SRMS IMS
10.21761/jms.v7i02.04

ORIGINAL RESEARCH ARTICLE

# Setup Errors in Interfraction Radiotherapy in Patients of Head and Neck Cancer

**Rashmi Yadav[1], Arvind K. Chauhan[2], Piyush Kumar[2], Pavan Kumar[3], Jitendra Nigam[4], Silambarasan N. Sivaji[4]**

## ABSTRACT

**Introduction:** Reproducibility of daily position is necessary for efficacious delivery of radiotherapy. There are uncertainties during the delivery of radiotherapy which increases the risk of inadequate dose delivery to the target as well as unnecessary irradiation of nearby normal tissues. These uncertainties, known as setup errors, should be clinically in order to attain optimum planning target volume (PTV) margins. The present study aims to find out the optimum PTV margins in our department with existing immobilization system and imaging facilities.

**Material and Methods:** Histopathologically proved 50 head and neck squamous cell carcinoma patients were selected from October 2018 to March 2020. All patients were planned concurrent chemoradiation where cisplatin 35mg/m2 was used weekly. The patients were immobilized on a fixed 5-point thermoplastic cast and contrast enhanced CT scan (CECT) was done with 3 mm slice thickness for radiotherapy planning. The PTV and organs at risk (OARs) were delineated. All the patients were planned and delivered standard radiotherapy at a dose of 70 Gy in 35 fractions over 7 weeks. The setup errors were recorded as per imaging protocols. After the calculation of systematic and random error values, PTV margin was calculated based on the three formulae, Van Herk, Stroom's, ICRU 62.

**Results:** Most patients were in 5th and 6th decades with a male-female ratio of 2.12. The oropharynx was most commonly involved subsite and the majority presented in stage IV (54%). The total portal images taken were 2100. Maximum and minimum random errors in various coordinates were 0.14 and -0.21 (X coordinate), 0.22 and -0.25 (Y coordinate) and 0.15 and 0.09 (Z coordinate), respectively. Similarly, maximum and minimum systematic errors in various coordinates were 0.22 and 0.09 (X coordinate), 0.31 and 0.08 (Y coordinate) and 0.28 and 0.09 (Z coordinate), respectively. The systematic and random errors in X, Y and Z were 0.233 and 0.088, 0.286 and 0.098, 0.214 and 0.081, respectively. Maximum setup error was observed in the anteroposterior direction, followed by the mediolateral direction. While least error was seen in the cranio-caudal direction. In all the 3 coordinates the setup errors were less than 5 mm.

**Conclusion:** Our study suggested PTV margins of 5 mm. All institutes should define their own set up margins per their infrastructure and available technology.

**Submission:** 03-08-2022; **Acceptance:** 24-08-2022; **Published:** 30-12-2022

[1]Ex-Junior Resident, [2]Professor, [3]Associate Professor, [4]Assistant Professor

Department of Radiation Oncology, SRMS Institute of Medical Sciences, Bareilly, Uttar Pradesh, India.

**Corresponding Author:** Piyush Kumar, Department of Radiation Oncology, SRMS Institute of Medical Sciences, Bareilly, Uttar Pradesh, India, e-mail: piykumagr@gmail.com

**Keywords:** Head neck cancers, Radiotherapy, Set up errors.

**How to cite this article:** Yadav, R., Chauhan, A.K., Kumar, P., Kumar, P., Nigam, J., Silambarasan, NS. Setup Errors in Interfraction Radiotherapy in Patients of Head and Neck Cancer. SRMS J Med Sci. 2022;7(2):46-55.

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

Accuracy and reproducibility of the patient's position is necessary for the efficacious delivery of radiation therapy. The precision and daily reproducibility determine the efficacy of successful radiotherapy delivery. In spite of all, some aspects of radiotherapy is always subjected to uncertainty. While the most common uncertainties which can be observed during radiotherapy delivery are the position of the target, clinical margin and the position of the surrounding patient anatomy with regard to the angle of beams. These uncertainties lead to delivery errors, i.e., differences in the dose distribution as proposed by a treatment plan and the actual distribution of the dose delivered to a patient during the treatment course.[1]

The immobilization in head and neck cancer patients is a challenging process due to the flexibility of the neck and close proximity of critical central nervous system structures near to target volus. Setup errors increase the risk of inadequate dose delivery to the target and unnecessary irradiation of nearby normal tissues. Excessive dose to normal tissue may cause lip reactions, oral mucositis, skin reactions, and dysphagia.[2]

Setup errors are divided into two main fundamental parts - systematic and random setup errors. Systematic errors are defined as variations that are persistent during the entire course of treatment. Systematic errors occur because of a wide variety of issues like human and computer errors, measurement errors or organ motion errors. It can be corrected mainly during the early three fractions of the treatment.

Random errors are defined as variations that may occur by chance. The random displacements relate to everyday setup variations during the span of treatment and are represented by the amount of dispersion of individual points around the mean. Patient daily setup and immobilization are considered to be complicated task. They can be reduced thru the use of correct setup procedures or equipment.[3-5]

Recent advances in technology such as diagnostic imaging and conformal radiotherapy, have increased the need for accuracy during patient positioning throughout radiotherapy delivery. An extreme level of precision is needed for the completion of the whole treatment. The main step is to maintain daily procreation the same position of the patient.

The use of head masks with well-fitting contour at neck region are capable of better immobilizing and repositioning patients. Accuracy in the positioning of patients improves the quality of radiotherapy delivered. Conformal radiotherapy provides tighter margins for the target volumes, preventing early and late toxicities by saving normal structures. With the help of 3D planning techniques, we can locate the exact shape and size of tumor based on the images achieved from CT scan. Beam angles can be planned for better dose distribution. Conformal techniques not only provide adequate dose to the target volume Clinical Target Volume (CTV) and planning target volume (PTV)) but also allows safe dose delivery to critical organs.

