A Pilot Comparison Study of Setup Verification Between Two-Dimensional Kilo-Voltage (2DkV) Matchand Kilo-Voltage Cone-Beam Computed Tomography (kV-CBCT) Match for Nasopharyngeal Cancer Patients

Kullathorn Thephamongkhol, M.D., M.Sc.*, Kanyanee Laebua, M.D., Pittaya Dankulchai, M.D.*, Janjira Petsuksiri, M.D.*, Chumpot Kakanaporn, M.Sc.*, Lalida Tuntipumiamorn, M.Sc.*, Porntip Iampongpaiboon, M.Sc.*, Yaowalak Chansilpa, M.D.*, Pittayapoom Pattaranutraporn, M.D.***

**Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, **Radiation Oncology Unit, Chulabhorn Hospital, Bangkok, Thailand.*

ABSTRACT

Objective: Setup verification is the critical part to make sure of the accuracy for Intensity-modulated radiotherapy in nasopharyngeal cancer patients. This pilot study was designed to answer whether and how much the kV-CBCT in addition to 2DkV is more accurate than 2DkV alone in terms of verification parameters.

Methods: **Images acquisition:** Offline images were displayed in the matched position between reference images. **2D and 3D matches:** The bony matches were done by using the location of the tumor in the nasopharyngeal and upper neck regions. The distances displaced from the isocenter were recorded in x-y-z directions. **Analysis:** The distance of the isocenter shift in each direction (X, Y, Z) were presented as point estimations. The alignment between the two methods was assessed with Pearson's and Spearman's correlation. The 3 mm difference within 90% is considered as an acceptable range of non-inferiority of 2DkV, compared with CBCT.

Results: 11 nasopharyngeal cancer patients were included into this study. The correlation between 2DkV and kV-CBCT were 0.46, 0.11 and 0.16 for Superior-inferior (SI), Anterior-posterior (AP) and Left-right (LR) directions, respectively. The central value for the kV-CBCT; SI, AP and LR directional shift were 0.07, 0.06 and 0.03 cm, respectively, whereas the central value for 2DkV; SI, AP and LR directional shift were 0.05, 0.07 and 0.04 cm. For the difference shift < 3 mm, the results > 90% were within acceptable value: 100% and 96.96% for SI and LR directions whereas the AP direction was 87.87%.

Conclusion: Compared with kV-CBCT by using our criteria, 2DkV images are accurate enough for treatment verification in nasopharyngeal cancer patients.

Keywords: 2DkV match, CBCT match, nasopharyngeal carcinoma, IMRT

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Nasopharyngeal cancer (NPC) is one of the head and neck cancers which has been treated with radiotherapy for many years. Nowadays the Intensity-Modulated Radiotherapy (IMRT) technique has been developed not only to conform the dose to the tumor, but also to avoid the dose to the parotid gland and internal ear, and therefore this contributes clinically to increase tumor control and decrease xerostomia.[1-4] To achieve these clinical objectives, this technique needs extreme accuracy of the setup of the patient's position; otherwise missing the tumor target in radiation therapy might reduce tumor control and translate into lower survival rate. In other words an easy way to understand is that the traditional way is using computed tomography to confirm the tumor area only before treatment, whereas the new innovative way is using computed tomography to confirm the tumor area not only before treatmentm but also during the course of radiotherapy, which usually takes

Correspondence to: Pittaya Dankulchai
E-mail: pittayawin@yahoo.com

about 6-7 weeks. Zhang et al.,[5] showed the variability in the set up correction for different regions of head-and-neck anatomy. Tumor and normal tissues localization need the image guided radiation therapy, which is one of the kilo-Voltage Cone Beam Computed Tomography (kV-CBCT) imaging systems. With a linear accelerator, this system is set to identify the change in tumor size and has become an important tool in adaptive radiotherapy.[6-7]

Despite these known issues of accurate treatment, in developing countries to treat with these IMRT techniques, daily setup precision and inter-treatment position reproducibility becomes a challenging issue because of the constraint of resources and time. Buelent Polat et al.,[8] studied using kV-CBCT to evaluate in IMRT for head and neck cancer which found that the patient setup error was 3.2 mm +/- 1.7 mm based on registration of the whole volume. There are also some reports for comparison of these two methods, but the difference between these two methods might not be clinically significant or still be questionable. Heng Li et al.,[9] showed systematic and random errors < 1.6 mm for both 2DkV and kV-CBCT. Among all CBCT couch shifts > 3 mm is 18.7% whereas 2DkV is only a little lower at 11.2%.

