Methods and Technology

Preliminary application of kilo-volt cone-beam computed tomography to intensity-modulated radiotherapy of nasopharyngeal carcinoma

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Background and Objective: The intensity-modulated radiotherapy (IMRT) with its highly conformed dose distribution to nasopharyngeal cancer (NPC) and the surrounding critical organs is being accepted increasingly in clinical practice. Due to the steep dose fall-offs of IMRT at the target margin, precise patient positioning and verification are required. This study was to evaluate the role of kilo-volt cone-beam computed tomography (kV-CBCT) in guiding the accurate positioning of IMRT for NPC. Methods: kV-CBCT was performed on 22 NPC patients before radiotherapy. The acquired CBCT were co-registered with the planning CT for online setup correction and offline planning target volume (PTV) analysis. Results: The 22 patients received a total of 754 kV-CBCT scans. Among the 505 scans before couch correction, the detection rates of deviation of ±2 mm were 76.4% in left-to-right (X) direction, 76.0% in superior-to-inferior (Y) direction, and 85.7% in anterior-to-posterior (Z) direction; among the 106 scans after correction, the detection rates were 97.2, 97.2, and 100% in X, Y and Z directions, respectively; among the 143 scans after treatment, the detection rates were 87.4, 87.6, and 90.0%, respectively. The overall setup errors in X, Y and Z directions were (-0.7 ± 1.6) mm, (-0.7 ± 1.8) mm and (-0.3 ± 1.7) mm, respectively, before correction; (-0.4 ± 0.8) mm, (0.3 ± 0.8) mm and (0.0 ± 0.7) mm, respectively, after correction; (0.2 ± 1.2) mm, (0.3 ± 1.3) mm and (0.1 ± 1.1) mm, respectively, after treatment. The maximal PTV margin was 4.0 mm before correction and 2.1 mm after correction. Conclusion: kV-CBCT image-guided radiotherapy may improve the setup precision of IMRT for NPC.

Radiotherapy is the preferred treatment for nasopharyngeal cancer (NPC). However, locoregional relapse after conventional radiotherapy remains the major cause of treatment failure. The local control rate of NPC at stage T3-T4 is 32–60%,1–4 which is closely related to wide invasion, insufficient irradiation dose and extent. Intensity-modulated radiotherapy (IMRT) is a promising radiotherapy technique for NPC, which provides highly conformal dose distribution to tumor and may enhance the therapeutic ratio by increasing the irradiation dose to target tumor volume only. IMRT obviously decreases acute and chronic irradiation-related toxicity, and the local control rate of NPC after IMRT is higher than that after conventional radiotherapy.2–4 The implementation of IMRT requires high precision due to the rapid dose fall-off at the boundary between tumor and its surrounding critical normal tissues. As the dose calculation of IMRT plan is based on the volumetric data of planning CT scan which only represent the status at the moment of CT scanning and may differ from the actual treated status, any error of isocenter during IMRT may have greater impact on tumor and normal tissues than conventional 3-dimensional (3D) radiotherapy. Recently, the rapid development of image-guided radiotherapy (IGRT) technique makes the implementation of radiotherapy with high precision possible. The Elekta SYNERGY™ is an IGRT system, which has integrated an X-ray volume imaging (XVI) on a digital linear accelerator. The West China Hospital of Sichuan University has started using Elekta SYNERGY™ system to treat patients since April 2006. This study was to evaluate the role of XVI image guide in positioning of NPC patients receiving IMRT.