PTV margin varies according to site, immobilization device and technique of radiotherapy. We need to clinically measure all the setup error and movement changes to attain a better PTV margin and Planning organ at risk volume (PRV) margin for structures. On reducing the CTV-PTV margin, there is a reduction in the toxicity profile of the patient. There is a reduction in acute and late toxicity and a decreased chance of second cancer. Overall it improves the long-term survival of patient in head and neck cancers. Achieving a reduction in margin resulted in the overall reduction in side effects along with maintenance of loco-regional disease control.[3]

As per our department protocol, the CTV-PTV margin is 7 mm in head and neck cancers. The present study was designed to evaluate whether we can decrease the PTV margins with the present immobilization system of thermoplastic mask and imaging protocols.

## MATERIAL AND METHODS

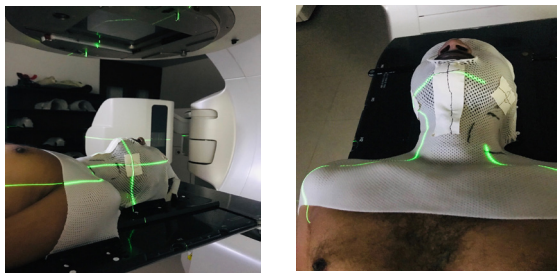
For the present study previously untreated fifty patients of head and neck malignancies were selected from October 2018 to March 2020. It was a single-arm study and all patients were treated by the IMRT technique.

### Patient Selection

#### *Inclusion Criteria*

Histologically proven squamous cell carcinoma of head and neck malignancies; Age ≥18 years; Karnofsky Performance Status >70; Normal haemogram. renal function and liver function tests and normal ECHO.
Exclusion Criteria are patients with prior or synchronous malignancy, who underwent prior surgery, distant metastasis, or previously treated patients with radiotherapy.

All patients were planned concurrent chemoradiation.



1(a) 1(b)

**Figure 1(a,b):** Showing immobilization with five point thermoplastic cast and head rest. The wall mounted lasers depict the position of isocentre

### Radiotherapy Planning and Technique

#### *Position and Immobilization*

Contrast enhanced CT (CECT) imaging was done in supine position with arms by the side of the body, shoulder retracted and neck in slight extension with immobilization cast. The head support was adapted according to the patient's neck length and curvature. All patients were planned on carbon base plate with a fixed 5-point thermoplastic cast was used for immobilization of the head, neck and along with shoulders retractor (Figure 1a and b).

#### *CECT RTP (Radiotherapy Planning)*

Fiducial lead ball markers were placed on bony landmarks in three points. The markers are placed over mentum anteriorly and two are placed over both sides of the angle of the mandible. These markers were placed with the help of CT lasers. The contrast enhanced CT of neck (CT-RTP) with 3 mm slice thickness were taken.

#### *Image Acquisition and Registration*

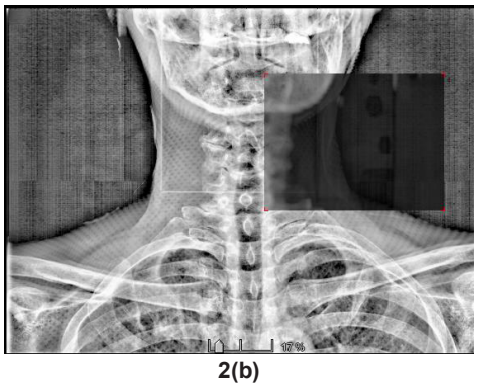
These images were then imported to the treatment planning system (TPS) via the Digital Imaging and Communication in Medicine (DIACOM). These CT slices were reconstructed, and the outline of the body contour is made. The CT study origin will be different from RTP origin. In the transverse view CT origin moved to the intersection point of all three fiducial lines.

#### *Delineation*

In accordance with the Radiation Therapy Oncology Group (RTOG 0225) following volumes were delineated -

- *GTV*: gross disease including the primary tumor and enlarged lymph nodes as demonstrated on clinical, radiological examination and fiberoptic laryngoscopy.

2(a)



2(b)

**Figure 2(a, b):** Figure showing superposition of DRR and portal image in antero-posterior and lateral direction

- $CTV_{primary:}$ (clinical target volume): was taken as an area adjacent to GTV suspicious of harboring sub-clinical disease considering the anatomical barriers. The entire subsite harboring the primary tumor was included in the CTV
- $CTV_{nodal}$: area inclusive of draining regional neck nodes.
- *Planning target volume (PTV)*: had a margin of 7 mm (as per departmental protocol) around CTVs, to account for patient setup errors.
- *Organ at Risk (OAR)*: The OARs of head and neck delineated were as the brain stem, spinal cord, lip, cochlea, eye, lens, optic nerve, optic chiasm, parotid and mandible.

The planning risk volume (PRV) for the spinal cord was defined as 5 mm isotropic expansion from the spinal cord. For cochlea and brain stem a PRV margin of 3 mm was given. Delineation was OARs was done based on the ICRU 62. Each structure was contoured separately with recommended colors.

### *Dose Prescription And Dose Constraints*

All the patients were planned and delivered standard radiotherapy at a dose of 70 Gy in 35 fractions over 7 weeks. The planning objective to PTV was dose ranging between -5 to +7% (95 to 107%) of the prescribed dose. The dose constraints were prescribed as per RTOG and QUANTEC- PRV spine ($D_{max}$ < 50 Gy), mandible ($D_{max}$ <70 Gy, 1cc<75 Gy), brainstem ($D_{max}$ <54 Gy), Parotid gland (mean dose <26Gy), cochlea (mean dose <45Gy), lips ($D_{mean}$ <30Gy), optic nerve / optic chiasma ($D_{max}$ <55Gy)

### *Plan Evaluation*

The dosimetric analysis was done by computing DVH and analyzing dose color wash. The following dosimetric parameters were assessed-PTV- $D_{95}$, $D_{mean.}$ $D_2$, $D_{98}$, $D_{50}$, HI, CI as per ICRU 62 and ICRU 83.

### *First Day Setup*

All patients were first positioned in alignment with wall mounted laser using external fiducial markers. Then positioning was done as per the isocenter coordinates. Onboard imaging imaging (PI) was taken and matched with the reference planning images. The setup error on the first day was documented, corrected and applied for subsequent sessions of treatment. After the first treatment session, the planned and verified isocentre position was marked on a thermoplastic cast (Figure 2a and b).

