Evaluation of Interfractional Setup Uncertainties and Calculation of Adequate CTV-PTV Margin for Head and Neck Radiotherapy using Electronic Portal Imaging Device

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ABSTRACT

Background: The evaluation of treatment-associated errors is important in the radiotherapy process, particularly those resulting related to patient setup.

Objective: This research aimed to assess the interfractional setup errors and determine the Clinical Target Volume to Planning Target Volume (CTV to PTV) margin in patients undergoing 3-Dimensional Conformal Radiation Therapy (3DCRT) for head and neck cancer by means of electronic portal imaging device.

Material and Methods: In this analytical study, 300 portal images were acquired from 50 patients undergoing 3DCRT for head and neck cancer. Using the portal images of Lateral (LAT) and Antero-Posterior (AP) fields, population systematic ($\sum$) and random (σ) errors were obtained in the lateral, longitudinal, and vertical directions. Finally, based on the International Commission on Radiation Units and Measurements (ICRU) Report 62's, Stroom's and Van Herk's methods, Planning target volume margins were determined.

Results: The translational shift ranges were 0-8.1 mm in the ML, 0-9 mm in the SI (AP), 0-8.8 mm in the SI (LAT), and 0-10 mm in the AP directions. The population systematic and random errors were respectively 3.230, 2.753, and 2.997 mm, and 1.476, 1.853, and 1.715 mm in X, Y, and Z directions. The calculated PTV margins using the ICRU-62, Stroom's, and Van Herk's formulae were ranging from 3.236-3.551, 6.605-7.493, and 7.932-9.108 mm, respectively.

Conclusion: A PTV margin of 7.5-9.5 mm seems safe for ensuring adequate treatment volume coverage. In addition, the EPID is an effective equipment for verifying patient positioning and reducing treatment setup errors.

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Keywords

Head and Neck Cancer; Radiotherapy; Patient Positioning; Setup Errors; Systematic Error

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Introduction

Head and neck cancers (H&N) constitute the sixth most prevalent disease around the world [1]. Squamous cell carcinoma, which affects the epithelium of the upper gastrointestinal tract, is the most common histology in this region, accounting for more than 90% of cases

[2]. Annually, more than 650,000 new cases of the disease and over 350,000 deaths are reported worldwide [3]. By 2030, the global burden of head and neck cancers is projected to increase by approximately 34% (1031479 new cases and 576563 deaths) [2]. In Iran, there is limited evidence regarding the epidemiology of head and neck cancer [4]. According to Mirzaei et al., 25,952 cases of H&N cancer were recorded in Iran from 2003 to 2009, and laryngeal cancer is the most prevalent cancer in this area among the Iranian population [5]. The etiology of cancer is multifactorial, including smoking and alcohol consumption, pan-chewing, herpes virus, and Epstein-Barr virus [6]. According to international guidelines, the standard cancer treatment is radiotherapy and platinum or cetuximab-based chemotherapy [3].

Radiotherapy aimed for the least dose to the surrounding healthy organs and the highest conformity in delivering the dose to the target tissues [7]. The effectiveness of radiation therapy relies in part on the patient setup at each session, particularly when treating regions of the head and neck; because in this area, the safety margin is limited due to the proximity of vital organs like the spinal cord and brainstem [8]. Therefore, a key part of the radiation treatment process is the assessment of treatment-associated errors, particularly those related to patient setup and organ motion [9].

Setup errors are described as any difference between the patient's reference position at Computed Tomography (CT) scan and the patient's position during each treatment session [10]. These errors are divided into systematic error, which is constant and repetitive errors in identical size and direction, and random error, changing in direction and size. However, systematic errors lead to a shift in the cumulative dose distribution, random errors can cause a blurring of the target dose distribution [11]. Daily setup errors during a standard radiotherapy period may lead to significant deviations from the designed dose distribution, increasing the hazard of geographical mistargeting and/or overdosing of vital tissues [12]. To make sure desired target volume dose coverage in the presence of misalignment errors due to patient adjustment and organ movement, the Clinical Target Volume (CTV) is enclosed with a safety margin to establish the Planning Target Volume (PTV) [13].

Increasing treatment frequency with portal imaging is an effective way to reduce setup errors [14]. In the 1990 s, the accuracy of patient positioning was assessed using weekly port films as a standard method [15]. Such a process is time-consuming when using the port video, and it is difficult to interpret a small geometric difference. The need for an improved portal imaging system to validate conformal radiotherapy has led to the development of Electronic Portal Imaging Devices (EPIDs) [14].

The accuracy of the radiation field displacement can be effectively determined using the EPID method. The digital nature of EPID supplies quantitative tools for population-based or individual patient analyzing setup errors (systematic and random). This method replaces the various manual steps of filming (setup, processing, review) by capturing, processing, and displaying a computer-controlled image [16].