In Siriraj Hospital, nowadays, we have used the new on-board imaging (OBI) systems to allow reconstruction of cone-beam computed tomography (CBCT) using a kilo-voltage (kV) source for patient positioning since 2009. In this situation, we have faced two options. The first one is to use the old 2DkV alone, which is easy, fast, comfortable and has a low dose of radiation exposure, but might not be highly accurate. The second one is to add this new technique, which might be more accurate than the old one, but requires more time and resources. This pilot study was designed to answer whether and how much the kV-CBCT in addition to 2DkV is more accurate than 2DkV alone for bony anatomy matching. The primary objective was to explore whether the 2DkV match is accurate enough (or non-inferior) in terms of correlation and/or shift difference for setup verification when compared with kV-CBCT in NPC patients. The secondary objective was to explore the degree of difference in the region of sixth cervical vertebral body (C6), which is representative of the lower neck when we use our region of interest (ROI), the upper neck, as a referent point.

MATERIALS AND METHODS

This is retrospective analytical study of setup data (2DkV versus kV-CBCT) in the radiation treatment planning system from March to December 2009 at the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital. The patients' data were eligible if they were diagnosed histologically as nasopharyngeal cancer stage I-IVB, if they underwent IMRT treatment with curative intent, were aged 15-70 years and if 2DkV simulation was used as reference images with at least 3 sets of kV-OBI images during the course of radiotherapy. We excluded the data of patients who have no pairing of kV simulator images with kV-OBI during their radiotherapy course, the patients who were used Digital Reconstruction (DRR) as reference images, and if IMRT techniques were re-planned during the radiation course.

Images acquisition

Offline images were displayed in the matched position between reference images (kV simulation and CT simulation) and OBI images (kV OBI and kV cone beam CT). The researcher then re-performed the bony match on each pair of images (kV simulation versus kV OBI and CT simulation versus kV-CBCT) by using the bony structures for anatomy matching on the lateral view in the specific region of interest. The anatomical borders were occipital protuberan as superior and posterior border, lower border of the mandible as inferior border, and anterior border of the mandible as anterior border. For the antero-lateral view, the anatomical borders were occipital protuberan as superior border, lower border of the mandible as inferior border, and most lateral of the mandible as lateral border.

ROI was chosen on the basis of the most interesting location of the primary tumor in the nasopharyngeal and upper neck regions. The level of the C6 vertebra was selected to represent the lower neck match in all axes. When facing difficulty of matching for the head and neck region with discordance between upper and lower necks, we preferred to fix the upper neck ROI and evaluated the range of mismatch in the lower neck as to whether this range was acceptable.

Intensity range for bone auto-match was set as a default (intensity range 200-3000). After the auto-match, the fine tune manual match by the researcher was performed on each image for comparison. The data were then reviewed in both 2D (kV simulation versus kV-OBI) and 3D (CT simulation versus CBCT) matches. The workflow is shown in Fig 1.

2D kV match (Reference 2D simulation versus kV-OBI)

After the complete matching, the distances displaced from isocenter were recorded in x-y-z directions. For AP images, the data were recorded within L-R direction(X axis). For the lateral images, the data were recorded within A-P direction(Y axis), and S-I direction (Z axis).

3D match (CT simulation versus kV-CBCT)

3D match was performed in the same ROI described in the 2D match. The CBCT images delivered on board were overlaid and matched with the CT-simulation images. The matching process was identical to the 2D match.

Statistical methods

To represent the whole population, the distance of isocenter shift in each direction (X, Y, Z) and each session (1^{st} -10^{th}, 11^{st}-20^{th}, and 21^{st}-33^{rd}) were calculated and represented as point estimation in both 2DkV and CBCT. The mean of absolute shift was calculated to see the average of absolute shift regardless of the direction (+,-), but the mean shift was to allow seeing the point or coordinator when the direction is considered.

To present as the difference between the two methods (2DkV versus CBCT) within individual sessions (33 session in 11 patients), the assessment alignments between 2DkV and CBCT images were used with Pearson's and Spearman's correlation.