### *Imaging Protocol*

Foronboard portal imaging, an orthogonal pair of X-ray based MV imaging that is anteroposterior and lateral with double exposure portal images was acquired using Varian aS500 flat electronic portal imaging device (EPID) (Varian Medical System). The defined field size for portal image was of 20×20 $cm^2$.

### *Setup Error Detection*

- All images were manually matched using reproducible bony landmarks for evaluating the setup error.
- PI and digitally reconstructed radiograph (DRR) superposition was performed by achieving the maximum possible matching of the bony landmarks. The considered daily setup errors was the displacement measured between the landmarks of the DRR and the ones of the daily PI.
- The craniocaudal displacement (CC) was measured according to the superior orbital ridges, and the mediolateral (ML) displacement was measured according to the nasal septum; both on the anterior portal imaging. The anterior border of the mandible determined the anterior-posterior (AP) displacement on the lateral imaging.

### *Set Up Error Documentation*

- Data were collected for alternative days of treatment in offline mode.
- Data was documented taking into account the negativity and positivity of each displacement. Positive x values indicate a lateral movement to the right, positive y values represent a posterior movement and positive z values represent a cranial

movement. Negative x values indicate a lateral movement to the left, negative y values indicate anterior movement and negative z value represents a caudal movement.

- The whole data was collected by only one observer (myself) to minimize the interobserver variation. In order to avoid error and observer bias all the data was recorded by single observer.

*Steps of Setup Error Analysis*

- Individual systematic and random error was calculated in each direction,
- After the collection of individual data population systematic and random error was calculated based on royal college of radiologist.
- A statistical analysis were performed on the measured displacements or setup errors. For the setup errors, random (day-to-day variation, σ), systematic (the variation of the mean displacement of patients, Σ), and overall standard deviations (total variation around the overall mean, SD), as well as the overall mean displacement, M) was determined.
- Individual mean setup error $M_{individual}$ , the mean setup error for an individual patient.
- Overall population mean setup error $M_{pop}$ was the overall mean for the total population.
- The systematic error for the total study population $\sum^2_{set\text{-}up}$ which was calculated as the standard deviation of the individual observation of set up error in relation to the overall mean for the population $M_{pop}$.
- The random error for an individual $\sigma^2_{individual}$ was the standard deviation of the setup error for the individual mean value $M_{individual}$.
- The random error for the population $\sigma_{set\text{-}up}$ was the sum of all the individual random error $\sigma_{individual}$.

*Calculation of CTV-PTV*

- After the calculation of systematic and random error values PTV margin was calculated based on the three formulae, van herk, stroom's, ICRU 62.
- Both the data analysis and the PTV margin were calculated with the use of Microsoft office excel.
- PTV-margins was calculated according to the three methods proposed by Stroom *et al.*[6], Van Herk *et al.*[7] and ICRU-62[8]. These methods were defined using measured distributions of geometrical uncertainties for groups of previously treated patients, which allow attributing a different weight to systematic and random errors.
- ICRU 62 mentions that systematic and random uncertainties should, in an ideal approach", be added in quadrature to obtain one SD, which should then be used for margin calculation. A margin equal to 1.96* $SD_{tot}$ would then include 95% of the CTV.
- Stroom *et al.*[6] proposed a CTV-to-PTV margin recipe that properly accounts for the different consequences of systematic and random errors. They found that a margin equal to $2\Sigma_{tot}+0.7\sigma_{tot}$ ensured adequate CTV coverage. This recipe implies that the effect of systematic errors is about three times more important than the effect of random errors.
- Van Herk *et al.*[7] using another criterion for margins prescription than that of Stroom *et al*., resulted in margins equal to $2.5\Sigma_{tot}+0.7\sigma_{tot}$.

### Chemotherapy Administration

Patients had received Cisplatin0 35 mg/$m^2$ on a weekly basis along with radiotherapy. They were adequately hydrated with 2–2.5 litres of I.V fluids and supplemented with Inj. KCL, Inj. $MgSo_4$ and Inj. MVI. Radiotherapy was delivered within 1-hr of administration of Cisplatin. Before chemotherapy administration, proper antiemetic therapy with 5-HT3 antagonist, dexamethasone, and ranitidine was given.

### Ethical Consideration

The study was approved by an institutional ethical committee prior to its inception. Informed consent was obtained from every patient prior to participation in the study.

## RESULTS

In a study population of fifty patients, all patients had received radiotherapy to a total dose of 70 Gray in 35 fractions at rate of 2 Gray per fraction over five weeks along with weekly concurrent cisplatin chemotherapy.

### Patient characteristics

Most patients were in 5th and 6th decades of their life, accounting for 70% of study group with a male-female ratio of 2.12. The oropharynx was most common involved subsite followed by larynx, oral cavity and hypopharynx, besides other rare subsites - nasopharynx and maxillary sinus.

The majority patients presented in stage IV (54%) followed by Stage II / III (46%). None of the patient was of Stage I.

### Set up errors

This study analyzed setup errors in mediolateral, craniocaudal and anteroposterior (x, y, z) directions. Alternate day imaging protocol (preferably Monday, Wednesday and Friday) was done where all the patients'

**Table 1:** Showing portal images taken subsite wise

| S.No. | Site | No. of Patients | Weeks | Portal Images (AP+LAT) | Total Portal Images |
|---|---|---|---|---|---|
| 1. | Oral cavity | 6 | 7 | 126 + 126 | 252 |
| 2. | Oropharynx | 17 | 7 | 357 + 357 | 714 |
| 3. | Hypopharynx | 9 | 7 | 189 + 189 | 378 |
| 4. | Larynx | 16 | 7 | 336 + 336 | 672 |
| 5. | Nasopharynx | 1 | 7 | 21 + 21 | 42 |
| 6. | Maxillary sinus | 1 | 7 | 21 + 21 | 42 |

