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DETERMINATION OF SETUP MARGIN FOR NASOPHARYNGEAL CARCINOMA BY USING ELECTRONIC PORTAL IMAGING DEVICE

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Introduction: This study aimed to assess three-dimensional (3D) setup mistakes and provide optimal margins for planned target volume (PTV) coverage in head and neck radiation. Methods: Ten patients participated in the trial, receiving IMRT in conjunction with weekly electronic portal imaging (EPI). A total of 170 portal pictures were analyzed. The systematic (S) and random (s) errors in the population of patients with head and neck cancer were assessed using portal images in the caudocranial longitudinal (CC) and left-right lateral (LR) orientations, measured within the anterior-posterior (AP) field. The clinical-to-planning target volume (CTV-PTV) margins were determined in accordance with ICRU Report 62 guidelines and van Herk's formulae. **Results:** The group systematic errors and random errors were 0.19 and 0.26 cm , respectively in the anteroposterior direction; the group systematic errors and random errors were 0.15 cm and 0.24 cm in SI direction, respectively; the group systematic errors and random errors were 0.13 cm and 0.25 cm in LR direction, respectively; According to the classical van-Herk formula MPTV =2.5Σ +0.7σ, we figured out the ideal PTV margins (MPTV) based on the setup errors and 0.65 cm, 0.55 cm, and 0.5 cm were required in the AP, SI, and RL directions. **Discussion and conclusions:** we can conclude that a 6-mm extension of CTV to PTV margin, as the optimal margin and can be reduced with increasing frequency of online verification (daily imaging) or for patients where the prescribed does not exceed tolerance doses for organs at risk.
Keywords: *Nasopharyngeal Radiotherapy; Intensity-modulated radiotherapy (IMRT); Set-up uncertainty*
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INTRODUCTION

With the extensive use of intensity-modulated conformal radiation and the strengthening of the principle of comprehensive treatment, the curative effect of nasopharyngeal cancer and patients' quality of life have been greatly improved [1–4].The success of radiotherapy largely depends on precise patient positioning and the accuracy of immobilization strategies for patients with head and neck tumors during each treatment session, particularly in the head and neck area where critical organs such as the salivary glands, spinal cord, and brain stem are in close proximity, allowing for minimal error and consequently minimise risk of toxicity and long-term morbidity [5,6]. Optimized intensity-modulated radiation therapy (IMRT) plans typically generate sharp dose gradients between the tumor and adjacent healthy tissues. Any misalignment in patient positioning can lead to insufficient tumor irradiation, heightening the risk of local recurrence, and unnecessary radiation exposure to surrounding tissues. Previous studies analyzed the influence of setup uncertainties on target volume coverage and doses to organs at risk (OAR) in HNC patients treated with image-guided radiation (IGRT) [7–9]. Geometric uncertainties present a greater challenge in IMRT planning compared to conventional methods, emphasizing the need to identify and reduce setup errors throughout the treatment process. The main difficulty lies in consistently replicating the patient's position in every treatment session, as determined by the planning CT scan. Positioning errors during treatment arise when the patient's anatomy does not align with the planned CT. These errors might be systematic (reproducible consistent errors in the same direction and amount) or random errors (variations in direction and magnitude). Systematic errors can cause changes in the cumulative dosage distribution [10–15]. Portal imaging (PI) allows for consistent imaging, quick identification of setup errors, and automated verification of treatment fields. Numerous studies have reported the use of PI-guided setup corrections for both conformal and IMRT techniques [16–29]. However, since PI is a two-dimensional imaging method, it cannot detect errors resulting from out-of-plane rotations [30–34]. That said, the dosimetric impact of rotational setup errors should be carefully considered from case to case when organs at risk are in close proximity to the target [35]. This study focused on measuring random and systematic inter-fractional setup errors using electronic portal imaging (EPI) for 10 patients diagnosed with locally advanced nasopharyngeal carcinoma undergoing IMRT, with the goal of determining the optimal clinical target volume (CTV) to planning target volume (PTV) margins necessary to ensure complete target coverage.

MATERIAL AND METHOD

Patient selection

This retrospective study was approved by the appropriate institutional review. The research focused on 10 patients diagnosed with locally advanced nasopharyngeal carcinoma, who were treated using IMRT with the simultaneous integrated boost (SIB) technique and concurrent chemotherapy [36].