Siebers et al.,[10] studied the effect of patient setup errors in IMRT treatment of head and neck cancer. The results showed that the dose to the gross tumor volume evaluated with the inclusion of simulated 3 mm random and 3 mm systematic setup errors differed from the effective Planning Target Volume (PTV) by more than 5% in only 5.4% of the plans simulated. Thus, in this research, we will consider 3 mm difference within 90% as an acceptable range of non-inferiority of 2DkV, compared with CBCT.

For each patient (p), all ROIs were registered in the available localization scans. The patient systematic deformation (Σp) for ROI is the mean displacement over all fractions. The patient random deformation (σp) is the standard deviation (SD) of the displacements over all fractions.

Margins resulting from setup uncertainty could be estimated from both the systematic and random errors. We used the Van Herk formula (margin = $2.5\Sigma + 0.7\sigma$) and the Stroom formula (margin = $2.0\Sigma + 0.7\sigma$) as a residual error.

Our study was certified by the Siriraj Institutional Review Board to be in full Compliance with International Guidelines for Human Research Protection (EC Number: 657/2552).

RESULTS

From March to December 2009, we had 64 NPC patients who underwent IMRT treatment. We excluded 9 patients with recurrence or residual diseases. From 55 patients who completed radiotherapy, we excluded more than 38 patients who had no 2DkV simulation as a reference image with at least 3 sets of kV-OBI images during the course of RT (during 1st-10th, 11th -20th and 21st-33rd fraction of the treatment within the same position). Thus, the remaining 17 patients were evaluated. A further 5 patients were excluded from the analysis because of using DRR as reference image. The last one using KV simulation with DRR was also excluded. Finally, we had 11 evaluable patients for this analysis.

Standard central and variation value with direction (directional vector)

The central values (mean shift with directional orientation), variation of 2Dkv and CBCT, and absolute shifts (non-directional orientation) were recorded using the methodology above. We found that the central value for CBCT, our proposed new standard method, SI directional shift is slightly more that the distant (mean = 0.0758 cm, median = 0.1 cm), compared with the AP (mean = 0.0575 cm, median = 0 cm) and the LR direction (mean = 0.0273 cm, median = 0 cm); whereas the central value for 2DKV, our conventional one, AP directional shift was a slightly more distant (mean = 0.0758, median = 0.1), compared with the SI (mean = 0.0455, median = 0 cm) and the LR (mean = 0.0394, median = 0 cm) direction. (Table 1)

Absolute shift (magnitude of shift regardless of direction)

Another terminology was introduced as “the absolute shift” or the degree of shift regardless of direction. The absolute shift for CBCT showed slightly more distance of mean absolute shift in LR (0.3073 cm) direction, compared with the AP (0.2738 cm) and SI (0.2905 cm) directions. The absolute distance values for 2DkV showed slightly more distance in the AP (0.0839 cm) direction, compared with the SI (0.0815 cm) and LR (0.0753 cm) directions. (Table 2)

TABLE 1. The result of mean, range, SD and median of the translation values (central value)

		AP(cm)	SI(cm)	LR(cm)
CBCT	Mean	0.0575	0.0758	0.0273
	SD	0.1890	0.1678	0.1701
	Median	0.0000	0.1000	0.0000
	Range	-0.6 - 0.3	-0.2 - 0.4	-0.4 -0.3
2DkV	Mean	0.0758	0.0455	0.0394
	SD	0.1582	0.1034	0.1391
	Median	0.1000	0.0000	0.0000
	Range	-0.2 - 0.5	-0.2 - 0.3	-0.4 - 0.4

AP = Antero-Posterior, SI = Supero-Inferior, LR = Left-Right

TABLE 2. For absolute difference of translation values (magnitude)

		AP(cm)	SI(cm)	LR(cm)
CBCT	Range	0 - 0.5	0 - 0.3	0 - 0.4
	Mean of absolute shift	0.2738	0.2905	0.3073
	SD	0.3994	0.4197	0.4421
2DkV	Range	0 - 0.6	0 - 0.4	0 - 0.4
	Mean of absolute shift	0.0839	0.0815	0.0753
	SD	0.0727	0.0780	0.0832

AP = Antero-Posterior, SI = Supero-Inferior, LR = Left-Right

Standard terminology of systematic, random errors and margin (in the setting after first shift - or residual margin)

Regarding the distribution of setup error for all patients, including the population mean setup error μ (mm) and their ranges, the standard deviations (Σ) of the corresponding systematic shift, and the random component (σ) in all three directions for the entire patient population were demonstrated. Both the systematic and random errors were less than 1.5 mm for both 2DkV and kV-CBCT images. CBCT images show the average random shift is more in the AP direction (0.1483 cm) than the other directions, while the systematic shift was comparable in all directions. Again, very clearly, we found that the systematic shift for the CBCT in the SI, LR directions (0.1423 cm, 0.1373 cm, respectively) were much more than in the 2DkV direction (0.0620 cm, 0.0919 cm, respectively). In addition, systematic shift and average random shift of the CBCT was more than the 2DkV image.