Materials and Methods

Patients’ data. From April 2006 to September 2006, 22 NPC patients received IMRT in West China Hospital, including 17 men and five women, with a median age of 53 years (range, 19–76 years). All patients had poorly differentiated squamous cell carcinoma. According to 1997 AJCC staging system, one (4.5%) case was at stage I, seven (31.8%) at stage II including one case of relapse, eight (36.4%) at stage III including two cases of relapse, and six (27.3%) at stage IV including two cases of relapse. The numbers of patients with stage T1–T4 disease were four, seven, seven and four, respectively; the numbers of patients with stage N0-N3 disease were three, eight, seven and three, respectively. Of the 22 patients, 17 received primary course of irradiation and five received second course of irradiation for tumor relapse. Except for six patients (1 at stage I, one at stage II and four with tumor relapse), 16 patients received concurrent chemotherapy with cisplatin (80 mg/m2, d1) plus 5-fluorouracil (0.5 g/m2, d1–5, d9–13) and radiotherapy.
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Simulation and planning of radiotherapy. All patients were fixed in treatment position with MedTech head and neck frame and thermoplastic facial masks, underwent virtual CT simulation using helical CT scan starting from the roof of skull to sternoclavicular joint with 3 mm slices. The CT images were transferred to Elekta PrecisePLAN (Release 2.10) workstation to design IMRT plan. Patients were treated with 6 MV photons using step-and-shoot technique. Gross tumor volume (GTV) was contoured as primary tumor (GTVnx) and metastatic cervical lymph nodes (GTVnd) detected by physical examination, endoscopy and imaging. Clinical target volume (CTV) included GTV and sub-clinical lesions: CTVnx was GTVnx plus 5 mm margin; CTV1 included the high risk structure surrounding primary tumor and all upper cervical nodes at risk; CTV2 included all mid-lower nodes at risk. Planning target volume (PTV) was CTV plus 3 mm margin. The nasopharynx and upper cervical nodes (PTVnx plus PTV1) were irradiated by IMRT with 7–9 coplanar beams around the head and neck. CTV2 was irradiated with conventional anterior-to-posterior opposing portals. Splitting of neck fields on enlarged nodes was avoided. Half beam technique was applied for the upper boundary of the lower neck field. Cold or hot dose spot was avoided during planning. At least 95% of PTV should receive the prescribed dose. For primary course of irradiation, PTVnx and PTVnd were prescribed to 66–74 Gy by 33–37 fractions; for second course of irradiation, PTVnx and PTVnd were prescribed to 60–65 Gy by 30–32 fractions; 60 Gy by 30 fractions for PTV1 and 50 Gy by 25 fractions for PTV2.

IGRT system. Elekta SYNERGY system consists of a digital linear accelerator (Elekta®) and an imaging system. The accelerator is equipped with a beam modulator which is an 80-leaf MLC with a leaf width of 0.4 cm and a maximal field size of 16 cm × 21 cm at the isocenter. The imaging system includes a kilo-volt cone-beam computed tomography (kV-CBCT) and a mega-volt portal imaging system (iViewGT™).

To acquire CBCT, the gantry was rotated once around the patient in treatment position, starting from 260° and stopping at 100°, at a speed of 3° per second. Field of view (FOV): 26 cm both in diameter and in length using S20 filter. Spatial resolution was 0.100 cm. XVI was acquired at 5.5 frames/s to a total of 361 frames, 36.1 mAs. The dose for each acquisition was 0.9 mGy. 2D and 3D X-ray kV images of patients in treatment position could be reconstructed and registered to planning CT.

Online detection and correction of setup errors. The first CBCT scan was performed after patient positioning. The acquired images were registered to the planning CT using automatic bone matching algorithm to obtain translational errors of target center on the left-to-right (X), superior-to-inferior (Y) and anterior-to-posterior (Z) directions. The isocenter of the IMRT plan was defined as the matching reference point; therefore, the setup errors in three directions could be calculated and corrected. The patients received radiotherapy when the errors in three directions were ≤ 2 mm. If errors were > 2 mm in any of the three directions, online correction was applied and a second verification CBCT was performed. To study the target motion during treatment, a third CBCT was done.

Offline analysis of setup error. The setup errors of the 22 patients were analyzed using software SPSS 13.0 and Microsoft Excel. The systematic errors were calculated as the means of all errors and the random errors were the standard deviation (SD) of the means. The setup errors were analyzed by T test. A p value of < 0.05 was considered significant.