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Definition of volumes of interest and IMRT treatment

Patients were immobilized in a supine position using standard thermoplastic head-neck-shoulder casts with five fixation points and the base plate was not fixed to the table couch of the linac. High-resolution computed tomography (CT) scans were taken in helical mode with a 3 mm slice thickness, covering the area from the skull vertex to mid-chest.

The dose to the PTV70, which includes the primary and nodal gross tumor volumes and positive lymph nodes, had been set at 70 Gy. The dose for PTV60, which encompassed the high-risk clinical target volume (CTV) and nodal CTV, was established at 60 Gy. The dose to PTV54 contained the low risk CTV was set at 54 Gy. All patients were optimized using dynamic technique (Eclipse software (Version 13.7, Varian Medical Systems, USA). Dosimetric calculations were performed using the Anisotropic Analytical Algorithm (AAA) on a 2.5 mm calculation grid, optimized with a dose volume optimizer. All patients were treated by a Clinac 600C linear accelerator equipped with 6 MV photons and an 80-leaf multileaf collimator.

Generation of DRR and portal imaging

Two orthogonal DRRs obtained from the treatment planning software, with a field size of 10×10 cm^2, gantry angle of 0° (anterior) and 90° (lateral), were transferred to the treatment unit as reference images. Portal images were acquired with the same gantry by using the EPID system attached to Varian linear accelerators

Anatomic reference landmarks included at least two well visible bony structures: external mandible profile, nasal septum, maxillary sinus and the spinous process of one of lower cervical vertebrae were generally used for the anterior images, while internal and external mandible profiles, skull base and cervical vertebral bodies, i.e. C2 and C4, were usually outlined on the lateral images (Figure 1a and b). The images were analyzed by two radiation oncologists adequately trained to reduce interobserver variability.

Measurement of set-up errors was performed at least three times during the first week of treatment and on a weekly basis thereafter. Images were matched on-line during the first week, off-line thereafter. In case of displacement exceeding 2 mm along one direction, the linac couch was adjusted to match the treatment isocenter and new EPIs were acquired.

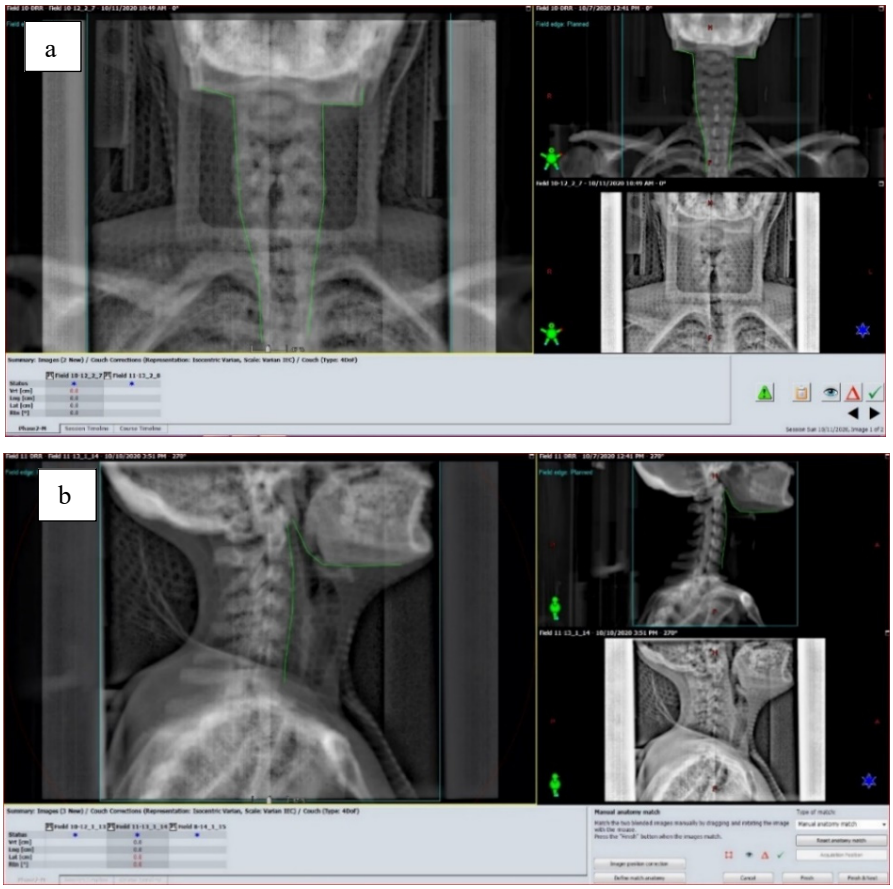

Figure 1. Matching between digitally reconstructed image (DRR) and image taken prior to treatment
(a) AP images; (b) Lateral images