**Table 2:** Random individual setup error ($\sigma_{individual}$) values

| S.no. | X(cm) | Y(cm) | Z(cm) | S.No | X(cm) | Y(cm) | Z(cm) |
|---|---|---|---|---|---|---|---|
| 1 | 0.17 | 0.31 | 0.18 | 26 | 0.09 | 0.12 | 0.14 |
| 2 | 0.22 | 0.20 | 0.18 | 27 | 0.16 | 0.24 | 0.12 |
| 3 | 0.14 | 0.25 | 0.21 | 28 | 0.09 | 0.13 | 0.14 |
| 4 | 0.19 | 0.15 | 0.22 | 29 | 0.09 | 0.08 | 0.13 |
| 5 | 0.11 | 0.14 | 0.18 | 30 | 0.15 | 0.25 | 0.15 |
| 6 | 0.11 | 0.10 | 0.28 | 31 | 0.10 | 0.17 | 0.13 |
| 7 | 0.19 | 0.17 | 0.17 | 32 | 0.14 | 0.12 | 0.11 |
| 8 | 0.15 | 0.24 | 0.15 | 33 | 0.17 | 0.13 | 0.09 |
| 9 | 0.19 | 0.11 | 0.10 | 34 | 0.17 | 0.20 | 0.13 |
| 10 | 0.12 | 0.12 | 0.15 | 35 | 0.15 | 0.14 | 0.15 |
| 11 | 0.14 | 0.19 | 0.19 | 36 | 0.15 | 0.13 | 0.10 |
| 12 | 0.11 | 0.13 | 0.10 | 37 | 0.18 | 0.21 | 0.12 |
| 13 | 0.13 | 0.18 | 0.13 | 38 | 0.09 | 0.15 | 0.15 |
| 14 | 0.12 | 0.12 | 0.10 | 39 | 0.12 | 0.14 | 0.12 |
| 15 | 0.11 | 0.17 | 0.10 | 40 | 0.12 | 0.29 | 0.20 |
| 16 | 0.22 | 0.18 | 0.10 | 41 | 0.19 | 0.15 | 0.22 |
| 17 | 0.20 | 0.15 | 0.20 | 42 | 0.19 | 0.15 | 0.09 |
| 18 | 0.18 | 0.27 | 0.19 | 43 | 0.15 | 0.18 | 0.13 |
| 19 | 0.17 | 0.20 | 0.11 | 44 | 0.14 | 0.13 | 0.11 |
| 20 | 0.12 | 0.11 | 0.19 | 45 | 0.20 | 0.20 | 0.17 |
| 21 | 0.17 | 0.20 | 0.22 | 46 | 0.15 | 0.18 | 0.13 |
| 22 | 0.21 | 0.21 | 0.19 | 47 | 0.13 | 0.15 | 0.15 |
| 23 | 0.12 | 0.23 | 0.17 | 48 | 0.15 | 0.19 | 0.18 |
| 24 | 0.13 | 0.13 | 0.15 | 49 | 0.20 | 0.19 | 0.17 |
| 25 | 0.09 | 0.12 | 0.14 | 50 | 0.14 | 0.20 | 0.20 |

anteroposterior and lateral portal images were taken. Total portal images taken were 2100 (Table 1).

Random individual set up errors are shown in Table 2. Displacement charts for X, Y and Z are shown in Figure 3 a-c. Maximum and minimum of individual random error is shown in Table 3 and the individual mean is shown in Table 4.

Table 5 shows the maximum and minimum set up error for the population.

The maximum and minimum random errors in various coordinates were 0.14 and -0.21 (X coordinate), 0.22 and -0.25 (Y coordinate) and 0.15 and 0.09 (Z coordinate), respectively. Similarly, maximum and minimum systematic errors in various coordinates were 0.22 and 0.09 (X coordinate), 0.31 and 0.08 (Y coordinate) and 0.28 and 0.09 (Z coordinate), respectively.

The systematic and random errors in X, Y and Z were 0.233 and 0.088, 0.286 and 0.098, 0.214 and 0.081, respectively.

Table 6 shows the calculated setup errors in each coordinate by the three methods proposed by Stroom *et al.*[12], Van Herk *et al.*[21] and ICRU-62[41]. Maximum setup error was observed in the anteroposterior direction followed by the mediolateral direction. While least error was seen in the craniocaudal direction. In all the 3 coordinates the setup errors were less than 5 mm.

## DISCUSSION

Set up margin is an important determinant of the outcomes and potential benefits of IMRT technique. A smaller margin increases the chances of a marginal miss. While a higher margin could lead to the inclusion of higher volume of surrounding OARs inside the PTV posing a major problem in its avoidance and sparing.[6] Further, even a minor deviation in the isodose shift may significantly lower the dose in the target volume and increase the doses administered to the OARs during the whole course of the IMRT treatment. When the target region receives a reduced radiation dose, this can possibly increase the chances of local recurrence, over-irradiation of normal tissues, which causes unnecessary toxicity, ultimately increasing the probability of further complications.

**Table 3:** Minimum and maximum of individual $_{\text{random error}}$

| S. no. | $Min_{individual}$ (cm) | $Max_{individual}$ (cm) | S. no. | $Min_{individual}$ (cm) | $Max_{individual}$ (cm) |
|---|---|---|---|---|---|
| 1 | -0.50 | 0.50 | 26 | -0.30 | 0.26 |
| 2 | -0.33 | 0.70 | 27 | -0.30 | 0.50 |
| 3 | -0.42 | 0.42 | 28 | -0.20 | 0.40 |
| 4 | -0.49 | 0.40 | 29 | -0.30 | 0.22 |
| 5 | -0.33 | 0.70 | 30 | -0.49 | 0.40 |
| 6 | -0.80 | 0.50 | 31 | -0.35 | 0.30 |
| 7 | -0.44 | 0.33 | 32 | -0.44 | 0.30 |
| 8 | -0.30 | 0.49 | 33 | -0.30 | 0.20 |
| 9 | -0.29 | 0.49 | 34 | -0.50 | 0.40 |
| 10 | -0.28 | 0.30 | 35 | -0.52 | 0.25 |
| 11 | -0.35 | 0.50 | 36 | -0.30 | 0.20 |
| 12 | -0.20 | 0.30 | 37 | -0.90 | 0.49 |
| 13 | -0.41 | 0.33 | 38 | -0.22 | 0.35 |
| 14 | -0.30 | 0.22 | 39 | -0.44 | 0.27 |
| 15 | -0.38 | 0.20 | 40 | -0.80 | 0.33 |
| 16 | -0.49 | 0.35 | 41 | -0.45 | 0.50 |
| 17 | -0.50 | 0.53 | 42 | -0.49 | 0.50 |
| 18 | -0.44 | 0.41 | 43 | -0.50 | 0.40 |
| 19 | -0.40 | 0.40 | 44 | -0.22 | 0.22 |
| 20 | -0.27 | 0.44 | 45 | -0.40 | 0.40 |
| 21 | -0.40 | 0.44 | 46 | -0.50 | 0.35 |
| 22 | -0.40 | 0.45 | 47 | -0.29 | 0.35 |
| 23 | -0.40 | 0.50 | 48 | -0.44 | 0.50 |
| 24 | -0.30 | 0.33 | 49 | -0.40 | 0.40 |
| 25 | -0.30 | 0.26 | 50 | -0.49 | 0.35 |

