Original Article

Comparison of setup errors based on bony landmarks in high precision radiotherapy in head and neck cancer: Results of a prospective study

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ABSTRACT

Background: Comparison of setup errors for various immobilization devices in head and neck cancer and to determine the treatment margin in high precision radiotherapy using bony landmark based matching. **Materials and Methods:** Total 20 patients were immobilized with BrainLAB immobilization device (BL) or thermoplastic ray cast (RC) for high precision radiotherapy. Total, systematic, and random errors in mediolateral (ML), craniocaudal (CC) and antero-posterior directions were determined and clinical target volume (CTV) to planning target volume (PTV) margin by Stroom's formula was compared. Unpaired *t*-test was used for comparing errors. The standard deviations (systematic and random errors) in different groups were compared by variance ratio test (Levene's test) and $P \leq 0.05$ was considered significant. **Results:** The total error in ML direction (BL vs. RC) was 1.00 mm versus 1.39 mm ($P = 0.03$), systematic error 0.09 cm versus 0.197 cm and random error 0.116 cm versus 0.258 cm (*F*-test, $P = 0.001$). CTV to PTV margin was significantly lower in BL (0.26 cm vs. 0.57 cm, $P < 0.05$). In CC direction, BL system had lower total error (0.075 cm vs. 0.157 cm) and a significantly less systematic error (0.116 cm vs. 0.258 cm, $F = 7.149$, $P = 0.015$). CTV to PTV margin was less in BL than RC in CC direction (0.34 cm vs. 0.92 cm, $P = 0.06$). **Conclusion:** In head and neck region, when electronic portal imaging device based verification is used, for BL margins ranged from 2.6 to 3.7 mm. For RC in the PTV margin was 5.7–9.2 mm. Therefore, a margin of 3 mm for BL and 5–10 mm for RC with online correction in head and neck is adequate.

Key words: Random error, set up error, systematic error

INTRODUCTION

Intensity-modulated radiotherapy (IMRT) in head and neck cancer requires accurate image guidance and dose delivery to the target organs. The two main objectives of IMRT in head and neck cancer are dose escalation and sparing of the normal organs.[1] This represents a paradigm shift of conventional radiotherapy techniques. To achieve the goal of dose escalation with simultaneous sparing of the normal tissue, tight margin to the clinical target volume (CTV) is imperative. Errors of any kind (systematic or random) can result into geographic miss resulting in tumor recurrence. Therefore, rigorous verification of set up errors is an integral part of quality assurance in high precision radiotherapy. This is particularly relevant in head and neck cancer due to the proximity of many dose limiting critical organs.[2] As high-precision radiotherapy is gradually becoming the standard of care in this condition, it is of paramount importance for every radiotherapy centers to audit the radiotherapy practice and characterize the setup errors.[3] Even though cone beam computed tomography (CT) scan is becoming more popular, there are many centers in resource-constrained countries of South-East Asia using bony anatomy based treatment

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verification like electronic portal imaging. It is needless to say that head and neck cancer constitutes a high burden of disease in this region due to various socioeconomic reasons.[4] In this report, we present our experience of setup verification based on electronic portal imaging before cone beam CT scan was introduced for treatment verification of high precision radiotherapy in our institute. This may still be relevant for centers using electronic portal imaging for set up verification based on bony landmarks. The aim of this study was to compare various immobilization devices used in head and neck cancer in terms of set-up errors and positional accuracy and to quantify total, systematic and random errors in different directions. This data were needed to obtain institutional data of margin needed to expand CTV to compensate the errors.

MATERIALS AND METHODS

Total 20 patients with head and neck cancer who were planned for high precision radiotherapy (either IMRT or three-dimensional conformal radiotherapy) were included in the trial. All patients were provided with a written description of the nature of the study after being explained the details of the study and were included after they signed the informed consent form. The study was cleared by Ethics and Research Committee of Institutional Review Board. Ten patients were immobilized in each of the BrainLAB (BL) immobilization device or thermoplastic ray cast (RC).

Simulation and imaging

Following immobilization, patients were simulated using Varian Ximatron simulator and three isocenters (one anterior and two laterals) were marked on the mask in the region of study with the help of laser beams. CT images were acquired in the same position with the immobilization device with radio-opaque markers were placed at isocenter and planning CT scan was acquired.

