of HNC patients. A new PTV margin for the patients was also determined using Van Herk formula based on the measured setup errors.

2. Materials and methods

2.1. Patient characteristics

A total of 25 HNC IMRT patients were enrolled in this study from April 2016 to August 2016. The patients were treated with fractional dose of 200-220 cGy in 33-35 fractions over 6.5 weeks. The patients consisted of 9 nasopharyngeal, 7 larynx, 4 oropharynx, 3 oral cavity and 2 hypopharynx cases. Ethics approval was obtained through local ethics committee in January 2017 and informed consent was obtained from all patients.

2.2. Radiotherapy stimulation and planning

All patients were immobilised in supine position using the HeadSTEP™ iFRAME based immobilisation system which used iCAST thermoplastic mask that covers the head, neck and shoulders (Elekta, Stockholm, Sweden). Target volumes and organ at risk volumes were delineated by oncologist and physicist according to International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62.[4, 5, 8] The PTVs and planning organ-at-risk volumes were generated by adding a margin of 4 mm in all directions to the respective CTVs and corresponding structures such as spinal cord and brainstem. The 4 mm margin was determined based on the previous studies using the same immobilisation device.[10, 11] The contoured critical structures were the brain stem, chiasm, optic nerves, spinal cord, eyes, lenses, cochleas and parotid glands. Number of beams planned for all the cases studied was 7 with gantry angles as follows; 0˚, 51˚, 102˚, 153˚, 204˚, 255˚and 306˚. Optimisation and dose calculation were performed using Monte Carlo algorithm of Monaco treatment planning system (Elekta, Stockholm, Sweden). All patients were treated with one fraction daily for 5 days per week using 6 MV photon beam of linear accelerator (Elekta, Stockholm, Sweden).

2.3. Setup and image registration

The pre-treatment CBCT images were acquired daily after patient setup for the first three fractions in the first week, followed by a weekly imaging at the first fraction in the subsequent weeks. The CBCT images were acquired after aligning the in-room lasers with the corresponding mark drawn on the thermoplastic mask. The pre-treatment CBCT scans were performed using following x-ray tube parameters; kVp, 100 kV; nominal milliamperes per frame, 10 mA and nominal milliseconds, 10 ms. Number of projections imaged was 183 frames for a total gantry angle of 200 degree. The collimator used was S20 to provide field of view of 26 cm in diameter and 26 cm in length. All CBCT images were registered to the planning CT using automatic bone matching (correlation coefficient algorithm) of Elekta Medical System XVI software to obtain setup error on the left-right (LR), anterior-posterior (AP) and superior-inferior (SI) directions. The setup errors were defined as the offset between CBCT and planning CT in the LR, AP and SI directions.

An online protocol with action level of 3 mm was performed throughout the study. Setup errors was corrected if the error ≥3 mm. The impact of online protocol on errors distributions and margin was also investigated in this study.

2.4. Determination of PTV margin

The PTV geometric margin encompasses the systematic error, $\sum$ and random error, σ of patient setup. The calculation of these two errors were based on setup error of the 'treatment population' to represent all patients treated. Based on Van Herk formula in Eq.1, the margin was calculated by obtaining the value of, individual mean, m_n population mean, M_{pop}, individual standard deviation, σ_n and population standard deviation, σ_{pop}.

$$PTV = 2.5\sum \times 0.7\sigma \tag{1}$$

Table 1, shows the individual mean from each patient, m_n obtained by measuring the setup error, d_n. The population mean, M_{pop} was then calculated by summing up all value of individual mean, m_n from each patient. These two values, M_{pop} and m_n were used to measure systematic error, $\sum$ using Eq.2. To characterise the random errors, in a given population, an appropriate average of the error is calculated by the root-mean square of the individual standard deviation of all patients, denoted by σ_n in Eq.3. The value of individual standard deviation was acquired using Eq.4.

