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EVALUATION OF SETUP ERRORS IN INTENSITY MODULATED RADIOTHERAPY (IMRT) FOR NASOPHARYNGEAL CARCINOMA USING AN ELECTRONIC PORTAL IMAGING DEVICE (EPID)

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ABSTRACT

Background& Aims: *Accurate patient positioning is crucial in Intensity-Modulated Radiation Therapy (IMRT) for nasopharyngeal carcinoma (NPC) to ensure effective dose delivery. This study aims to quantify setup errors using an Electronic Portal Imaging Device (EPID) and to compute appropriate planning target volume (PTV) margins using established margin recipes*

Materials and Methods: *A retrospective analysis was conducted on 175 NPC patients treated with IMRT at CENAR, Quetta, from January 2022 to November 2024. A total of 2100 portal images were evaluated using anterior-posterior and lateral views. Translational setup deviations in vertical, longitudinal, and lateral directions were measured. Systematic (Σ) and random (σ) errors were calculated using the Royal College of Radiologists guidelines. PTV margins were computed using Van Herk's, Stroom's, and Landberg's formulas.*

Results: *Mean setup errors were -0.01 cm (lateral), 0.03 cm (longitudinal), and 0.04 cm (vertical). The largest systematic error was 0.10 cm (lateral), and the largest random error was 0.04 cm (longitudinal). Based on Van Herk's formula, the required PTV margin in all directions was 0.2 cm. These findings align with previously published studies, supporting the validity of the adopted protocols.*

Conclusion: *Setup errors in NPC IMRT, though minimal, can affect dose coverage if unaccounted for. EPID is a reliable tool for detecting and minimising these errors. The recommended PTV margin of 0.2 cm ensures adequate target coverage and should be incorporated into clinical planning at this centre. Further studies are suggested to assess rotational and internal anatomical variations.*

KEYWORDS: *Nasopharyngeal Carcinoma, Intensity Modulated Radiotherapy, Setup Error, Electronic Portal Imaging Device, Systematic Error, Random Error*

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1. INTRODUCTION

For cancer patients, radiation therapy is an important treatment option, with approximately 60% receiving it either with curative (radical) intent or for palliation during their course of treatment Hernandez et al 2020). High-energy radiation is used in radiotherapy to kill cancer cells and stop their spread. It damages the cells' genetic material, deoxyribonucleic acid (DNA), thereby preventing them from proliferating and dividing further **(**Chen et al 2017**)**. Normal cells typically repair themselves and return to normal function more quickly than cancer cells. High-energy radiation can cause differential cell death due to the cancer cells' impaired repair mechanism **(**Barazzuol et al 2020).

Intensity-modulated radiation treatment (IMRT), image-guided radiation therapy (IGRT), three-dimensional conformal radiation (3D-CRT), particle therapy, stereotactic body radiation therapy (SBRT), stereotactic radiotherapy (SRT), and stereotactic radiosurgery (SRS) are examples of modern teletherapy techniques. **(**Abbas et al 2018). Additionally, IMRT is an advanced technique that uses 3D anatomic data and sophisticated treatment planning systems to create highly conformal treatment fields, allowing sufficient coverage of the target volume with a 3D dose distribution while minimizing normal tissue irradiation. **(**Cho B 2018).

Although IMRT is highly effective, it has some drawbacks related to tumor volume planning and contouring. Accurate definition of tumors and organs at risk (OAR) is essential; even minor contouring errors can result in inadequate dose delivery or unnecessary exposure to nearby healthy tissue. Observer variability during contouring can also impact the precision of treatment. Because IMRT plans are sensitive to tumor motion, such as breathing or organ movement, the predicted and administered doses may not match. This is particularly important for areas like the liver, prostate, and lungs. IMRT often increases the volume of normal tissue receiving low to moderate doses, which may increase the risk of secondary malignancies or late effects, even as it decreases high-dose exposure to critical structures. The quality of imaging (CT, MRI, PET) used to define the tumor has a significant impact on the accuracy of IMRT. Artifacts or low image resolution can impair accurate contouring and dose distribution. Furthermore, because IMRT delivers highly conformal doses with steep dose gradients, even small errors in setup, contouring, or patient positioning could be dangerous, potentially leading to underdosing of the tumor or overdosing surrounding tissues **(**Miften M et al 2018).