Advanced EPIDs are used in modern linear accelerators equipped with amorphous silicon technology (flat panels) with better image quality than former devices with video camera-based EPIDs or ion chambers. The Digitally Reconstructed Radiograph (DRR) of the treatment plan is usually compared with portal images, either analog (radiograph) or digital with the EPID to verify patient positioning [17].

The present study, which evaluated systematic and random setup uncertainties using both EPID and DRR techniques, aimed to assess interfractional setup errors and propose an optimal CTV-PTV margin for patients undergoing 3-Dimensional Conformal Radiotherapy (3DCRT) for head and neck cancer by means of EPID.

Material and Methods

It is an analytical study.

Patient, Treatment Simulation, and Treatment Planning

A total of 300 portal images were analyzed, which were obtained from 50 randomly selected patients treated with 3DCRT. H&N cancer types were treated in the nasopharynx (16), larynx (10), hypopharynx (8), tongue (7), thyroid (5), parotid (3), and oral cavity (1). The patients were instructed to lie in the supine position on a NeuViz 16 Slices CT scan system (Neusoft Medical System Co., Shenyang, China) and underwent planning CT using a 3 mm slice thickness. A 5-point head-shoulder thermoplastic mask was used to immobilize the patients. The application of a thermoplastic immobilization tool for the head and shoulders makes the setup procedure reproducible and leads to the identification of systematic errors after a few guiding sessions [3]. To determine a reference point based on the localization of treatment volume, the room lasers' positions were marked on the thermoplastic mask using radiopaque markers at the intersections of laser. The image data were entered into the treatment planning system (Isogray software, Dosisoft, Cachan, France) for 3DCRT treatment planning. The DRRs were calculated and saved in the treatment planning system and subsequently purposed as reference images. The delineation of the target volumes and OARs was performed by an oncologist. Isotropic margins to overcome geometric displacements were added to the relevant CTVs and the PTVs were constructed. 3DCRT plans were created using three-photon energies (6, 10, and 15 MV) in the Isogray treatment planning system. All patients received a prescribed dose of 70 Gy in 35 fractions using the 3DCRT technique in an Elekta Precise linear accelerator (Stockholm, Sweden). The accelerator contained an 80-leaf multileaf collimator (MLC) and amorphous silicon EPID.

Treatment Verification

The patients were transferred to the treatment room with immobilization tools for daily setup before treatment, and the marks on the mask were set with the sagittal and transverse lasers of the treatment room. Orthogonal portal images were obtained through amorphous silicon (a-Si) EPID with an active area of 41×41 cm^2 and consisted of 1024×1024 pixels at a gantry angle of 0 and 90 degrees (i.e., Antero-posterior (AP) and Lateral (LAT) directions) utilizing 6 MV X-ray beam and 3 Monitor Unit (MU) with a dose rate of 50 MU/min in each field.

In all patients, portal images were obtained before treatment in the first three consecutive sessions of irradiation. Portal images and DRRs (as reference images) were matched to estimate deviations using the MOSAIQ software (Figure 1). Bone landmarks can be used as references to compare EPIs and DRRs, such as the external mandible profile, maxillary sinus, nasal septum, and spinous process of cervical vertebrae for LAT images and skull base, clavicle, and mandible for AP images. The offline correction protocol was performed in regard to a mismatch of more than 3 mm in each direction. If the translational deviations of

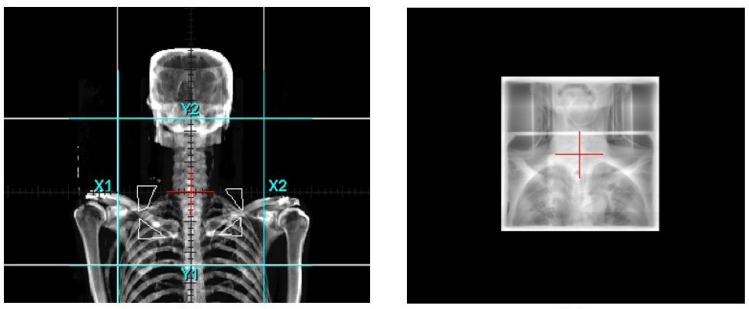

Figure 1: Position verification using MOSAIQ software offline review; (**a**) Digitally reconstructed radiograph (**b**) Antero-posterior portal image.

the setup were up to 3 mm in all directions, no action was done [18]. Then, the portal image was repeated weekly for the entire treatment duration; If translational shifts were larger than 3 mm in each direction, they were corrected. Setup deviations were measured on 150 AP and 150 LAT portal images. The translational displacements observed in two directions of the lateral field (i.e., Superior-Inferior (SI) and AP), and Medial-lateral (ML) and SI directions of the AP field were registered.

Statistical Analysis

The displacement between the DRR and EPI was a combination of random and systematic errors (i.e., setup deviation that symbolized as μ), determined in all patients by using translocations in three translational directions. The distribution of group systematic error ($\sum_{setup}$) was specified qua the standard deviation (SD) of each mean setup uncertainties for the overall population means (M_{pop}), and the average of whole patient-specific random uncertainties was determined as the group random uncertainty (σ_{setup}) [13].