$$\Sigma = \sqrt{\frac{\left(m_1 - M_{pop}\right)^2 + \left(m_2 - M_{pop}\right)^2 + ... + \left(m_n - M_{pop}\right)^2}{p-1}} \tag{2}$$

$$\sigma_{pop} = \sqrt{\frac{\sigma_1{}^2 + \sigma_2{}^2 + \sigma_3{}^2 .... + \sigma_n{}^2}{p}} \tag{3}$$

$$\sigma_n = \sqrt{\frac{\left(d_1 - m_1\right)^2 + \left(d_2 - m_2\right)^2 + ... + \left(d_n - m_n\right)^2}{n-1}} \tag{4}$$

Table 1. Setup errors for several patients in LR direction.

Setup errors (mm)	Patient 1	Patient 2	Patient 3
Fraction 1	-0.60 (d_1)	-1.70	0.90
Fraction 2	-3.00 (d_2)	-1.60	1.50
Fraction 3	-0.80 (d_3)	-0.50	1.20
Mean	-1.47 (m_1)	-1.27 (m_2)	1.20 (m_3)
Standard deviation	1.33 (σ_1)	0.67(σ_2)	0.30 (σ_3)

3. Results and discussion

3.1 Analysis of setup errors using CBCT based-IGRT

A total of 231 CBCT images were collected during initial patient setup in each translational direction; left-right (LR), anterior-posterior (AP) and superior-inferior (SI). From Figure 1, it can be seen that most of CBCT positioning errors were distributed between -0.50 mm to 0.50 mm in all three directions. The range of setup errors for the procedures without online CBCT based-IGRT were from -3.40 mm to 3.00 mm for LR direction, from -4.40 mm to 3.00 mm for AP direction and from -3.60 mm to 4.80 mm for SI direction.

The frequencies of initial setup errors exceeding 1 mm were 41.9%, 42.4% and 48.1%, respectively, on the LR, AP and SI axes; the frequencies exceeding 2 mm were 14.3%, 10.8% and 21.2%, respectively, and frequencies exceeding 3 mm were 2.2%, 1.7% and 6.5%, respectively. There were 0.9% and 1.3% setup error exceeded the 4 mm margin in AP and SI directions respectively. Lu *et al.* evaluated the study on setup errors of patients undergoing IMRT for nasopharyngeal carcinoma cancer (NPC), and found setup errors of ≥3 mm occurred in 5.2% of setups in LR, 3.6% in AP and 15.6% in SI direction, respectively.[12] Only 1.90% of patients had error exceeding 5 mm in SI direction. However, in the present study, no setup errors exceeded 5 mm in all three directions. The maximum setup error was recorded in the SI direction with value of 4.80 mm.

The individual mean of setup errors for each patient ranged from -2.08 mm to 1.68 mm in LR direction, -1.82 mm to 1.19 mm in AP direction and from -1.88 mm to 2.28 mm in SI direction as shown in Figure 2 (a-c). The largest value of individual mean setup error was 2.28 mm which lies on SI direction. Based on individual's mean setup errors, the population mean in LR, AP and SI directions were calculated to be -0.03 mm, 0.01 mm and 0.55 mm respectively. This can be observed from dashed line plotted on each diagram in Figure 2. The values of population mean and individual mean of setup error were then used to calculate for systematic error, ∑.

The individual standard deviations were also calculated from each patient. The range of individual standard deviation was observed to be from 0.34 mm to 2.44 mm in all three directions. The root mean square of these individual standard deviation will give the value of random errors which were tabulated in Table 2. From the table, the largest value of systematic and random error was recorded in SI position. Based on the values of systematic and random error recorded, a PTV margin of 2.96 mm, 2.55 mm and 3.30 mm was required in LR, AP and SI directions respectively, when online corrections were not performed.