The International Commission on Radiation Units and Measurements (ICRU) has provided important recommendations and definitions for target volume delineation. The Gross Tumor Volume (GTV) refers to the location and gross demonstrable extent of malignant growth. ―The microscopic spread of malignant disease that needs to be eradicated is included in the Clinical Target Volume (CTV), this is determined by summing up the margins surrounding GTV. **(**Lee AW et al 2018**).** The Clinical Target Volume (CTV), which is determined by adding a margin around GTV, includes the microscopic progression of a malignant disease that must be destroyed. The dose distribution in CTV may deviate from the intended plan due to geometrical errors. The ICRU has identified three main causes of geometrical uncertainty machine-related errors, organ motion and deformation, and variations in patient setup. To account for anatomical and geometrical errors and to ensure adequate CTV coverage, the ICRU recommends two types of margins: the internal margin (IM) and the setup margin. The internal margin compensates for internal organ motion caused by physiological processes such as breathing, bladder filling, rectum filling, etc. The internal target volume (ITV) is defined as the sum of the CTV and IM **(**van der Veen J et al 2019).

Any variation between the intended and actual treatment sites is known as a set-up error, and it is calculated by matching the reference image with the treatment image and determining the displacement of the treatment field position. Setup errors are divided into two components: systematic and random errors. The systematic component refers to errors that occur during treatment preparation, while the random component accounts for faults that arise during treatment execution. Systematic errors cause the dose

distribution to deviate from the CTV, whereas random errors make the dose distribution around the CTV less distinct. **(**Zhao J et al 2018).

Radiation verification methods help ensure that the target volume matches what was specified in the treatment plan. Among various verification techniques, portal imaging is commonly used in many institutions due to its ability to identify and minimize setup errors for a large number of methods. During portal imaging, the reference image, either a digitally reconstructed radiograph (DRR) generated by the planning system or a simulated film from a treatment simulator is visually compared with the image captured while in the treatment position. Deviations are quantified relative to the isocenter. Translational errors in three dimensions can be identified and corrected using the institution's adjustment protocols if necessary. Modern technologies are also capable of detecting rotational errors; however, corrections are often limited by the available couch movement capabilities. A relationship exists between geometric setup errors and the PTV margin. This margin ~~for error~~ is determined during treatment planning to ensure adequate CTV dose coverage in the presence of setup errors. Margin recipes, which are formulas that calculate the necessary PTV margin based on biological, physical, and dose coverage considerations, have been proposed by several authors **(**Bharati A et al 2020).

To ensure the precision and reproducibility of treatment, image reviews are required at the beginning of the radiotherapy and regularly thereafter. Each institution should individually determine how to manage couch positional changes (setup uncertainties), which may necessitate setup review or modification before treatment delivery. Using an electronic portal image device (EPID) to compare the reference and treatment position images, the deviations identified can be used to assess the margin added to the CTV according to the margin recipes established under ICRU guidelines **(**Contesini M et al 2017).

In Pakistan, few studies have systematically quantified setup errors in IMRT for nasopharyngeal carcinoma. A recent study by Shafiq et al. (2023) conducted at CENAR, Quetta, emphasized the importance of minimizing setup deviations and recommended sub-centimeter margins for optimal target coverage using EPID verification **(**Shafiq S et al 2023). Similarly, Abassi et al. (2013) highlighted the challenges in achieving adequate PTV coverage using conventional 3D-CRT and stressed the need for adopting advanced image-guided techniques. These findings reinforce the significance of our study in the regional context and underscore the need for consistent margin evaluation protocols **(**Abbasi AN et al 2013).

Despite global advancements, limited published data exist from Pakistan on quantifying setup errors in IMRT for nasopharyngeal carcinoma using electronic portal imaging devices. Most local institutions still rely on broad empirical margins without formal validation. This study fills this gap by providing institution-specific setup error data to justify appropriate PTV margins and enhance treatment quality assurance in a resource-limited setting.

The primary objective of this study was to quantitatively evaluate the translational setup errors in NPC patients treated with IMRT at CENAR using an Electronic Portal Imaging Device (EPID). The study further aimed to calculate systematic (Σ) and random (σ) errors and recommend institution-specific PTV margins based on Van Herk, Stroom, and Landberg margin recipes.