The number of acquired images (N) and patients (P) determine the reliability of the statistical method for estimating standard deviations [9].

Individual mean setup error (m_{ind}) of *n* images for an individual patient given by [13]:

$$m_{ind} = \frac{\sum_{i=1}^{n} \mu_{(PI-DRR)_i}}{n} \quad (1)$$

A patient-specific random error was obtained as the SD of setup uncertainties of the m_{ind} derived from equation (1) in the given direction [13]:

$$\sigma_{ind} = \sqrt{\frac{\sum_{i=1}^{n}\left(\mu_{(PI-DRR)i} - m_{ind}\right)^2}{(n-1)}} \quad (2)$$

The equation for the overall mean setup error (M_{pop}) calculation is the overall mean for all patients p [13]:

$$M_{pop} = \frac{\sum_{p=1}^{p}(m_{ind})_p}{p} \quad (3)$$

The group random setup uncertainty (σ_{setup}) in the given direction is calculated as [13]:

$$\sigma_{setup} = \frac{\sum_{p=1}^{p}\sigma_{ind}}{p} \quad (4)$$

The equation for calculating the population systematic setup error ($\sum_{setup}$) for the patient group in this study in a given direction is as follows [13]:

$$\sum_{setup} = \sqrt{\frac{\sum_{p=1}^{p}\left(m_{ind} - M_{pop}\right)^2}{(p-1)}} \quad (5)$$

Calculation of CTV-PTV Margin

Using the ICRU-62 [19], Stroom et al. [20], and Van Herk et al. [21] formulae PTV margins were calculated. Based on the International Commission on Radiation Units and Measurements (ICRU)-62, a quadratic combination approach is given to generate the PTV margin for the two random and systematic uncertainties. The authors assumed that the consequence of both random and systematic uncertainties on the target dose distribution is the same, which may not necessarily be true. Systematic errors have greater dosimetric outcomes than random errors and result in a target-relative shift in the cumulative dose distribution, but random uncertainties lead the target dose distribution to be blurred [22]. The Stroom and Van Herk margin recipes recognize the effects of these two types of errors on the dose distributions. The Stroom formula states that, on average, over 99% of the CTV takes at least 95% of the prescription dose. The method of Van Herk used this criterion to calculate the margins so that 90% of the patients obtained the least cumulative dose of CTV of a minimum of 95% of the prescription dose.

ICRU-62 formula: $\sqrt{\sum^2 + \sigma^2}$ [19]
Stroom et al. formula: $2\sum + 0.7\sigma$ [20]
Van Herk et al. formula: $2.5\sum + 0.7\sigma$ [21]

Results

A total of 300 portal images (150 anterior and 150 lateral) were obtained and analyzed in 50 patients with H&N cancers treated with 3DCRT. The general distribution of translational shifts in the ML and SI axes of the AP field and the SI and AP axes of the LAT field are shown in

Figure 2. The translational displacement ranges were 0-8.8 mm in the SI, and 0-10 mm in the AP (LAT field) directions, 0-8.1 mm in the ML, and 0-9 mm in the SI (AP field) directions.

Table 1 reports the frequencies of the translational shifts from the setup errors. The frequency of setup shifts >3 mm was 17.33% in the ML axis, 27.33% in the SI (AP field) axis, 25.33% in the SI (LAT field) axis, and 28% in the AP axis. The percentages of setup displacements >5 mm were 14% in the ML axis, 12.66% in the SI (AP field) axis, 8% in the SI (LAT field) axis, and 10.66% in the AP axis (Table 1).

Using Equations (3, 4, and 5) were calculated the overall mean setup error (M_{pop}), population systematic setup error ($\sum_{setup}$), and population random setup error (σ_{setup}), respectively. The population systematic setup errors ($\sum_{setup}$) in the ML, SI (AP), SI (LAT), and AP directions were 3.230, 2.753, 2.654, and 2.997 mm, respectively. The population random setup error (σ_{setup}) from the anterior portal was 1.476 mm for ML and 1.823 mm for SI, and 1.853 mm and 1.715 mm for SI (LAT) and AP in the lateral field, respectively (Table 2).

The individual mean setup error (m_{ind}) and individual random error (σ_{ind}) in the ML, SI (AP), SI (LAT), and AP directions for each patient are indicated in Figure 3.