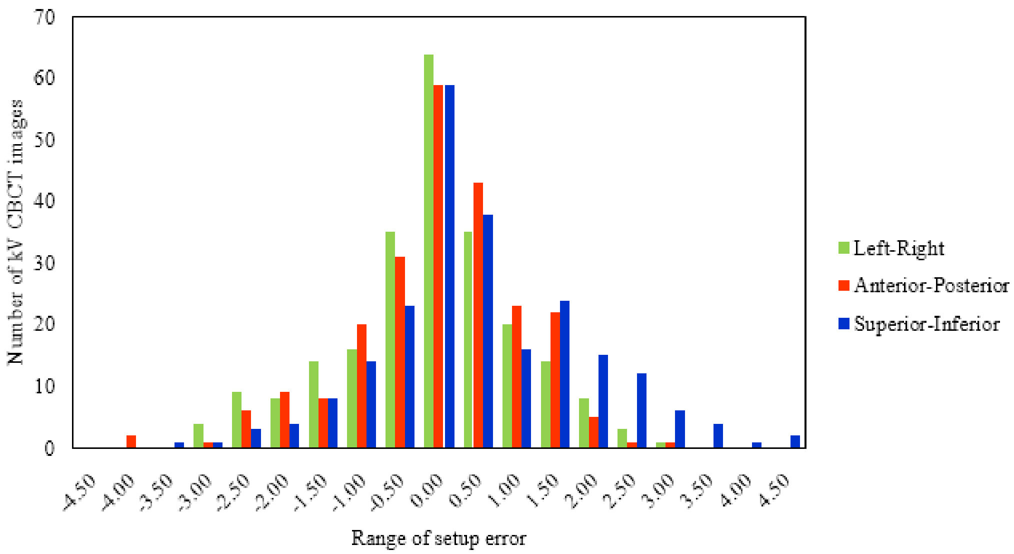

Figure 1. The range of setup errors of 231 CBCT images in LR, AP and SI directions

Table 2. Systematic and random error for initial setup errors in LR, AP and SI directions.

Protocol	LR position (mm)		AP position (mm)		SI position (mm)	
	∑	σ	∑	σ	∑	Σ
Initial setup	0.93	0.92	0.75	0.96	0.99	1.18