PTV margin prediction. According to the method proposed by van Herk et al., the required setup (CTV-PTV) margin which ensures a minimal CTV dose of > 95% of prescribed dose for 90%
of the patients was calculated as $2.5 \Sigma_{\text{total}} + 0.7 \sigma_{\text{total}}$ (Sigma was the SD of the systematic error and $\sigma$ was the root mean square of the random error). $\Sigma_{\text{total}}^2 = \Sigma_{\text{SM}}^2 + \Sigma_{\text{SLM}}^2$ ($S_{\text{M}}$ was the margin for setup error, $S_{\text{IM}}$ was the margin for internal target motion). In this study, only setup errors were taken into account for PTV margin calculation, and in real treatment the mechanical uncertainty should be included.

### Results

**Comparison of CBCT iso-center errors.** The 22 patients received 6–32 CBCT scans (median, 24.5 scans) during radiotherapy, with a total of 754 scans (505 pre-correction scans, 106 post-correction scans and 143 post-treatment scans). The distribution of CBCT iso-center errors before and after correction, and after treatment was shown in Figure 1. The frequency of errors ≤ 2 mm in the X, Y and Z directions of CBCT scans were 76.4, 76.0 and 85.7% respectively before correction. According to all verification CBCT scans performed after correction for errors > 2 mm, five errors of 2–2.5 mm were detected in X and Y directions in two patients, of which four errors occurred in three successive irradiation fractions of the same patient. The systematic and random errors were shown in Table 1.

**Comparison of $\Sigma$, $\sigma$ and PTV margin.** As shown in Table 2, the systematic setup uncertainty $\Sigma$ and random uncertainty $\sigma$ of the 22 patients in X, Y and Z directions were reduced after correction as compared with those before correction. The PTV margins in the three directions were all within 4 mm. As 2 mm threshold was used for correction before treatment delivery, the patients receiving irradiation included those who had errors ≤ 2 mm at initial CBCT and received treatment directly without correction, and who had errors > 2 mm and underwent the second CBCT for verification after correction. Accordingly, the setup uncertainty and PTV margins of the 22 patients at the beginning of treatment were calculated, and the maximal PTV margin was 2.1 mm.

Comparing the variation of post-treatment CBCT with pre-treatment CBCT (including pre-correction and post-correction CBCT), the position of patients was found somewhat changed. The PTV extension based on this variation could reflect the internal margin (IM) of tumor irradiation. The post-treatment setup errors were greater than pre-treatment errors, but the differences were not significant (p > 0.05).

### Discussion

Using image guidance system before radiotherapy, the displacement of treatment iso-center, tumor and critical organs between the actual position and planning CT could be detected and quantified, which can be corrected to guarantee the accordance of actual dose distribution and radiotherapy plan. The planning CT scan only shows the anatomic structures before radiotherapy, which could deviate during treatment, and the deviation could not be detected by body surface markers or an external fixation device. It is critical to use reliable means of imaging to verify that the patient's actual position is consistent with those showed on planning CT scan before the implementation of high precision radiotherapy. Currently, the mega-volt electronic portal imaging (EPI) is the standard method for verification of treatment positions, which is based only on evaluation of bony landmarks, while the internal organ movement or variations can not be evaluated. In IMRT for NPC where complex structures of adjacent tissues are present and multiple small beams are used, the resulting EPI image shows an overlapping of structures with poor soft tissue discrimination. High precision is required for IMRT of NPC as critical organs surround the nasopharynx with limited irradiation tolerance. The PTV margin should be designed more accurately, whereas a few millimeter shifts could have deleterious effects on clinical outcome.

The application of volumetric imaging technique provides strong support for implementation of precision radiotherapy. The volumetric imaging device used in clinic at present could be classified according to its X-ray source into mega-volt (MV) and kilo-volt (kV) CBCT. Though some progress has been made in MV-CBCT, it still has the shortcoming of poor soft tissue discrimination and considerably high imaging dose. Jaffray et al. reported the application of kV-X-ray CBCT to acquire patient’s images in treatment and the re-construction of 3D volumetric data. McBain et al. found that the imaging dose to patients from kV-CBCT guide
was 0.003 Gy, with good soft tissue discrimination. It shows great advantages in research on head and neck cancer, which contains fine and complex structures.