Using population setup errors, the CTV-PTV margins were determined utilizing the ICRU-62 [19], Stroom's [20], and Van Herk's [21] methods (Table 3). The PTV margins determined by the ICRU-62 method were 3.551 mm,

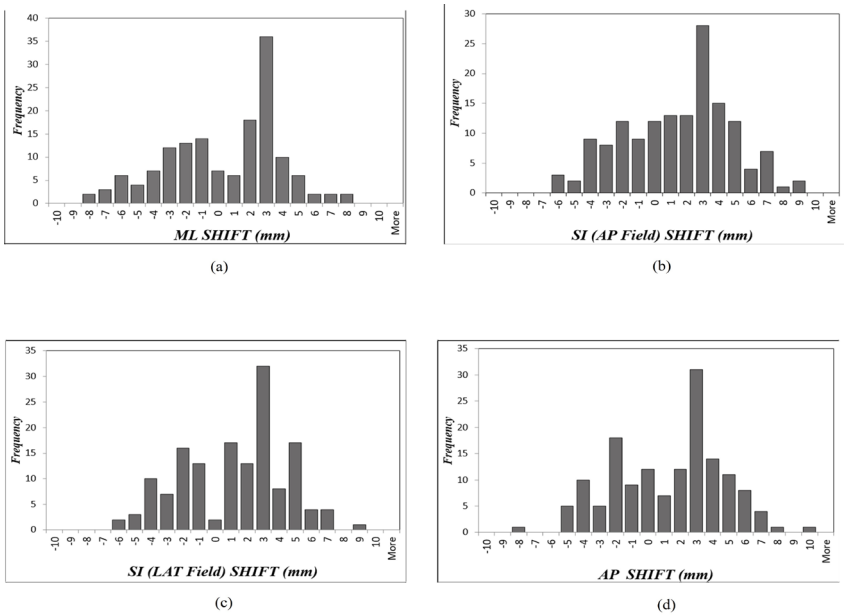

Figure 2: Distribution of translational shift at (**a**) Medial-Lateral (ML), (**b**) Superior-Inferior (SI) directions from the Anterior-Posterior (AP) field, (**c**) Superior-Inferior (SI), (**d**) Anterior-Posterior (AP) axes from the Lateral (LAT) field.

Table 1: Frequencies of setup displacements more than 3 and 5 mm in Medial-Lateral (ML), Superior-Inferior (SI) (Anterior-Posterior (AP) field), SI and AP (lateral (LAT) field) axes

	ML	SI (AP)	SI (LAT)	AP
Shifts >3 mm	26 (17.33%)	41 (27.33%)	38 (25.33%)	42 (28%)
Shifts >5 mm	21 (14%)	19 (12.66%)	12 (8%)	16 (10.66%)

ML: Medial-Lateral, SI: Superior-Inferior, AP: Anterior-Posterior, LAT: Lateral
Values are stated as numbers (%)

3.301 mm, 3.236 mm, and 3.452 mm. Using Stroom's formula, these were 7.493 mm, 6.782 mm, 6.605 mm, and 7.194 mm; according to Van Herk's formula, these were 9.108 mm, 8.161 mm, 7.932 mm, and 8.693 mm in directions of ML and SI of the AP field and SI and AP of the LAT field, respectively.

Discussion

The 3DCRT requires good geometrical accuracy. Normally, the objective of radiotherapy is to achieve dose delivery conformity to the target tissue and consequently minimize the dose to adjacent healthy organs. Although several studies have concluded that the CTV-PTV margin for head and neck tumors varies between 3-10 mm [15, 23, 24], it is recommended that each radiotherapy department develops its data and protocol to achieve optimal margins.

According to Xing et al., a 3-mm displace-

Table 2: The systematic ($\sum_{setup}$) and random (σ_{setup}) set-up errors in each direction

Field	Antero-Posterior		Lateral	
Direction	Medial-Lateral (ML)	Superior-Inferior (SI)	Superior-Inferior (SI)	Antero-Posterior (AP)
M_{pop} (mm)	0.119	1.173	0.941	1.002
Systematic set-up error ($\sum_{setup}$) (mm)	3.230	2.753	2.654	2.997
Random set-up error (σ_{setup}) (mm)	1.476	1.823	1.853	1.715