We used the systematic error and the random error to calculate the margin, which we considered as the residual error. The results showed that the margin for CBCT was more than for 2DkV images. The margin of CBCT was 0.35- 0.42 cm in all directions. The margin of 2DkV was 0.31- 0.36 cm in the AP direction, which is lower than the CBCT in the SI (0.18 - 0.21 cm) and LR (0.25 - 0.29 cm) directions.

Correlations of 2DkV and 3D-CBCT setup shift

The alignment between the CBCT and 2DkV images was demonstrated by using Pearson’s correlation and Spearman’s correlation, respectively, as in Table 3.

With the consensus of our team, we set the cut-off point to accept non-inferiority of 2DkV when the individual difference values between 2DkV and kV-CBCT were lower or equal to 3 mm by the AP, SI, and LR axes. Also, if these results were represented in more than 90% in our

TABLE 3. The Pearson’s and Spearman’s correlation in AP, SI and LR directions

Direction (axis)	Pearson’s correlation	Spearman’s correlation
AP (y)	0.1092	0.1236
SI (z)	0.462	0.4572
LR (x)	0.1646	0.1536

TABLE 4. The variables of 2DkV technique is not lower than 3D-CBCT

	AP(mm)	SI(mm)	LR(mm)
Acceptable difference <3 mm	29/33	33/33	32/33
(Percent)	87.87%	100%	96.96%
Range	0 - 0.9	0 - 0.3	0 - 0.6
Mean	0.1939	0.1273	0.1515
SD	0.1836	0.0839	0.1302

AP = Antero-Posterior, SI = Supero-Inferior, LR = Left-Right

population, we might be able to accept that 2DkV applied in setup verification was not inferior to kV-CBCT as in Table 4.

The ancillary analysis: the result of difference distance of C6-vertebra

The results basically showed comparable different distances between the C6 vertebrae in the 2DkV images and the CBCT images (Table 5). We found the mean of absolute shift for CBCT was about 0.2 cm in all directions with variations of 0.13 to 0.18 cm. Whereas, the mean of absolute distance for C6-2DkV was lower in the LR (0.09 cm) and SI (0.13 cm) directions than in the AP (0.18 cm) direction. The variation was about 0.13 to 0.18 cm. Overall, the distant differences were within 2 mm in all directions. The LR direction showed more different distance than the other directions because the CBCT images might have better image quality than the 2DkV images.

DISCUSSION

The CBCT volumetric imaging integrated with the linear accelerator is a novel application used for incident reduction, residual error and organ at risk (OAR) avoidance. The ability to see soft tissue, including target volume and normal structures, is the real beneficiary of CBCT; however, we used the bony anatomy (location of primary nasopharyngeal tumor, the high-risk neck regions) and bony intensity matched within the ROI because we wanted to compare directly with the 2DkV in the same setting.

Our data indicated the low mean error for in co-ordination values while absolute shift values and standard deviation were higher within 3-6 mm. From the absolute values, we found comparable difference shifts in all directions with the maximum difference in the AP axis in some patients. One of the possible explanations for these findings was the variation in position of the patient's neck (flexion and extension of neck).