Statistical methods

We followed the definition and notations of setup errors described elsewhere [37]. If we denote patients as p $\epsilon\{_p1; {}_p2;.{}_pM\}$, and image sections for each patient as f ϵ {1; 2;.;N}, then the setup error $E_{pf} = \{E_{pf}^{AP}; E_{pf}^{SI}; E_{pf}^{RL}\}$ can be written as $E_{pf} = S_p + R_{pf}$, where S_p is the systematic error for each patient, whereas R_{pf} is the random error introduced in

each image section. The patient (p)-specific random error $\sigma_p$is the standard deviation (SD) of R_{pf} over f. The population systematic and random variations are then calculated by the following equations [37],

$$S_p = \sum_{f=1}^{N} \frac{E_{pf}}{N}$$

$$\mu = \sum_{p=p1}^{pM} \frac{S_p}{M}$$

$$\Sigma = \left(\frac{1}{M}\sum_{p=p1}^{pM}(S_p - \mu)^2\right)^{1/2}$$

$$\sigma_p = \left(\frac{1}{N}\sum_{f=1}^{N}(R_{pf} - \overline{R_{pf}})^2\right)^{1/2}$$

$$\sigma = \left(\frac{1}{M}\sum_{p=p1}^{pM}\sigma_p{}^2\right)^{1/2}$$

where μ is the population mean of systematic variations, Σ is the standard deviation of the systematic variations, and σ is the average root-mean-square of individual random variations.

Margins resulting from setup uncertainty alone could then be estimated from the systematic and random variations. Van Herk has provided a review of margin formulae [38], and the commonly used form is $M = 2.5\Sigma + 0.7\sigma$ Margins determined by this equation assume that the minimum dose to CTV is 95% for 90% of the patients [39]. The 90% confidence range, which is lower bounded by the 5th percentile and upper bounded by the 95th percentile, could also indicate the setup margin [37].

RESULTS

A total of 170 position verification scans were acquired and analyzed (0^o anterior, 90^o lateral) were obtained for 10 patients, with a mean of 19 images for each patient range (18-23).

The quantification of patient set-up errors was given by the determination of the displacement frequency (μ), and it was plotted in different directions: Figure 2a anteroposterior (AP), Figure 2b craniocaudal (CC) and Figure 2c left–right (L-R), directions. It demonstrates that the largest displacement was in the A-P direction 8 mm in the posterior direction. As regards A-P direction, frequency for displacement 0.4 cm reaches to 9.83%. The frequencies of setup errors ≤ 0.3 cm in AP, SI, and RL, directions were (68.81%), (77%), and (83.5%), respectively (Figure 2).

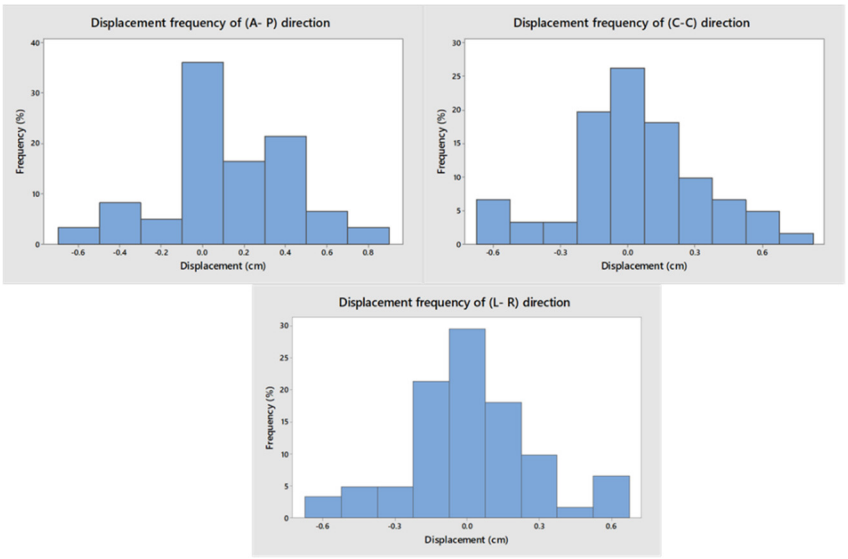

Figure 2. The distribution of the interfractional patient set-up errors for the nasopharynx: the displacements (m) of the coordinate of the nasopharynx between the digitally reconstructed radiograph and imaging portals plotted for the (a), anteroposterior (A-P) (b) craniocaudal (CC) (c) left–right (L-R) directions.