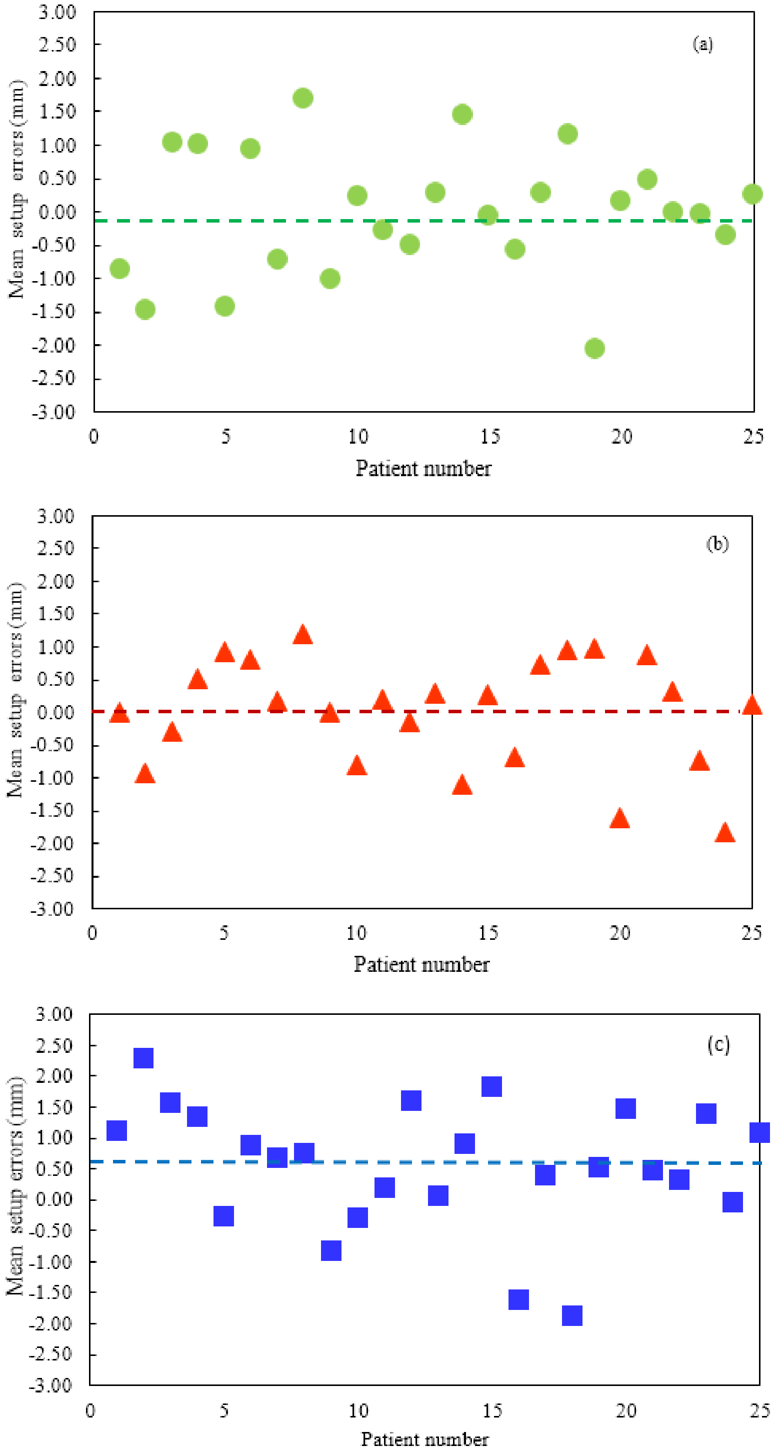

Figure 2. Scattered plot illustrating individual mean setup errors in (a) LR, (b) AP and (c) SI directions. The dashed line denoted population mean was plotted for each diagram.

3.2 Analysis of setup errors after application of online correction

After application of online correction protocol with threshold of ≥3 mm, 36.8%, 36.4% and 40.7% of setup errors were observed exceeding 1 mm in LR, AP and SI directions respectively. A reduction of 5.2%-7.4% compared to setup errors without online-IGRT. For setup error exceeding 2 mm, the frequencies were reduced about 2.6%-6.5%. This resulted the frequencies of 10.4% (LR), 8.2% (AP) and 14.7% (SI). There were no more setup errors recorded ≥3 mm in LR, AP and SI directions. All setup errors ≥3 mm were corrected to the range of -0.50 mm to 0.50 mm for all three directions. The maximum setup error recorded was 2.80 mm which lies on SI direction.

The population mean value were then calculated from 25 HNC patients to be 0.03 mm, 0.04 mm and 0.36 mm in LR, AP and SI directions respectively. The differences when compared to setup error without online protocol were 6.5%-19.1% for the three respective dimensions. After online correction protocol was performed, a 11.8%-15.3% reduction of systematic error was observed in LR and SI directions respectively resulted the systematic error to be 0.77 mm in LR direction and 0.87 mm in SI direction. For AP direction, the systematic error was calculated to be 0.73 mm. The reduction was only 2.2% compared to systematic error without online correction. This is due to only 4 out of 231 setup errors ≥3 mm margin in AP direction. In comparison, there were 5 and 9 patients which had setup error ≥3 mm in RL and SI directions, respectively. A further reduction in systematic error value was expected if a lower action-level ≤3 mm was used in the online correction. Houghton *et al*. mentioned that reducing the action-level at which systematic errors of pre-treatment deviations were corrected improved the probability of accurate treatment delivery.[13]

The values of individual standard deviation were calculated to be in the range from 0.34 mm to 1.48 mm (LR), 0.34 mm to 1.39 mm (AP) and 0.31 mm to 1.73 mm (SI). A bar graph was plotted in Figure 3 to show the difference in random error with and without application of online IGRT protocol. The random error recorded for LR direction was 0.84 mm, a 7.1% reduction compared to setup error of non-IGRT setting. For AP and SI directions, both recorded a random error of 0.80 mm and 0.90 mm respectively. The highest percentage of random error reduction occurred in SI directions with 28.2% followed by 15.2% reduction in AP direction.