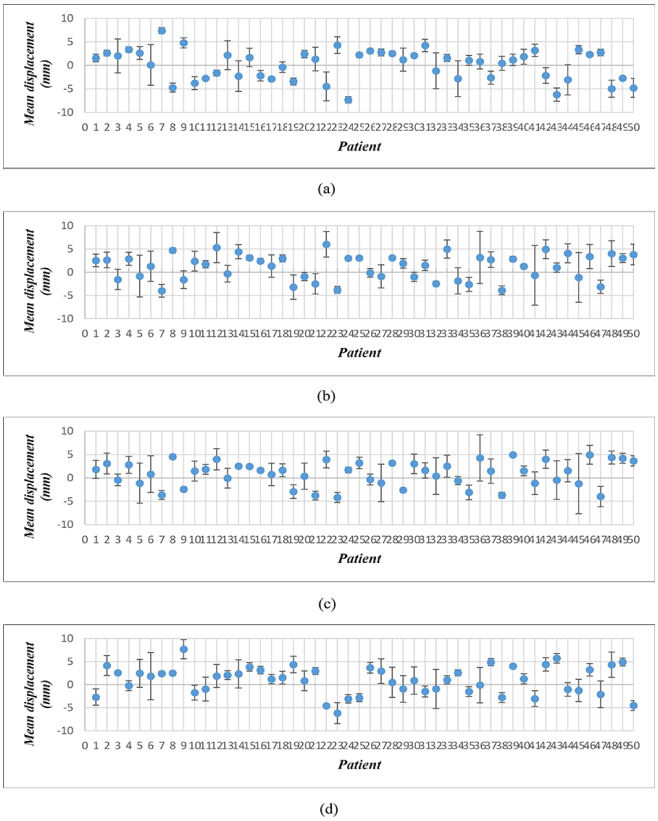

Figure 3: The individual mean±standard deviation (SD) for all 50 patients in (**a**) Medial-Lateral (ML), (**b**) Superior-Inferior (SI) axis of the Antero-Posterior (AP) field, and (**c**) SI, (**d**) AP axis of the lateral (LAT) field.

Table 3: Population random and systematic errors and CTV (Clinical Target Volume)- PTV (Planning Target Volume) margins obtained by all three margin formulae.

Direction	Population set-up errors (mm)			CTV-PTV Margins (mm)	
	Systematic ($\sum_{setup}$)	Random (σ_{setup})	ICRU-62 ($\sqrt{\sum^2+\sigma^2}$)	Stroom ($2\sum+0.7\sigma$)	Van Herk ($2.5\sum+0.7\sigma$)
Medial-Lateral (ML)	3.230	1.476	3.551	7.493	9.108
Superior-Inferior (SI) (AP field)	2.753	1.823	3.301	6.782	8.161
Superior-Inferior (SI) (LAT field)	2.654	1.853	3.236	6.605	7.932
Anterior-Posterior (AP)	2.997	1.715	3.452	7.194	8.693

CTV: Clinical Target Volume, PTV: Planning Target Volume, ICRU: International Commission on Radiation Units and Measurements

ment of the patient couch location in the anterior-posterior axis causes a reduction (38%) in the minimum target dose or an increase (41%) in the maximum spinal cord dose [25]. Accordingly, the calculation and reduction of setup uncertainties are necessary. In this study, the setup accuracy was analyzed in 50 patients who received 3DCRT for head and neck cancers using EPID and subsequently defined the optimal PTV margin. In our department (Imam Reza Hospital, radiation oncology department), the action level is 3 mm in H&N cases, in the translational direction. The finding of this study demonstrated that 68.66%, 60%, 66.66%, and 61.33% of the setup displacements in the MI, SI (AP), SI (LAT), and AP directions were within 3 mm, respectively.

According to previous studies [10, 11, 15], setup deviations were analyzed based on systematic and random errors. The results of the current research are in line with those of similar literature [9, 22, 26-31]. Zhang et al. investigated the set-up uncertainties of 14 patients with head and neck cancer. The calculated SD of systematic and random errors ranged from 1.5-3.2 mm and 1.1-2.9 mm, respectively [32]. The difference between our department setup deviations and other studies could be due to several differences, including: (I) the accuracy of the laser alignment and LINAC, (II) daily patient set-up procedure variations, or (III) anatomical changes due to tumor shrinkage or weight change during radiation therapy (at our institution, these occurrences were low. If these issues were observed, we performed a new CT planning with a change in the degree of patient immobilization). According to Hurkmans et al., the setup accuracy differs depending on the immobilization method, the area being treated, and the department. They reported that for the head and neck the SD of systematic and random setup errors were, respectively, between 1.6-4.6 mm and 1.1-2.5 mm [33].

As shown in Table 2, the random error in the superior-inferior direction was slightly greater than that in the other two directions, which may be due to the optical illusion and uncertainty in the matching (adjusting) of the laser and sign on the thermoplastic mask. Hurkmans et al. reported that the random error could be less than 2 mm for head and neck tumors [33]. In the present study, the magnitude of random errors was consistent with those of the Hurkmans study.

According to the ICRU-50 [34], adding a margin to the CTV to generate the PTV is a regular approach to overcome patient setup and organ motion uncertainties. In this study, the required CTV-PTV margins for full target coverage in all three axes using the ICRU-62, Stroom, and Van Herk formulae were <4 mm, <7.5 mm, and <9.5 mm, respectively.

Offline corrections were performed on 170 of the 300 portal images (56.66%). We have an institutional protocol for "correction" based on literature [35, 36]. According to our protocol, if the displacement between the portal and the DRR is more than 3 mm in each direction, the "correction" is performed before

the next fraction. Then, the portal imaging is repeated weekly.

The geometric accuracy of the treatment machine, accuracy of the lasers in the treatment room, imaging device, immobilization device, time spent, and patient cooperation in performing the setup procedure are factors that can affect setup accuracy [37]. After evaluating the results of the present study, we found that offline correction can reduce setup uncertainties to acceptable levels; however, these are not eliminated and intrafractional uncertainties still exist [38]. Therefore, it is recommended for high-precision radiotherapy techniques (CRT or IMRT) [35].