The distribution of all setup errors in three directions is shown in (Figure 3). Regardless of the duration of the fractionated radiotherapy course. The population mean and standard deviation were 0.0831±0.307, 0.0508±0.293 and 0.0051±0.26 in AP, SI and LR directions, respectively. The deviation of bony reference points in the range of (-0.6-0.8) cm, (-0.6–0.7)cm and (-0.6–0.6) cm in AP, SI and LR directions; The group systematic errors and random errors were 0.19 and 0.26 cm , respectively in the anteroposterior direction; the group systematic errors and random errors were 0.15 cm and 0.24 cm in SI direction, respectively; the group systematic errors and random errors were 0.13 cm and 0.25 cm in LR direction, respectively; According to the classical van-Herk formula MPTV =2.5Σ +0.7σ, we figured out the ideal PTV margins (MPTV) based on the setup errors. Considering the setup errors and the accuracy of deliver

radiation doses to the targets and their surrounding normal structures, margins of 0.65 cm, 0.55 cm, and 0.5 cm were required in the AP, SI, and RL directions, respectively, Table 1.

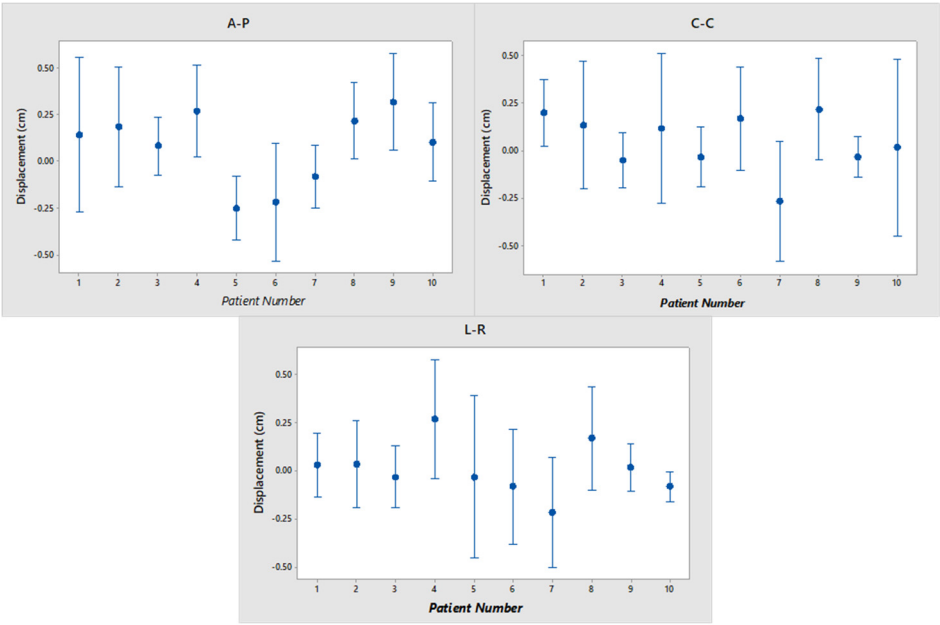

Figure 3. The distribution of all setup errors in three directions obtained EPID

Table 1. Summary of interfraction translational error (mm) in each dimension

	AP	SI	RL
M	0.0831	0.0508	0.0051
SD	0.307	0.293	0.26
Minimum	-0.6	-0.6	-0.6
Maximum	0.8	0.7	0.6
Σ	0.19	0.15	0.13
σ	0.26	0.24	0.25
MPTV	0.65	0.55	0.5

Abbreviations: M, mean of all patients' mean; SD, standard deviation; Σ, systematic setup uncertainty; σ, random setup uncertainty; RL, right–left; SI, superior–inferior; AP, anterior–posterior; MPTV, PTV margins.