A new PTV margin of 2.53 mm (LR), 2.39 mm (AP) and 2.81 mm (SI) was calculated based on setup errors after online correction. A 43.2%-49.3% reduction in margin size was observed in LR and SI directions, respectively. Only 16.1% reduction in margin size was observed in AP direction. Overall, the new PTV margin size obtained after online kV CBCT correction was ≤ 3 mm in all three dimensions.

The smaller PTV margin would be valuable in improving the treatment accuracy. The routine 4 mm PTV margin used for HNC patients with daily CBCT guided-IMRT at our institute can be further reduced. This could theoretically

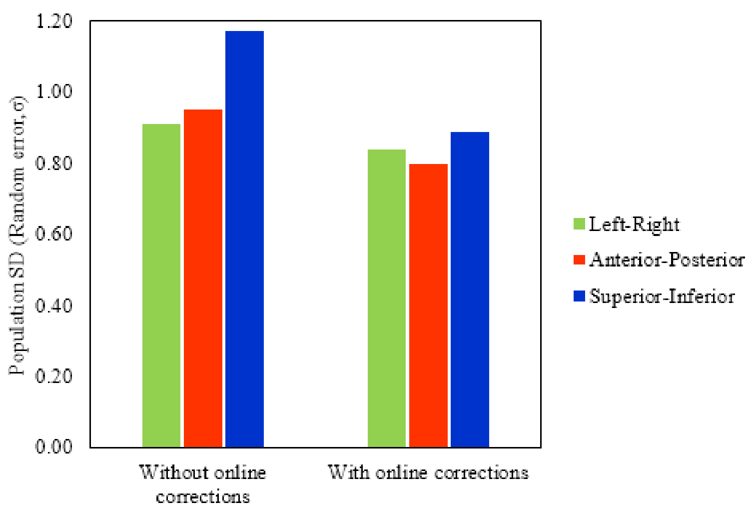

Figure 3. Bar graph showing the difference of random error, σ calculated during setup error without online correction and with online kV CBCT correction.

allow less normal tissue to be involved in high dose region. Moreover, a smaller action level could be employed through online correction to correct for any existing deviation at primary target and account for possible intrafraction movement.

4. Conclusion

The range of setup uncertainty of HNC patients were from -3.40 mm to 3.00 mm in LR direction, -4.40 mm to 3.00 mm in AP direction and from -3.60 mm to 4.80 mm in SI direction. The recommended margins were calculated to be 2.96 mm (LR), 2.55 mm (AP) and 3.30 mm (SI). We have observed a reduction in systematic and random displacements when online CBCT corrections were applied on setup error exceeding action-level of 3 mm. We have found that through online CBCT corrections, the systematic displacements were reduced from 0.93 mm, 0.75 mm and 0.99 mm for, respectively LR, AP and SI directions to 0.73-0.87 mm. The random errors were also reduced for about 7.1% in LR direction, 15.2% in AP direction and 28.2% in SI direction. With online correction protocol and 3 mm action level, a margin of 2.53 mm (LR), 2.39 mm (AP) and 2.81 mm (SI) were required to ensure adequate coverage of CTV. In conclusion, CBCT-based IGRT is an effective modality to further evaluate and improve the accuracy of IMRT in HNC patients. Further work will explore application of offline correction technique to further improve the setup uncertainty and efficiency of IG-IMRT treatment of HNC patients**.**

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