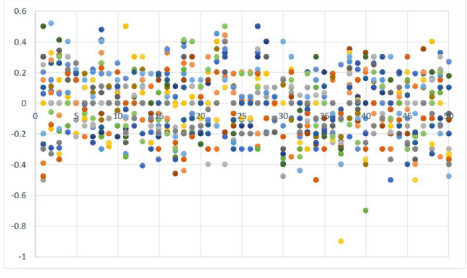


**Figure 3(a):** Displacement chart for X coordinate

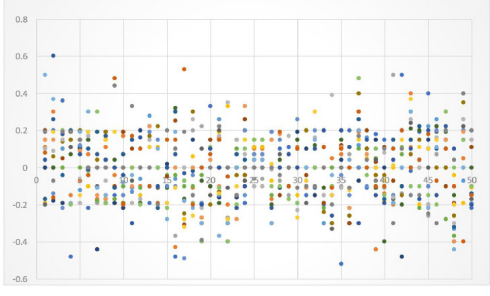


**Figure 3(b):** Displacement chart for Y coordinate

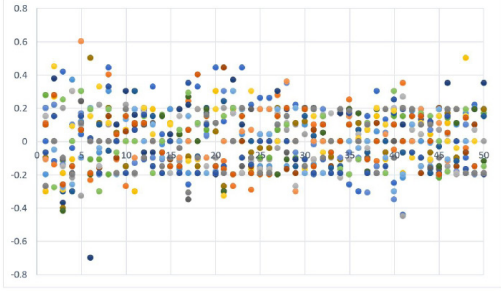


**Figure 3(c):** Displacement chart for Z coordinate

### *Immobilisation Technique*

The immobilization plays a vital role in daily reproducibility of the patient's treatment position, thereby decreasing the set up errors. A study by Lalida *et al.*[9] assessed interfraction error in head and neck cancer patients treated by IMRT technique using a uni-frame head to facial mask. It was a non-extended thermoplastic cast and laser alignment technique. They concluded there is no difference in set up error in conventional and non-extended thermoplastic cast. There setup error was upto 5 mm. In our study we used a five-point thermoplastic cast covering the patient's head and neck. Appropriate neck rest was used as per the curvature of patient's neck. Shoulder traction used to keep them away from the treatment field. We had set up error upto 3-5 mm in all directions, which showed appropriate immobilization can reduce the setup margin.

A study by Contestini *et al.*[10], including all head and neck cancer patients, studied immobilization system and its effect on daily reproducibility. They used five-point thermoplastic cast with different size of neck and patient was lied on carbon base plate for the patient's stability. Our study has similar patient setup before CT stimulation. Carbon base plate was used for the patient's immobility along with five-point thermoplastic cast and neck rest as per patients neck curvature. It has seen that mask prevents unnecessary movement of head and reduces set up errors. Appropriate neck rest is necessary for reducing error in y coordinate.

**Table 4:** Individual Mean ($M_{individual}$)

| S.No | X | Y | Z | S.No | X | Y | Z |
|---|---|---|---|---|---|---|---|
| 1 | 0.05 | -0.04 | 0.02 | 26 | 0.05 | -0.04 | -0.07 |
| 2 | 0.1 | 0.04 | 0.07 | 27 | -0.03 | 0.13 | 0.07 |
| 3 | 0.1 | 0.01 | -0.17 | 28 | 0.01 | 0.02 | 0.07 |
| 4 | 0.09 | 0.12 | -0.03 | 29 | -0.02 | -0.04 | -0.02 |
| 5 | 0.08 | 0.08 | 0.11 | 30 | 0.00 | -0.15 | 0.07 |
| 6 | 0.04 | 0.00 | -0.05 | 31 | -0.03 | 0.10 | 0.0 |
| 7 | -0.07 | -0.03 | -0.06 | 32 | 0.02 | -0.19 | 0.03 |
| 8 | -0.02 | 0.08 | 0.15 | 33 | -0.07 | -0.03 | -0.05 |
| 9 | 0.00 | -0.01 | -0.04 | 34 | -0.12 | -0.08 | -0.07 |
| 10 | -0.02 | 0.01 | 0.02 | 35 | 0.03 | -0.1 | 0.07 |
| 11 | -0.01 | -0.08 | 0.04 | 36 | -0.1 | -0.10 | -0.01 |
| 12 | -0.05 | 0.04 | 0.1 | 37 | 0.14 | -0.24 | -0.03 |
| 13 | 0.07 | 0.03 | 0.0 | 38 | 0.04 | 0.1 | -0.03 |
| 14 | -0.05 | -0.09 | -0.05 | 39 | -0.02 | -0.01 | -0.03 |
| 15 | -0.04 | -0.08 | -0.02 | 40 | -0.09 | -0.1 | 0.02 |
| 16 | 0.01 | 0.03 | -0.02 | 41 | -0.05 | 0.1 | 0.00 |
| 17 | -0.1 | -0.19 | 0.01 | 42 | 0.01 | 0.02 | 0.04 |
| 18 | -0.02 | 0.04 | -0.02 | 43 | 0.13 | -0.11 | 0.04 |
| 19 | -0.19 | 0.00 | 0.09 | 44 | 0.03 | 0.00 | -0.02 |
| 20 | 0.01 | -0.06 | -0.04 | 45 | -0.01 | -0.07 | 0.00 |
| 21 | 0.00 | -0.05 | -0.01 | 46 | 0.07 | -0.21 | 0.07 |
| 22 | -0.14 | 0.08 | 0.06 | 47 | 0.12 | 0.03 | -0.03 |
| 23 | -0.05 | 0.22 | 0.06 | 48 | -0.21 | 0.00 | 0.00 |
| 24 | 0.02 | -0.05 | -0.08 | 49 | 0.12 | 0.03 | -0.08 |
| 25 | 0.05 | -0.04 | -0.07 | 50 | -0.07 | -0.22 | -0.02 |