A total of 2100 portal images captured before treatment on the first two days and after every two fractions for 175 patients were evaluated.

2. MATERIALS AND METHODS

A retrospective analysis of 175 NPC patients was carried out. All patients completed their IMRT treatment on the Varian 2300iX linear accelerator unit at CENAR Hospital Quetta, between January 1, 2022, and November 1, 2024. The hospital administration approved authorization to carry out this investigation. This study was exempt from ethical approval because it did not involve patients' usual course of treatment. Participants in this study ranged in age from 18 to 80. Varian Linac's ARIATM oncology information system provided the data.

Before each radiation treatment session, patients were positioned using the EPID. The EPID captured

anterior-posterior and lateral projections of radiological images to identify the patient's location and position based on the bony features. The selected reference bony landmarks for this study is shown in Table 1.

Table:1: Reference landmarks in electronic portal images

Location of Treatment	**Lateral image's bony markers.**	**AP image's bony markers.**
Nasopharynx	External mandibular profile One of the lower cervical vertebrae's spinous processes	Mandibular profiles, both internal External, skull base, Cervical vertebra bodies (C2-C4)

In the treatment room, the patient is set up exactly as during the CT simulation. The iso-centre was analysed in three directions (longitudinal [Lng], lateral [Lat], and vertical [Vrt]) using CT reference markers on the first day of therapy. For every two fractions, the setup accuracy was assessed using 2D imaging with EPID. A total of 2100 images captured by an MV imager for 175 patients were used in this study. Following this approach, 12 image sets were collected for each patient after the first two days of treatment and then every two fractions thereafter. A medical physicist checked the patient's images before each subsequent course of treatment. The translational errors in the vertical "Z," longitudinal "Y," and lateral "X" directions were recorded. Throughout the treatment process, each portal image was compared to a digitally reconstructed radiograph (DRR) as a reference image generated by the treatment planning system.

The DRR image is produced by the treatment planning system using images imported from the CT simulator. A DRR can be generated on any plane except the original image acquisition plane. Although the treatment planner can make minor adjustments to the quality of the DRR, it primarily depends on the quality of the CT data. The clarity of the DRR determines how well the bone anatomical structures are visualized. DRR's distinctive bone architectural ridges help create a good comparison of portal images. In the current study context, the Varian Eclipse treatment planning system produced DRRs. A portal image is a crucial tool for confirming the patient configuration about the radiation beam's location. The Varian Portal Vision electronic portal imaging equipment was installed isocentrically and used to obtain electronic portal images (EPI). A radiation beam with an energy of 6 MV is usually used to expose 1 MU (Monitor Unit) at a dosage rate of 600 MU/min in order to obtain a portal image. EPI and DRR are visually compared by comparing prominent, stiff bony features in the area of interest. The EPI software provides information on the shifts needed to deal with identified uncertainties. All images are automatically saved to the database, and the offline image review feature of the ARIA oncology information system is used for image assessment The displacements between the DRR and portal images in the superior to inferior and right to lateral directions were estimated using an image obtained at a 0^0 gantry angle by matching rigid bony markers. Additionally, a lateral image taken at about 90^0 gantry angles was used to determine displacements in the superior to inferior and anterior to posterior directions. For this study, shifts in the superior, anterior, and left directions were considered positive, while shifts in the inferior, posterior, and right directions were considered negative.

After image acquisition, translational displacements in the vertical (Z), longitudinal (Y), and lateral (X) directions were recorded for each patient. For each direction, the following steps were performed:

1. Calculation of Systematic and Random Errors:

- Systematic error (Σ) was calculated as the standard deviation of the mean setup errors across all patients in each direction.
- Random error (σ) was calculated as the root mean square of individual patient standard deviations in each direction.

These calculations followed the methodology outlined in the Royal College of Radiologists (RCR) Report, 2008.

1. **PTV Margin Estimation:**
   Using the obtained Σ and σ values, planning target volume (PTV) margins were computed in the lateral, longitudinal, and vertical directions using three standard margin recipes:
   - Van Herk et al. (2000): $2.5\Sigma + 0.7\sigma$
     Ensures that 90% of patients receive ≥95% of the prescribed dose to the CTV.
   - Stroom et al. (1999): $2\Sigma + 0.7\sigma$
     Aimed at population-averaged coverage for routine planning.
   - Landberg et al. (ICRU-62, 1999): $\sqrt{(\Sigma^2 + \sigma^2)}$
     Represents an equal contribution model from both error types.