Our study showed that by using kV-CBCT imaging function, the 3D setup errors for each scan could be accurately calculated. On kV-CBCT images, the 3D structures and variations of all tissues and organs as well as the size, location and variation of tumor during irradiation are clearly displayed. It shows great value and potential in clinical treatment for head and neck tumor, especially NPC. Although the contrast of kV-CBCT image is reduced due to the decreased patient-detector distance and increased scattered photon ratio, which limits its diagnostic value, by matching with bones surrounding the nasopharynx, kV-CBCT can fully meet the requirement for setup verification in radiotherapy. All kV-CBCT images acquired in this study fully superimposed upon the planning CT by automatic bone matching tool. The extra time required for three CBCT scans and correction were 10–12 min, only 2–3 min for 76% by automatic bone matching tool. The extra time required for three CBCT scans and correction were 10–12 min, only 2–3 min for 76% patients whose initial setup errors were < 2 mm, and 3–5 min for those who needed correction and verification scan.

A total of 754 kV-CBCT scans were performed in our study. The frequency of iso-center errors ± 2 mm in X, Y and Z directions were 76.4, 76.0 and 85.7%, respectively, before correction while increased to 97.2, 97.2 and 100%, respectively, after online correction. The results imply quite accurate initial positioning for NPC patients, and after online correction the accuracy could be kept within 2 mm, which provides basis for improving the precision in IMRT for NPC. However, about 10% of the patients still have position deviation during treatment with the errors increase to over 2 mm.

In this study, comparing the pre- and post-correction CBCT, both the systematic and random errors were decreased after online correction. Scatter plot (Figure 1) intuitively shows that the iso-center distribution in the transverse, coronal and sagittal planes was more congregated after correction with the maximal deviation within 0.5 cm, while the iso-center distribution was more scattered before correction with the maximal deviation of 1 cm, proposing the significant role of kV-CBCT in detection and correction of isocenter deviation in radiotherapy. The results also showed that the isocenter errors after treatment were smaller than that before correction, but larger than just after correction, indicating movement of target during treatment. The internal target motion of head and neck tumors during treatment was considered to be caused mainly by swallowing. As IMRT was applied for all patients in this study, the target motion during irradiation might be related to swallowing or involuntary motion due to longer irradiation time.

It has been reported that PTV margin could be reduced by applying online and offline analysis and correction. Our results revealed that the maximal PTV margin was 4 mm before online correction, and only 2 mm after online CBCT correction. The errors detected by post-treatment CBCT demonstrated target motion during irradiation delivery and a maximal PTV margin of 3 mm in Y direction would be needed, indicating only small shift of isocenter during treatment which has little impact on PTV margin generation. Therefore, we postulated that for this group of NPC patients receiving IMRT, when CBCT verification had not been performed, the total PTV margin should be 6–8 mm to account for any intra-fraction motion and mechanical uncertainty; however, when CBCT online correction was applied, the PTV margin should be reduced to 4–5 mm. The results suggest that application of kV-CBCT detection and online correction in IMRT of NPC could effectively reduce irradiation margin and irradiation volume, therefore, has great value on protection of surrounding critical organs, particularly in the cases of dose escalation, re-irradiation for relapses or when tumor foci lie adjacent to critical organs, where kV-CBCT has even greater value.

In conclusion, the kV-CBCT integrated in the Elekta SYNERGY system provides good image quality for clinical application, which can be applied in IMRT of NPC. Online detection and correction using kV-CBCT can increase the setup accuracy of IMRT for NPC and reduce PTV margin, which provide the basis for further dose escalation and is clinically applicable. It should be pointed out that due to the application of single lower neck field irradiation, the matching of field margin should be carefully managed. As the lower border of the nasopharyngeal IMRT fields was changed after online correction, the position of the lower neck field should be adjusted accordingly, which may result in overlapping or insufficient dose coverage at the portal junction. In our study, we used portal film to analyze and adjust the junction. No tumor relapse or severe irradiation-related injury has been observed at the site of field junction in patients during follow-up.

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