The present study has several limitations. Since the portal images did not provide details about the motion of organ errors, we did not include these uncertainties in the calculation of the CTV-PTV margin. Gilbeau et al. asserted that intrafractional organ motions in H&N cancers could be ignored when calculating CTV-PTV margins because the values were small and negligible [28]. Suzuki et al. showed that during the 15 minutes of treatment, random and systematic setup errors for organ motion were 0.3-0.6 mm and 0.2-0.8 mm, respectively [31]. Next, the limitation was that possible rotational errors could not be estimated since portal imaging in the LAT and AP did not capture them. In this study, we did not study target volume delineation uncertainties or interobserver variability. A radiation oncologist delineated and checked the target volume based on the delineation guidelines, which is a common protocol at our center. Therefore, this data should be evaluated in future studies.

Conclusion

To ensure proper coverage of the target volume, the factors that potentially affect the margin should also be considered before adopting the margin guidelines. The present study was conducted on systematic and random errors in H&N patients receiving 3DCRT using EPID; the results were comparable to those reported in the published literature. Therefore, EPID is an efficient tool for patient positioning verification and assessment of these radiotherapy treatments.

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Authors' Contribution

E. Ahmadi was involved in preparing and writing the original draft and editing. H. Gholamhosseinian and M. Mohammadi conceived the presented idea and supervised the project. E. Ahmadi, M. Naji, and A. Eskandari gathered the data. E. Ahmadi, H. Gholamhosseinian, and Sh. Naseri were involved in analyzing the data. All authors read, modified, and approved the final version of the manuscript.

Ethical Approval

The Mashhad University of Medical Sciences approved the study with index IR.MUMS.MEDICAL.REC.1398.646.

Informed Consent

This study was approved by the Mashhad University of Medical Sciences with index. Informed consent was obtained.

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Conflict of Interest

None

References

1. Coca-Pelaz A, Rodrigo JP, Suárez C, Nixon IJ, Mäkitie A, Sanabria A, et al. The risk of second primary tumors in head and neck cancer: A systematic review. *Head Neck.* 2020;**42**(3):456-66. doi: 10.1002/hed.26016. PubMed PMID: 31750595.
2. Perdomo S, Roa GM, Brennan P, Forman D, Sierra MS. Head and neck cancer burden and preventive measures in Central and South America. *Cancer Epidemiology.* 2016;**44**:S43-52. doi: 10.1016/j.

canep.2016.03.012. PubMed PMID: 27678322.