**Table 5:** Maximum and minimum set up error of population

| | *Population Max (cm)* | *Population Min (cm)* |
|---|---|---|
| X | 0.60 | -0.52 |
| Y | 0.52 | -0.90 |
| Z | 0.60 | -0.70 |

### *Imaging Protocols*

The image guidance protocols of MV/KV images and or CBCT protocol varies between different institutions, In a study done by Delishaj *et al.*[11], total of 360 CBCT images were taken in sixty patients of head and neck cancer patients. In all the patients imaging was done on first three days of treatment followed by weekly imaging. Based on the offline imaging error was calculated in all three directions. In our study we had taken 2100 images of all fifty patients, including imaging on 3 alternative days of a week. More images were taken in our study, providing better data for error calculation. Errors were analyzed on offline mode in all directions x, y, z separately.

## Set Up Errors

A study by Pehlivan *et al.*[12] included 20 patients of head and neck cancer and a total of 567 images (anterior and lateral portal). Systematic error after correction was less than 1-mm and random error was upto 2 mm, with CTV-PTV margin between 3–5 mm. In our study, the calculated margin ranged from a minimum of 0.22 mm to a maximum of 0.44 mm. the possible explanation for a lesser value of setup margin observed in our study is that along with daily portal imaging thrice weekly CBCT imaging was also taken. CBCT imaging generates multiple slices in sagittal and coronal planes and also generates multiple axial slices but in portal imaging only single sagittal and coronal imaging is obtained. This property along with soft tissue resolution allows for better correction of set up error.

**Table 6:** Calculated set-up errors in each coordinates

| *ICRU 62* | | | *Stroom's* | | | *Van Herk* | | |
|---|---|---|---|---|---|---|---|---|
| LR (cm) | AP (cm) | CC (cm) | LR (cm) | AP (cm) | CC (cm) | LR (cm) | AP (cm) | CC (cm) |
| 0.24 | 0.30 | 0.22 | 0.34 | 0.40 | 0.32 | 0.38 | 0.44 | 0.38 |

Figure 15(a): Table showing calculated setup errors in each coordinates

In a study by Lal P *et al.*[13], having thirty- three HNC patients, 226 paired Portal Images (PIs) were obtained. As per their institutional protocol for IMRT planning, the immobilization of the face, neck, and shoulder area of patients was obtained with an "S" plain mask ("S") and a 5 mm isotropic CTV-PTV expansion was being utilised. a study done to evaluate the PTV margins showed that the setup errors were higher. The calculated values were 8, 5, and 7 mm in craniocaudal (C-C), mediolateral (M-L), and anteroposterior (A-P) directions and the margins were accordingly changed. In order to reduce the PTV margins, modification of mask was evaluated by applying extra thermoplastic bead reinforcements at the nasion (N) and chin (C) areas denoted as "S"-NC.A similar changes was applied to the extended "U" type mask ("U"-NC) in postoperative patients. NC type chosen when surgical neck levels inclusive of level IV were in the CTV, while the extended "U"-NC was chosen when at most surgical level III was in the CTV. A comparison of PTV margins using the plain "S," "S"-NC, and extended "U"- NC masks revealed that the A-P margins were largest (0.78 cm) in the neck region for the "S" type mask , and reduced to 0.5 cm when the NC modifications. Also, the C-C movements both in the head and neck region reduced from 0.7–0.8 to 0.3 cm with the use of NC modification. In our study, using standard five-point thermoplastic cast the final PTV as per van herk formula was 0.38, 0.44 and 0.38 cm in the CC, LR and AP directions. This highlights that our margins were larger in ML and AP directions but lesser in CC direction as compared to their study. In our study while analyzing the setup errors we observed that the maximum displacement was observed in the cranio-caudal direction because of less restriction in movements

of chin and mandible region. The findings of their study showed that a necessary modification introduced in thermoplastic cast with better reinforcements at the nasal and chin regions lead to a meaningful reduction in the setup errors. This suggest that necessary modifications introduced in the immobilization system may allow for a further reduction in set up errors even upto 3 mm. This approach needs to be validated and tested in further studies as it seems to be a cost-effective and simpler variation.

A study by Biswas P *et al.*[14], analyzed the setup margins in a total of They applied Van Herk formula which showed PTV margin was 0.35, 0.32 and 0.34 cm in ML, AP and CC directions. Their study concluded that a margin of 5 mm from CTV-PTV was adequate to account for set up errors. In our study the recorded CTV-PTV margin were 0.38 cm, 0.44 cm and 0.38 cm in LR, AP and CC as per the Van Herk formulae. The margins were slightly higher compared to their study in all three directions. In their study pre-treatment online correction of the isocentric position on the first five daily fractions was restricted to only setup errors of more than 5 mm, but in our study, there was no such restriction and the maximum possible online correction was done. in our study the imaging protocol was also different as CBCT imaging was done thrice weekly, while in their study only CBCT was taken on first five days of treatment. This might have led to the detection of higher average value of setup error in our study.