DISCUSSION

The dose distribution in IMRT for head and neck cancer patients relies solely on volume data from the pretreatment CT scan, which reflects the patient's anatomical structure at that particular moment. However, this method does not consider daily changes in target volumes, organs at risk (OARs), or anatomical positioning [40]. The impact of patient setup errors is especially significant in IMRT planning because of the steep dose gradients aimed at protecting nearby OARs from excessive radiation exposure. Studies have shown that a 3 mm error in couch positioning can greatly affect the minimum dose delivered to target areas and the maximum dose to the spinal cord and brainstem in the anterior-posterior (AP) direction [41–43]. Therefore, it is essential to accurately measure and reduce patient setup errors during radiation treatment. Several studies have investigated setup accuracy in head and neck cancer patients, with results varying widely depending on factors such as tumor location, treatment techniques, fixation devices, imaging and registration methods, and the types of setup errors analyze [44–53].

This study investigated the set-up accuracy of head and neck cancer patients undergoing IMRT using EPIs to define appropriate planning margins that satisfy a target dose criterion.

In our study, we investigated set-up variations in a homogeneous patient group treated with standard thermoplastic mask immobilization with five fixation points, no base plate attachment to the linac couch, 2D-alignment procedures, and EPID-based imaging. According to Bentel [54], fixing the base plate to the treatment couch may reduce set-up mistakes by improving repeatability and preventing patient misalignment on the table, which causes out-of-plane rotations. This is most likely the reason for the decreased set-up errors observed by Humphreys et al [55]. The enhanced and reproducible setup precision in the head and neck region was likely attributable to superior immobilization for accurate treatment delivery, as even small changes from the reference anatomy of the patient's planning CT scan (pCT) have the potential to compromise the PTV coverage or sparing of healthy tissues. The use of patient immobilisation devices, such as customized headrests rather than the standard headrest provides a more reliable level of immobilization and hence minimizing the radiation dose to normal tissue structures and consequently minimize risk of toxicity and long-term morbidity [56–60].

We evaluated the accuracy of patient setup by examining systematic and random mistakes. The systematic component of an error is characterized by a consistent deviation in the same direction and of comparable magnitude across all treatment fractions (treatment preparation errors), while the random component is defined by deviations that fluctuate in both direction and magnitude for each administered treatment fraction (treatment execution errors).

There are a limitations in our study concerning the frequency of online verifications of the patient set-up, we performed EPID first 3 PIs in first week then weekly PI and the setup errors values may be affected as reported in [61-64], their results showed that the overall standard deviations of the displacements increase significantly between daily and weekly measurements so they decided to perform daily images for certain directions as like Pehlivan [61] recommended that a PI in the AP and ML orientations be conducted weekly, while in the CC orientation, it should occur every two days to effectively mitigate set-up problems. A previous study by Strabac et al. [64] has shown that the overall standard deviations of the displacements increase significantly between daily and weekly measurements in the dorsoventral and caudocranial directions, measured in the lateral PIs. The PIs measured in the AP fields in the caudocranial and left-right lateral directions, have shown no significant increase in the overall SD of the displacement due to the frequency of measurements. Marnouche et al. [65] evaluated three-dimensional 3D set-up errors using EPID and also investigated if other imaging frequency protocols were as effective as the daily imaging protocol and compered it with No Action Level 5, extended No Action Level, weekly, protocols. The study reported that a 5-mm extension of CTV to PTV margin was the optimal margin and The Daily online verification protocol was the advised verification protocol for patients treated with IMRT. The results of Youssoufi et al. [66] which obtained by weekly EPID setup verifications, almost likely aligned with our results and reported that the Setup margins 4·27, 4·2 and 4·7 mm in X, Y and Z directions, respectively.

According to our findings, the population systematic errors and random errors were 0.19 and 0.26 cm, respectively in the anteroposterior direction; the group systematic errors and random errors were 0.15 cm and 0.24 cm in SI direction, respectively; the group systematic errors and random errors were 0.13 cm and 0.25 cm in LR direction, respectively. The largest displacement was in the A-P direction 8 mm in the posterior direction and the frequency for displacement 0.4 cm reaches to 9.83% followed by SI and RL directions.

The results align with Durim et al. [67], whose investigation indicated that the overall incidence of set-up displacements above 3 mm was 3.9% in the medial-lateral (ML) direction, 8% in the superior-inferior (SI) direction, and 15.5% in the anterior-posterior (AP) direction.