These margin values were compared to validate consistency and to guide clinical decision-making for margin setting at our institution (Table 2).

Table: 2 Formulas for calculating the CTV to PTV margin.

Formula	Author	Statement
$2.5\sum+0.7\sigma$	Van Herk et al.,2000	A minimum cumulative CTV dose of at least 95% of the recommended dose is given to 90% of patients in the community.
$2\sum+0.7\sigma$	Stroom et al.,1999	On average, 99% of CTV get at least 95% of the recommended dosage.
$\sqrt{\sum^2+\sigma^2}$	Landberg et al., 1999 – ICRU 62	Both the random and systemic components of setup error contribute equally to the dosage distribution.

- Σ- Standard Deviation of systematic errors
- σ- Standard Deviation of random errors

3. RESULTS

In this study, 2100 images from ~~pictures of~~ 175 patients were chosen for analysis ~~examination~~. Tables 3(a) and 3(b)~~3(a&b)~~ present the patients' demographic details.

Table:3 (a) Number of patients according to age group.

Age(Years)	No.of Patients	Percentage
18-30	23	13.14
30-42	29	16.57
42-54	77	44
54-66	18	10.29
66-80	28	16

Table:3(b) Number of patients according to gender.

Age(Years)	Male	Female
18-30	20	3
30-42	19	10
42-54	62	15
54-66	11	7
66-80	23	5

Table 4 summarizes the inclusive mean setup error, population systematic (Σ) and random (σ) errors, as well as the minimum, and ~~the~~ maximum deviations in each direction.

Table: 4 Summary of the systematic (Σ) and random (σ) errors.

Direction	Mean	Systematic (Σ) Error	Random (σ) error
Lateral	-0.01	0.10	0.01
Longitudinal	0.03	0.06	0.04
Vertical	0.04	0.07	0.0

The final setup errors were determined using Van Herk's method. The calculated setup margins were 0.2 cm in the lateral (X), longitudinal (Y), and vertical (Z) directions, as shown in Table 5.

Table: 5 Final setup errors in the lateral (Lat), longitudinal (Lng), and vertical (Vrt).

Direction	Setup Error in X, Y, Z direction, using Van Herk's formula.
Lateral	0.2
Longitudinal	0.2
Vertical	0.2

4. DISCUSSION

According to the current study, an average of 60–80 patients are treated daily at CENAR Quetta using the VARIAN 2300iX linear accelerator, which offers 3D-CRT, IMRT, and electron beam therapy over 12–16 hours. Head and neck cancer is a multifaceted disease characterized by aggressive and uncontrollable cell

growth in various locations, including the larynx, pharynx, oropharynx, hypopharynx, and oral cavity. Among the top 10 cancers in the world, head and neck cancer is becoming more common. Males are much more likely than females to develop head and neck cancer, ranking sixth among all diagnosed cancers. **(**Sun XS et al 2019).

The Nasopharynx is a large cavity located in the middle of the skull extending approximately 10 cm in three dimensions from either side. It typically remains asymptomatic until a lesion, such as a cancerous mass, completely blocks the nasal passages and compresses and nasopharynx or damages nearby nerves through mass effect or direct invasion **(**Wong KC et al 2021).

Patient positioning reliability is a critical factor influenced by the correct use of immobilization devices, CT simulation, and treatment delivery, as well as the experience and attentiveness of the treatment team. According to the Van Herk formula, a margin of 2 to 3 mm around the PTV is required to ensure appropriate dose coverage of the target volume **(**Delishaj D et al 2018).

In the current study, offline review and EPID were used to evaluate setup errors and validate their effectiveness in lowering setup margins. The setup errors identified in this study showed random errors of 0.01 cm, 0.04 cm, and 0 cm, and systematic errors of 0.10 cm, 0.06 cm and 0.07 cm along the lateral, longitudinal, and vertical axes, respectively.