Hong *et al.* [15] observed that mean absolute set up error in any single direction was 3.33 mm with a population size of ten patients. Daily imaging in first week was done followed by weekly imaging. Optical guidance system was utilized. They calculated the average of set up error and standard deviation. They suggested the importance of head and neck immobilization and aggressive quality assurance. But in our study, the setup errors were comparatively higher up to a maximum value of 4.4 mm this is because in there. Spatial localization of each patient was accomplished through detection of four passive markers that were attached to a custom bite plate that utilizes the maxillary dentition to form a rigid system. It tracks translations of and rotations around the designated patient isocenter. It accomplished real-time imaging using an optical position sensor system that was rigidly mounted to the ceiling of the linear accelerator vault. It was interfaced with a computer for visual display. This allowed for better reproduction of daily position and minimal setup errors compared to our study.

A study by Sharon Q *et al.*[16], analyzed the interfraction setup error in head and neck and prostate cancer patients. Utilizing KV-CBCT imaging the systematic setup error was 1.0, 1.5 and 1.1 mm in ML, CC and AP directions. Whereas the random setup error was 1.1, 1.4 and 1.3 mm in ML, CC and AP. the calculated CTV-PTV margin was 3.3, 4.8 and 3.7 mm in ML, CC and AP directions. The better imaging quality of KVCBCT scans resulted in smaller random setup errors in translational directions for both H and N as compared with MVCBCT. In our study, utilizing KV-CBCT along with portal imaging the systematic error was 0.8, 0.9 and 0.8 mm in ML, AP and CC direction was slightly lesser compared to their study. Whereas the random setup error was 2.3, 2.8 and 2.1 mm in ML, AP and CC directions was slightly higher compared to their study. While our study also calculated the CTV-PTV margin using the Van Herk formula was 3.8, 4.4 and 3.8 mm in the LR, AP and CC directions. The overall CTV-PTV margin was nearly comparable among both studies. Their study showed larger CTV-PTV margin in MVCBCT may be required and KVCBCT is a more efficient modality for portal imaging. Both studies suggested that an anisotropic margin are obtained in three directions. This validates the finding of our study.

In a study done by Liu *et al.*[17], they included 113 patients who were treated by IMRT technique. Each patient had a minimum of three CBCT scan before the start of the treatment. Their study separately analyzed the deviation for head, upper neck and lower neck region. Their study revealed that deviation in the head was in the range of 0–4 mm in the AP direction, 0–3 mm in the LR direction and 0–2 mm in the CC direction Their results showed that CTV-PTV margin obtained was 1.5, 0.6 and 2.2 mm in the LR, CC and AP directions. In our study, the calculated CTV-PTV margin were higher compared to their study. The margins obtained were 3.8, 3.8 and 4.4 mm in LR, CC and AP directions. The systematic error ranged from 0.9, 0.8 mm and 0.9 mm for LR, AP and CC direction. The possible reason for the reduction in set up margin lies in the difference in imaging protocol during CT simulation and CBCT imaging. The reconstructed slice thickness was 3 mm in our study but in their study the slice thickness used was 1-mm allowing better resolution. Also, they used different bony landmark for recording the setup errors of head, upper neck and lower neck region. This led to more accuracy in daily treatment reproduction and hence allowed PTV margin of even less than 3 mm.

A study by Strbac B *et al.*[18], evaluating the setup errors in head and neck radiotherapy using electronic portal imaging concluded that a 6 mm extension of CTV to PTV margin, as the lower limit, is enough to ensure that 90% of the patients treated for head and neck cancer will receive a minimum cumulative CTV dose greater than or equal to 95% of the prescribed dose. They used 3 formulae for

CTV-PTV calculation which were Van Herk, ICRU 62, Stroom. The margin according to ICRU 62 was 2.40, 2.66 and 2.27 mm. As per Stroom, the margins were higher that is 4.32, 5.14, 4.08 mm. While the highest range was achieved by van herk formula 5.08 mm, 6.11 mm and 4.79 mm in the CC, LR and AP directions. Also in our study there was asymmetric PTV margin was obtained. The margin, according to ICRU 62 was 2.4, 3.0 and 2.2 mm in the LR, AP and CC. As per Stroom 3.4, 4.0, 3.2 mm in the LR, AP and CC. While higher range was achieved by Van Herk formula 3.8, 4.4 and 3.8 mm in the CC, LR and AP directions. It showed that 3–5 mm of margin was adequate for head and neck cancer tumor coverage. An asymmetric margin allows us to get better coverage with normal tissue sparing. 3 mm margin in ML direction prevents the parotids and provides benefit against the long-term side effect of xerostomia.

Lu H *et al.*[19], did a study to assess the interfractional and intrafraction errors by CBCT imaging. They incorporated ten patients in which position was setup and daily pre-treatment and post-treatment imaging was done in every treatment fraction. If any translational error was seen, it was corrected online only before the treatment delivery. When CBCT not done daily, the margin was 4.9, 4.0 and 6.3 mm in LR, SI and AP directions. While when imaging was done daily with CBCT reduction was seen in overall margin by 1.2 mm in all the directions. They concluded that radiotherapy along with CBCT imaging improves the quality of treatment. A 4.0 to 6.3 mm margin is adequate to cover the setup uncertainties. Online correction of setup error can reduce PTV margin by 70–81% and better treatment is delivered. Our study had difference in imaging, which was daily portal imaging for entire treatment, along with CBCT imaging on alternate days for overall treatment. Based on randomised and systematic error margin was calculated based on Van Herk formula. CTV-PTV margin based on Van Herk was 3.8 mm, 4.4 mm and 3.8 mm in LR, AP and SI direction. 5 mm margin was adequate for tumour volume coverage. CBCT plays crucial role in providing more precision in treatment.

### *Clinical Impact of Set Up Errors*

A study done by Chen *et al.*[20] of two hundred twenty five patients compared outcomes amongst patient treated by CTV-PTV margin of 3 mm and 5 mm IMRT with image guidance. The incidence of gastrostomy-tube dependence at 1 year was 10% and 3% for patients treated with a PTV margin of 5 and 3 mm, respectively. While the incidence of post-treatment esophageal stricture was 14 and 7%. The margins can be reduced from 5 mm to 3 mm if daily Image Guided Radiotherapy (IGRT) was done using either kV or mV beam imager. There was no significant difference in the 3-year loco-regional control for patient who were treated with PTV margin of 5 or 3 mm margins. While 3 mm margins resulted in less toxicities. While in our study, the marginswere reduced to nearly 5 mm from the previous institutional protocol of 7 mm. This may allow for sparing, which may translate into decreased incidence of xerostomia and dysphagia. This needs to be validated in future studies. Both studies emphasize imaging protocol, improving treatment delivery to the patient. Imaging not only precise treatment delivery to tumor but also saves normal tissue cells in the surrounding.