Volume delineation and treatment planning

CT images were transferred to Oncentra MasterPlan planning system that was used for contouring the volumes of interest (gross tumor volume or GTV, clinical target volume or CTV, planning target volume (PTV) or PTV, organs at risk or OAR). This was done as per International Commission of Radiation Units-50 (ICRU) and 62 guidelines.[5] A margin of 5 mm was given to CTV to obtain PTV. Treatment planning was done by the Plato Sunrise treatment planning system, and digitally reconstructed radiographs (DRR) were generated for orthogonal fields for referencing. After finalization of the plan, the information was transferred to local area network therapy information system. Quality assurance of the plan was carried out on the treatment unit before starting the course of treatment.

Radiotherapy treatment

Patients were treated in dual energy Primus Linear Accelerator (Siemens, USA) capable of delivering 6 and 15 MV photons and a range of electron energies. The accelerator is also fixed with a Si-based electronic portal imaging device (EPID) (Siemens, Germany). The EPID has a sensitive area of 41 cm × 41 cm (512 × 512 pixel matrix size).

Verification of electronic portal imaging device

During the course of radiotherapy treatment orthogonal images were analyzed online, and corrections were done if the displacements were gross (more than 5 mm. Imaging was done on day 1, 2, 3, and if values not acceptable requiring online correction imaging was continued until 3 acceptable values and then once a week.

Image analysis

All images were analyzed by image registration software and errors were measured. The software available allowed superimposing the DRR and EPID. It aided in detecting bony points and measuring the distance accurately was used. Several fixed bony points were used, for example, the medial angle of the eye, the angle of mandible, symphysis menti, external auditory meatus, and clivus. The total errors in mediolateral (ML), AP and craniocaudal directions (CC) were measured. Total 324 portal images (162 lateral and 162 AP) were studied. 164 images in RC group (82 anterior and 82 lateral images) and 160 images (80 anterior and 80 lateral) in BL group were analyzed.

Statistical analysis

Total errors in Mediolateral (ML), craniocaudal (CC) and Antero-posterior (AP) were measured. Displacements obtained on each day were compiled, and the arithmetic mean was calculated. This gives the systematic error for each patient. The random component of the error represents day to day variations during the treatment course. It is the fluctuating component of the total error. The total errors were compared by *t*-test and systematic and random errors were compared by variance ratio test (*F* statistics). In all cases, $P \leq 0.05$ were taken as significant.

Clinical target volume to planning target volume margin calculation

Several methods have been proposed in the literature to calculate CTV to PTV margin.[6] We calculated CTV to PTV margin using ICRU 62 ($\sum +0.7\ \sigma$) Stroom's ($2\sum +0.7\ \sigma$) and Van Herk's ($2.5\sum +0.7\ \sigma$) formula. However for comparison between the margins in different groups of immobilization Stroom's formula was used.[7] The difference between the CTV to PTV margin was compared by *t*-test of independent samples assuming unequal variance. For statistical significance $P \leq 0.05$ was considered to be significant.

Time trend analysis

For each immobilization device average total error for all patients in ML, CC and AP directions on day 1, day 2, day 3, and once weekly were plotted against time to see the trend of displacement with time.

RESULTS

A total of 20 patients were included in the study with 10 each in BL immobilization group (BL) and 10 in RC group. The characteristics of the patients are shown in Table 1a and 1b. Total 324 portal images (162 lateral and 162 AP) were studied. 164 images in RC group (82 anterior and 82 lateral) and 160 images (80 anterior and 80 lateral) in BL group were analyzed.

Translational shifts were measured in all 324 images. The mean displacements in ML, CC and AP directions were 0.057 cm (SD 0.257), 0.1169 cm (SD 0.359) and 0.074 cm (SD 0.282) respectively. The systematic errors were 0.17 cm, 0.26 cm and 0.16 cm in ML, CC and AP directions respectively. The random errors were 0.20 cm, 0.23 cm and 0.22 cm in ML, CC and AP directions. PTV margins calculated by Stroom's formula were 0.492 cm, 0.693 cm and 0.490 cm respectively in ML, CC and AP directions [Table 2]. The total errors in ML, CC and AP directions were normally distributed [Figure 1].

In the BrainLAB (BL) group, translational displacements in 160 images were studied for total 10 patients. The mean total displacements in ML, CC and AP directions were 0.100 cm (SD 0.149), 0.075 cm (SD 0.202) and 0.049 cm (SD 0.197). The systematic errors were 0.093 cm, 0.116 cm and 0.139 cm in ML, CC and AP directions respectively. The random errors were 0.258 cm, 0.288 cm and 0.290 cm in ML, CC and AP directions. PTV margins calculated by Stroom's formula were 0.27 cm, 0.35 cm and 0.38 cm respectively in ML, CC, and AP directions. The total errors in ML, CC, and AP directions were normally distributed.