Table 6: Calculated PTV margins (in cm) using Van Herk, Stroom, and Landberg formulas

Direction	**Van Herk ($2.5\Sigma + 0.7\sigma$)**	**Stroom ($2\Sigma + 0.7\sigma$)**	**Landberg ($\sqrt{(\Sigma^2 + \sigma^2)}$)**
Lateral	0.20	0.17	0.10
Longitudinal	0.20	0.15	0.07
Vertical	0.20	0.16	0.07

In addition to Van Herk's formula, PTV margins were also calculated using Stroom's and Landberg's equations. Table 6 summarizes the margin values derived from all three margin recipes. While Van Herk's formula yielded the most conservative margins (0.2 cm in all directions), Stroom and Landberg produced smaller values due to their different assumptions regarding dose coverage and the contribution of systematic and random errors.

Tables 7 and 8 compare the systemic-and random error results from the current study with those from similar research.

Table 7: Overview of the systematic errors found in the current study and four related studies on Nasopharyngeal irradiation.

Study	**Systematic Error (cm)**			
	R-L	A-P	S-I(Ant)	S-I (Lat)
Valeria et al., 2011	0.13	0.11	0.10	-
Mandy et al., 2005	0.09	-0.02	0.07	-
Present Study	0.10	0.06	0.07	-

Table 8: Overview of the random errors found in the current study and four related studies on Nasopharynx irradiation.

Study	**Random Error (cm)**			
	R-L	A-P	S-I(Ant)	S-I (Lat)
Valeria et al., 2011	0.13	0.13	0.15	-
Mandy et al., 2005	0.04	0.06	0.05	-
Current Study	0.01	0.04	0.01	-

The margin found in the present investigation is consistent with the margins reported in recent comparable studies by Valeria et al. -2011, **(**Mongioj V et al 2011) and Mandy et al. (2005), **(**Humphreys M et al 2005)**.**

Our findings also support those by Shafiq et al. (2023), who reported similar errors using EPID at the same treatment centre **[**Shafiq S et al 2023). However, unlike studies utilizing CBCT or helical tomotherapy (Yao et al., 2023), our EPID-based setup could not assess rotational or internal anatomical errors, which may contribute to residual uncertainties in dose delivery. This limitation underscores the importance of

advanced imaging and daily adaptive strategies in future implementations **(**Yao W et al 2023).

However, several limitations reduce the accuracy of the calculated margin values. The electronic portal imaging analysis did not account for internal structural changes, as it was based on a visual comparison of the portal image's bony anatomy with the DRR generated by the treatment planning system (TPS). Additionally, rotational errors were not analyzed in this study, as there was no method available to correct rotational faults. Error evaluation relied solely on two orthogonal portal pictures. The CTV-PTV margins in this study were therefore calculated without accounting for these limitations

All patients were immobilized using the same technique, making it impossible to compare the effectiveness of different immobilization methods. Although all three margin recipes provided clinically acceptable margins, Van Herk's approach was selected as the primary reference due to its higher confidence in dose coverage for individual patients. Stroom's and Landberg's results support the margin range but emphasize the importance of selecting margin strategies based on institutional safety policies and imaging capabilities.

The importance of rigorous QA protocols in radiotherapy is further supported by an IAEA-led international study (2021), which revealed a high prevalence of major protocol deviations in nasopharyngeal carcinoma plans, particularly in low- and middle-income countries. These findings highlight the need for systematic verification tools such as EPID and ongoing margin validation—critical elements our study contributes to the Pakistani clinical context **(**Corry J et al 2021).

5. CONCLUSION

Because implemented protocols influence both systematic and random errors, setup errors may vary across institutions. The setup errors observed in the current study are consistent with existing data on nasopharyngeal radiation techniques.

The study found that calculated systematic errors were greater than random errors, highlighting the importance of properly managing patient positioning processes to reduce setup variances daily 78.17% of deviations fell within the accepted tolerance range. According to ICRU guidelines, a safety margin of less than 0.3 cm in all directions is applied for–patients receiving IMRT for nasopharyngeal cancer, based on three different margin calculation formulas.

Before applying published margin recipes, it is essential to assess all factors that may influence margin calculation to ensure proper target coverage. Portal imaging studies can assist in monitoring clinical practice and evaluating changes resulting from new tools, technologies, and procedures.

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