3. De Felice F, Polimeni A, Valentini V, Brugnoletti O, Cassoni A, Greco A, et al. Radiotherapy Controversies and Prospective in Head and Neck Cancer: A Literature-Based Critical Review. *Neoplasia.* 2018;**20**(3):227-32. doi: 10.1016/j.neo.2018.01.002. PubMed PMID: 29448084. PubMed PMCID: PMC5849807.
4. Kadeh H, Saravani S, Moradbeiki B. Epidemiological aspects of head and neck cancers in a population of south east region of Iran. *Caspian Journal of Dental Research.* 2015;**4**(2):33-9. doi: 10.22088/cjdr.4.2.33.
5. Mirzaei M, Hosseini SA, Ghoncheh M, Soheilipour F, Soltani S, Soheilipour F, Salehiniya H. Epidemiology and Trend of Head and Neck Cancers in Iran. *Glob J Health Sci.* 2015;**8**(1):189-93. doi: 10.5539/gjhs.v8n1p189. PubMed PMID: 26234980. PubMed PMCID: PMC4803954.
6. Mourad M, Jetmore T, Jategaonkar AA, Moubayed S, Moshier E, Urken ML. Epidemiological Trends of Head and Neck Cancer in the United States: A SEER Population Study. *J Oral Maxillofac Surg.* 2017;**75**(12):2562-72. doi: 10.1016/j.joms.2017.05.008. PubMed PMID: 28618252. PubMed PMCID: PMC6053274.
7. Jomehzadeh A, Shokrani P, Mohammadi M, Amouheidari A. A quality assurance program for an amorphous silicon electronic portal imaging device using in-house developed phantoms: a method development for dosimetry purposes. *Int J Radiat Res.* 2014;**12**(3):257-64.
8. Pehlivan B, Pichenot C, Castaing M, Auperin A, Lefkopoulos D, Arriagada R, Bourhis J. Interfractional set-up errors evaluation by daily electronic portal imaging of IMRT in head and neck cancer patients. *Acta Oncol.* 2009;**48**(3):440-5. doi: 10.1080/02841860802400610. PubMed PMID: 19031160.
9. Strbac B, Jokic VS. Evaluation of set-up errors in head and neck radiotherapy using electronic portal imaging. *Phys Med.* 2013;**29**(5):531-6. doi: 10.1016/j.ejmp.2012.12.001. PubMed PMID: 23290565.
10. Delishaj D, Ursino S, Pasqualetti F, Matteucci F, Cristaudo A, Soatti CP, Barcellini A, Paiar F. Set-up errors in head and neck cancer treated with IMRT technique assessed by cone-beam computed tomography: a feasible protocol. *Radiat Oncol J.* 2018;**36**(1):54-62. doi: 10.3857/roj.2017.00493. PubMed PMID: 29621873. PubMed PMCID: PMC5903362.
11. Cubillos Mesías M, Boda-Heggemann J, Thoelking J, Lohr F, Wenz F, Wertz H. Quantification and Assessment of Interfraction Setup Errors Based on Cone Beam CT and Determination of Safety Margins for Radiotherapy. *PLoS One.* 2016;**11**(3):e0150326. doi: 10.1371/journal.pone.0150326. PubMed PMID: 26930196. PubMed PMCID: PMC4773093.
12. Ciardo D, Alterio D, Jereczek-Fossa BA, Riboldi M, Zerini D, Santoro L, et al. Set-up errors in head and neck cancer patients treated with intensity modulated radiation therapy: Quantitative comparison between three-dimensional cone-beam CT and two-dimensional kilovoltage images. *Phys Med.* 2015;**31**(8):1015-21. doi: 10.1016/j.ejmp.2015.08.004. PubMed PMID: 26459318.
13. Pramanik S, Ray DK, Bera S, Choudhury A, Iqbal A, Mondal S, et al. Analysis of setup uncertainties and determine the variation of the clinical target volume (CTV) to planning target volume (PTV) margin for various tumor sites treated with three-dimensional IGRT couch using KV-CBCT. *Journal of Radiation Oncology.* 2020;**9**:25-35. doi: 10.1007/s13566-020-00417-z.
14. Herman MG, Balter JM, Jaffray DA, McGee KP, Munro P, Shalev S, et al. Clinical use of electronic portal imaging: report of AAPM Radiation Therapy Committee Task Group 58. *Med Phys.* 2001;**28**(5):712-37. doi: 10.1118/1.1368128. PubMed PMID: 11393467.
15. Eldebawy E, Attalla E, Eldesoky I, Zaghloul MS. Geometrical uncertainty margins in 3D conformal radiotherapy in the pediatric age group. *J Egypt Natl Canc Inst.* 2011;**23**(2):55-60. doi: 10.1016/j.jnci.2011.09.001. PubMed PMID: 22099961.
16. Herman MG, Kruse JJ, Hagness CR. Guide to clinical use of electronic portal imaging. *J Appl Clin Med Phys.* 2000;**1**(2):38-57. doi: 10.1120/jacmp.v1i2.2645. PubMed PMID: 11674818. PubMed PMCID: PMC5726148.
17. Das IJ, Cao M, Cheng CW, Misic V, Scheuring K, Schüle E, Johnstone PA. A quality assurance phantom for electronic portal imaging devices. *J Appl Clin Med Phys.* 2011;**12**(2):3350. doi: 10.1120/jacmp.v12i2.3350. PubMed PMID: 21587179. PubMed PMCID: PMC5718680.
18. Court LE, Wolfsberger L, Allen AM, James S, Tishler RB. Clinical experience of the importance of daily portal imaging for head and neck IMRT treatments. *J Appl Clin Med Phys.* 2008;**9**(3):26-33. doi: 10.1120/jacmp.v9i3.2756. PubMed PMID: 18716586. PubMed PMCID: PMC5722295.
19. Stroom JC, Heijmen BJ. Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. *Radiother Oncol.* 2002;**64**(1):75-83. doi: 10.1016/s0167-8140(02)00140-8. PubMed PMID: 12208578.
20. Stroom JC, De Boer HC, Huizenga H, Visser AG. Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability. *Int J Radiat Oncol Biol Phys.* 1999;**43**(4):905-19. doi: 10.1016/s0360-3016(98)00468-4. PubMed

PMID: 10098447.