Mongioj et al. [68] reported that as the therapy progressed, the displacement > 3 mm were observed more commonly at instances of significant weight loss or tumor nodal reduction and confirmed the need for a strict monitoring of patient set-up in case of isocenter change due to sequential PTVs definition and in the presence of significant weight loss and/or tumor shrinkage.

The greater displacement A-P directions is attributed due to weight loss and the size of the neck is more likely to become smaller because there is more subcutaneous adipose tissue in the neck, patients may slide along the head-holder, therefore Ove et al. [69] and SU et al and Zhang et al. [37,70] proposed registration of multiple ROIs and took an analysis of 3D setup uncertainties for multiple ROIs in head and neck region and there was a statistically significant difference in setup error between the head and neck during radiation. However, the setup error of the neck was bigger than the head and They came to the conclusion that the setup errors among head, upper neck, and lower neck in SI directions were with homogeneity ($P>0.05$); hence, the setup errors with head, upper neck, and lower neck in RL and AP directions were not with homogeneity.

In order to prevent underestimation or overestimation of actual margin, the discrepancy of geometrical set-up errors must be considered in three directions. Based on our results we can conclude that a 6-mm extension of CTV to PTV margin, as the optimal margin. Our results are similar as Strabac [64] which reported that 6.1, 5.1, 4.8 mm CTV-PTV in LR, CC and 4.8 mm CTV-PTV DV direction, respectively.

In general, performing regular position corrections and improving patient positioning would lead to a small PTV margin and lower chance of normal tissue complications.

CONCLUSIONS

This study is a report on the set-up accuracy of patients treating for HNC with IMRT. CTV-PTV margins calculated according van Herk formula and we can conclude that a 6-mm extension of CTV to PTV margin, as the optimal margin and can be reduced with increasing frequency of online verification (daily imaging) or for patients where the prescribed doesn't exceed tolerance doses for organs at risk.

Conflict of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request**.**

Declaration: The information in this article is correct, ethical considerations have been assessed per hospital policy, Ethical Approval is 36265MD265/8/24

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ВИЗНАЧЕННЯ МЕЖІ НАЛАШТУВАННЯ ДЛЯ НОСОФАРИНГІАЛЬНОЇ КАРЦИНОМИ ЗА ДОПОМОГОЮ ЕЛЕКТРОННОГО ПОРТАЛЬНОГО ПРИСТРОЮ ВІДОБРАЖЕННЯ

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Вступ. Це дослідження мало на меті оцінити помилки тривимірного (3D) налаштування та забезпечити оптимальні межі для охоплення запланованого цільового об'єму (PTV) при випромінюванні голови та шиї. **Методи:** десять пацієнтів брали участь у дослідженні, отримували IMRT у поєднанні з щотижневою електронною портальною візуалізацією (EPI). Всього було проаналізовано 170 знімків порталу. Систематичні (S) та випадкові (s) помилки в популяції пацієнтів із раком голови та шиї оцінювали за допомогою портальних зображень у каудокраніальному поздовжньому (CC) та ліво-правому латеральному (LR) напрямках, виміряних у межах передньо-заднього (AP) поля. Межі цільового об'єму від клініки до планування (CTV-PTV) були визначені згідно з рекомендаціями ICRU Report 62 та формулами ван Герка. **Результати:** групові систематичні та випадкові помилки становили 0,19 і 0,26 см відповідно в передньо-задньому напрямку; групові систематичні похибки та випадкові похибки становили 0,15 см та 0,24 см у напрямку CI відповідно; групові систематичні похибки та випадкові похибки становили 0,13 см та 0,25 см у напрямку LR відповідно; Відповідно до класичної формули Ван-Херка MPTV =2,5Σ +0,7σ, ми розрахували ідеальні межі PTV (MPTV) на основі похибок налаштування та 0,65 см, 0,55 см і 0,5 см, необхідні для напрямків AP, SI та RL. **Обговорення та висновки:** ми можемо зробити висновок, що 6 мм розширення CTV до PTV межі є оптимальною межею і може бути зменшено зі збільшенням частоти онлайн-перевірки (щоденна візуалізація) або для пацієнтів, де призначені дози не перевищують допустимі дози для органів під загрозою.

Ключові слова: *променева терапія носоглотки; променева терапія з модуляцією інтенсивності (IMRT); невизначеність налаштування*