### *Recommendation from Present Study*

We assessed the various setup uncertainties in each direction to generate our own PTV margins. Our study showed that the measured setup uncertainties were lesser than that were estimated. a set up margin of even 5 mm seems to be appropriate compared to the institutional protocol of 7 mm.

Reduction in the setup margin would allow for a reduction in the absolute volume of PTV. This would possibly lead to a lesser overlap and lesser proximity with the OARs. This may allow for better exploitation of the sharp dose gradient of the IMRT technique with OARs sparing. Also, the region of PTV lining close proximity to critical structures such as (PRV brain stem, PRV cochlea, PRV spinal cord) seems to be compromised with a setup margin of 7mm. but possibly a better dosimetry of these regions can be obtained with reduced margins.

It amy be noted that relocation, other systematic errors can also impact the treatment planning process. These can be due to (delineation errors, misalignment of lasers, couch sags, stiff musculature and tense patients. The changes in patients' total weight and hence the tumor volume/body mass must also be ensured during the entire treatment course to optimize the setup errors. Appropriate immobilization system is a key factor determining setup errors and the appropriateness of thermoplastic cast and neck rest needs to be ensured.

The expertise of treatment team members and quality assurance is also important. While determining the institutional protocol for setup errors other than imaging protocols and immobilization, these numerous factors also need to be taken in account.

## CONCLUSION

Our study suggested PTV margins of 5 rather than 7 mm. The adoption of reduced setup margins would allow for a reduction in the absolute volume of PTV. This may

translate into better PTV dosimetry with simultaneous sparing of adjacent organ at risk. All institutes should define their own set up margins per their infrastructure and available technology.

## REFERENCES


1. Verhey, L. Immobilizing and positioning patients for radiotherapy. Seminars In Radiation Oncology,1995; 5(2), 100-114.
2. Rudat V, Flentje M, Oetzel D, Menke M, Schlegel W, Wannenmacher M. Influence of the positioning error on 3D conformal dose distributions during fractionated radiotherapy. Radiother. Oncol. 1994;33:56-63
3. Navran, A., Heemsbergen, W., Janssen, T *et al.* The impact of margin reduction on outcome and toxicity in head and neck cancer patients treated with image-guided volumetric modulated arc therapy (VMAT). Radiotherapy And Oncology,2019; 130, 25-31.
4. Siebers JV, Keall PJ, Wu Q *et al.* Effect of patient setup errors on simultaneously integrated boost head and neck IMRT treatment plans. Int J Radiat Oncol Biol Phys ;2005;63:422-33.
5. Hurkmans CW, Remeijer P, Lebesque JV *et al.* Setup verification using portal imaging; review of current clinical practice. Radiothererapy Oncology., 2001;Vol. 58 pp.105-120.
6. Stroom JC, de Boer HC, Huizenga H *et al.* Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability. Int J Radiat Oncol Biol Phys. 1999;43(4):905-19.
7. Van Herk M, Meijer Pasch C, Lebesgue 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
8. International Commission on Radiation Units and Measurements. ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy.1999. (Supplement to ICRU Report; vol 50).
9. Tuntipumiamorn, L. Assessment of Interfraction Setup Error of Non-Extended Standard Thermoplastic Mask for Head- and-Neck Intensity-Modulated Radiation Therapy Patients. Siriraj Medical Journal, 2013;65(2), 31-35.
10. Contesini M, Guberti M, Saccani R, *et al.* Setup errors in patients with head-neck cancer (HNC), treated using the Intensity Modulated Radiation Therapy (IMRT) technique: how it influences the customised immobilisation systems, patient's pain and anxiety. Radiat Oncol. 2017;12(1):72.
11. Delishaj D, Ursino S, Pasqualetti F, *et al.* Setup 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.
12. Pehlivan B, Pichenot C, Castaing M, *et al.* Interfractional setup errors evaluation by daily electronic portal imaging of IMRT in head and neck cancer patients. Acta Oncol. 2009;48(3):440-45.
13. Lal, P., Verma, M., Sait, A *et al.* An audit of setup reproducibility in radiotherapy of head and neck cancers. Journal Of Radiation And Cancer Research,2016; 7(3), 85.
14. Biswas P, Lhiri D, Roy S *et al.* prospective observational study to estimate setup errors and optimise PTV margins in patients undergoing IMRT for head and neck cancers from Government cancer centre of Eastern India. Journal of Radiotherapy in Practice, 19(1), 52-58
15. Hong TS, Tomé WA, Chappell RJ *et al.* The impact of daily setup variations on head-and-neck intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2005;61(3):779-88.
16. Qi XS, Hu AY, Lee SP, *et al.* Assessment of interfraction patient setup for head-and-neck cancer intensity modulated radiation therapy using multiple computed tomography-based image guidance. Int J Radiat Oncol Biol Phys. 2013;86(3):432-39.
17. Liu J, Lyman KM, Ding Z *et al.* Assessment of the therapeutic accuracy of cone beam computed tomography-guided nasopharyngeal carcinoma radiotherapy. Oncol Lett. 2019;18(2):1071-80.
18. Strbac B, Jokic VS. Evaluation of setup errors in head and neck radiotherapy using electronic portal imaging. Phys Med. 2013;29(5):531-36.
19. Lu H, Lin H, Feng G *et al.* Interfractional and intrafractional errors assessed by daily cone-beam computed tomography in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy: a prospective study. J Radiat Res. 2012 Nov 1;53(6):954-60.
20. Chen M, Farwell G, Luu Q *et al.* Evaluation of the planning target volume in the Treatment of Head and Neck Cancer With Intensity-Modulated Radiotherapy: What Is the Appropriate Expansion Margin in the Setting of Daily Image Guidance?. International journal of radiation oncology, biology, physics.2010; 81(4):943-9