21. Van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys.* 2000;**47**(4):1121-35. doi: 10.1016/s0360-3016(00)00518-6. PMID: 10863086.
22. Gupta T, Chopra S, Kadam A, Agarwal JP, Devi PR, Ghosh-Laskar S, Dinshaw KA. Assessment of three-dimensional set-up errors in conventional head and neck radiotherapy using electronic portal imaging device. *Radiat Oncol.* 2007;**2**:44. doi: 10.1186/1748-717X-2-44. PubMed PMID: 18081927. PubMed PMCID: PMC2238756.
23. Jalali R, Budrukkar A, Sarin R, Sharma DS. High precision conformal radiotherapy employing conservative margins in childhood benign and low-grade brain tumours. *Radiother Oncol.* 2005;**74**(1):37-44. doi: 10.1016/j.radonc.2004.09.014. PubMed PMID: 15683667.
24. Bayman E, Ataman ÖU, Kinay M, Akman F. How to determine margins for planning target volume (PTV): from 2D to 3D planning in radiotherapy for head and neck cancer? Portal imaging assessment for set-up errors. *Turkish Journal of Oncology.* 2010;**25**(3):104-10.
25. Xing L, Lin Z, Donaldson SS, Le QT, Tate D, Goffinet DR, et al. Dosimetric effects of patient displacement and collimator and gantry angle misalignment on intensity modulated radiation therapy. *Radiother Oncol.* 2000;**56**(1):97-108. doi: 10.1016/s0167-8140(00)00192-4. PubMed PMID: 10869760.
26. Hess CF, Kortmann RD, Jany R, Hamberger A, Bamberg M. Accuracy of field alignment in radiotherapy of head and neck cancer utilizing individualized face mask immobilization: a retrospective analysis of clinical practice. *Radiother Oncol.* 1995;**34**(1):69-72. doi: 10.1016/0167-8140(94)01497-q. PubMed PMID: 7792401.
27. Bentel GC, Marks LB, Hendren K, Brizel DM. Comparison of two head and neck immobilization systems. *Int J Radiat Oncol Biol Phys.* 1997;**38**(4):867-73. doi: 10.1016/s0360-3016(97)00075-8. PubMed PMID: 9240656.
28. Gilbeau L, Octave-Prignot M, Loncol T, Renard L, Scalliet P, Grégoire V. Comparison of setup accuracy of three different thermoplastic masks for the treatment of brain and head and neck tumors. *Radiother Oncol.* 2001;**58**(2):155-62. doi: 10.1016/s0167-8140(00)00280-2. PubMed PMID: 11166866.
29. De Boer HC, Van Sörnsen De Koste JR, Creutzberg CL, Visser AG, Levendag PC, Heijmen BJ. Electronic portal image assisted reduction of systematic set-up errors in head and neck irradiation. *Radiother Oncol.* 2001;**61**(3):299-308. doi: 10.1016/s0167-8140(01)00437-6. PubMed PMID: 11731000.
30. Humphreys M, Guerrero Urbano MT, Mubata C, Miles E, Harrington KJ, Bidmead M, Nutting CM. Assessment of a customised immobilisation system for head and neck IMRT using electronic portal imaging. *Radiother Oncol.* 2005;**77**(1):39-44. doi: 10.1016/j.radonc.2005.06.039. PubMed PMID: 16154217.
31. Suzuki M, Nishimura Y, Nakamatsu K, Okumura M, Hashiba H, Koike R, et al. Analysis of interfractional set-up errors and intrafractional organ motions during IMRT for head and neck tumors to define an appropriate planning target volume (PTV)- and planning organs at risk volume (PRV)-margins. *Radiother Oncol.* 2006;**78**(3):283-90. doi: 10.1016/j.radonc.2006.03.006. PubMed PMID: 16564594.
32. Zhang L, Garden AS, Lo J, Ang KK, Ahamad A, Morrison WH, et al. Multiple regions-of-interest analysis of setup uncertainties for head-and-neck cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2006;**64**(5):1559-69. doi: 10.1016/j.ijrobp.2005.12.023. PubMed PMID: 16580505.
33. Hurkmans CW, Remeijer P, Lebesque JV, Mijnheer BJ. Set-up verification using portal imaging; review of current clinical practice. *Radiother Oncol.* 2001;**58**(2):105-20. doi: 10.1016/s0167-8140(00)00260-7. PubMed PMID: 11166861.
34. Jones D. ICRU report 50-Prescribing, recording and reporting photon beam therapy. *Med Phys.* 1994;**21**(6):833-4. doi: 10.1118/1.597396.
35. Budrukkar A, Dutta D, Sharma D, Yadav P, Dantas S, Jalali R. Comparison of geometric uncertainties using electronic portal imaging device in focal three-dimensional conformal radiation therapy using different head supports. *J Cancer Res Ther.* 2008;**4**(2):70-6. doi: 10.4103/0973-1482.42252. PubMed PMID: 18688122.
36. Rosenthal SJ, Gall KP, Jackson M, Thornton AF Jr. A precision cranial immobilization system for conformal stereotactic fractionated radiation therapy. *Int J Radiat Oncol Biol Phys.* 1995;**33**(5):1239-45. doi: 10.1016/0360-3016(95)02009-8. PubMed PMID: 7493848.
37. Molana S, Arbabi F, Sanei M, Hashemi E, Tajvidi M, Rostami A, et al. Evaluation of patient setup accuracy and determination of optimal setup margin for external beam radiation therapy using electronic portal imaging device. *Canc Therapy & Oncol Int J.* 2018;**11**(2):48-55. doi: 10.19080/CTOIJ.2018.11.555808.
38. Beltran C, Krasin MJ, Merchant TE. Inter- and intrafractional positional uncertainties in pediatric radiotherapy patients with brain and head and neck tumors. *Int J Radiat Oncol Biol Phys.* 2011;**79**(4):1266-74. doi: 10.1016/j.ijrobp.2009.12.057. PubMed PMID: 20605345. PubMed PMCID: PMC3536549.