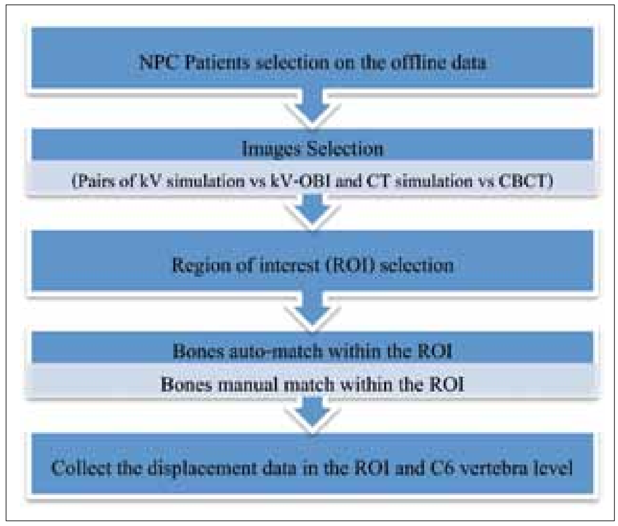

Fig 1. Reviewing Workflow

In our study, the shift distance values were high in both the 2DkV and kV-CBCT. Surprisingly, we found that the shift of kV-CBCT was higher than that of 2DkV. We thought that the 2DkV images might not be able to adjust their intensity range because of insufficient density difference, while the kV-CBCT images were easier to adjust because they showed the density match clearer. We do not think the issue of technique of 2DkV and kV-CBCT is the cause because both techniques were using the same algorithm of bony density match.

The correlation between 2DkV and 3D-CBCT in our study was much less than other studies. We used bone to bone matching and automatic with manual anatomy matching methods. These findings might result from the different ROI, individual patients, small sample size and algorithm of the equipment between CBCT, CT planning and 2DkV simulation images.

There were several studies using 3D-CBCT to measure setup deviation in the head and neck region. Buelent Polat et al.,[8] found that patient setup error was 0.32 ± 0.17 cm based on registration of the whole volume and margins for compensation of motion within a range of 0.5-1.0 cm. Simon Van Kranen et al.,[11] reported setup uncertainties of sub-regions in head and neck cancer with the large ROI in systematic error 0.12 cm, and in random error 0.15 cm for each direction. Heng Li et al.,[9] studied 21 patients and showed systematic and random errors < 1.6 mm for both 2DkV and kV-CBCT. Among all CBCT couch shifts > 3 mm was 18.7% whereas 2DkV was 11.2%. G. Mu et al.,[12]

TABLE 5. The results of range, mean, SD and median of C6 vertebra

		Difference distanceof C6 kV			Difference distances of C6 CBCT		
		AP(CM)	SI(cm)	LR(cm)	AP(CM)	SI(cm)	LR(cm)
Central values	Mean	0.02	0.01	0.05	0.02	0.00	-0.09
	SD	0.25	0.20	0.16	0.24	0.22	0.25
	Median	0.00	0.00	0.00	0.00	0.00	-0.12
	Range	-0.57- 0.63	-0.23- 0.70	-0.29- 0.4	-0.45 - 0.4	-0.3 - 0.42	-0.7 - 0.58
Absolute values	Mean of absolute	0.18	0.13	0.09	0.19	0.18	0.19
	SD of absolute	0.17	0.15	0.15	0.15	0.13	0.18
	Median	0.16	0.14	0.00	0.22	0.20	0.20
	Range	0 - 0.63	0 - 0.7	0 - 0.4	0 - 0.45	0 - 0.42	0 - 0.7

AP = Antero-Posterior, SI = Supero-Inferior, LR = Left-Right reported the average difference between 2D-3D method for 9 head and neck patients was 0.7 ± 0.9 mm for the LR shift, 1.0 ± 1.9 mm for the AP shift, and 0.8 ± 1.0 mm for the SI shift with SD from 1-2.2 mm. For both the systematic and random errors in our study, the setup uncertainty analysis for 2DkV and CBCT image was less than 0.15 cm, which was comparable with the others.

From the maximum acceptable (arbitrary) error at 0.3 cm between 2DkV and 3D-CBCT at 0.3 cm, the 2DkV images had sufficient accuracy with the 3D-CBCT. The central value of absolute shift difference was about 0.2 cm (maximum) in the AP direction and the variation was 0.2 cm, while the minimal absolute shift difference was 0.12 cm in the SI direction and the variation was low at about 0.08 cm.

Overall, the residual error was larger in 3D-CBCT, about 0.3-0.4 cm in all directions. Finally, from the results of different translation between these two techniques, we found that the 2DkV image was not inferior to be used in our setting.

CONCLUSION

In conclusion, from our data with using bone to bone match, 2DkV images, showed translation distance less than 3D-CBCT, which might be within the range of adjustment. The correlation of 2DkV and 3D-CBCT images was weak, although there was an individual shift difference of less than 3 mm, which was an acceptable range in our consensus. 2DkV images could be reliable enough to use, especially in a setting having limited resources and time.

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