In the ray cast (RC) group, translational displacements in 164 images were studied for total 10 patients. The mean total displacements in ML, CC, and AP directions were 0.14 cm (SD 0.325), 0.16 cm (SD 0.325) and 0.09 cm (SD 0.345). The systematic errors were 0.197 cm, 0.360 cm and 0.187 cm in ML, CC, and AP directions, respectively. The random errors were 0.258 cm, 0.288 cm and 0.290 cm in ML, CC, and AP directions. PTV margins calculated by Stroom's formula were 0.57 cm, 0.921 cm and 0.577 cm respectively in ML, CC, and AP directions. The total errors in ML, CC and AP directions were normally distributed.

Analysis of the result shows different CTV to PTV margins are required for different immobilization devices that vary with the direction [Tables 2 and 3]. In ML directions lesser margin was obtained in BL group compared to RC group (0.267 cm vs. 0.574 cm, Stroom's formula, $P = 0.002$). The margins in the CC and AP directions were also less in BL group compared to RC group (0.35 cm vs. 0.92 cm, CC direction and 0.37 cm vs. 0.57 cm AP direction, though it did not attain statistical significance at 5% level, $P = 0.06$ and 0.08 respectively).

Table 1a: Head and neck - BL immobilization: Patient characteristics

Patient number	Age	Sex	Diagnosis	Dose (Gy)	Fraction
1	32	Male	Osteosarcoma maxilla	66	33
2	74	Male	Glottis	66	33
3	47	Female	PFS	66	33
4	52	Female	Nasopharynx	66	33
5	52	Female	Nasal cavity	66	33
6	66	Male	BOT	66	33
7	54	Male	Maxilla	60	30
8	35	Male	BOT	66	33
9	68	Male	Glottis	70	35
10	60	Male	PFS	66	33

PFS: Progression-free survival, BL: BrainLAB, BOT: Base of the tongue

Table 1b: Head and neck - immobilization - RC: Patient characteristics

Patient number	Age	Sex	Diagnosis	Dose (Gy)	Fraction
1	62	Male	Supraglottis	66	33
2	64	Male	Glottis	66	33
3	38	Male	Nasopharynx	66	33
4	59	Male	Tongue	66	33
5	52	Male	PFS	66	33
6	62	Female	Sinonasal carcinoma	66	33
7	13	Male	Juvenile nasoppharyngeal angiofibroma	50	25
8	53	Female	Basal cell carcinoma	55	25
9	51	Female	Carcinoma thyroid with orbital metastasis	40	20
10	56	Male	Nasopharynx	66	33

RC: Ray cast, PFS: Progression-free survival

Table 2: Systematic, random errors and CTV-PTV margin in head and neck

	CTV–PTV margin (cm)				
	Systematic error (∑)	Random error (σ)	ICRU 62*	Stroom's**	Van Herk's***
All patients (*n*=324)					
ML	0.176	0.200	0.316	0.492	0.58
CC	0.264	0.235	0.4285	0.6925	0.8245
AP	0.166	0.227	0.3249	0.4909	0.5739
BL only (*n*=160)					
ML	0.093	0.116	0.1742	0.2672	0.3137
CC	0.116	0.166	0.2322	0.3482	0.4062
AP	0.139	0.139	0.2363	0.3753	0.4448
RC only (*n*=164)					
ML	0.197	0.258	0.3776	0.5746	0.6731
CC	0.360	0.288	0.5616	0.9216	1.1016
AP	0.187	0.290	0.39	0.577	0.6705

CTV-PTV margin: *ICRU ($\Sigma + 0.7 \times \sigma$), **Stroom's formula ($2 \times \Sigma + 0.7 \times \sigma$), ***Van Herk's formula ($2.5 \times \Sigma + 0.7 \times \sigma$). CTV: Clinical target volume, PTV: Planning target volume, ML: Mediolateral, CC: Craniocaudal, AP: Antero-posterior, BL: BrainLAB, RC: Ray cast

Addition of alpha cradle with BrainLAB immobilization

In the BL group, seven patients were immobilized with BL device only, whereas in three patients additional alpha cradle was used in addition to BL. Results show the use of alpha cradle with BL significantly reduced the PTV margin ($P \leq 0.05$). The results are shown in Tables 4 and 5.

Average of total error every week in each direction for 10 patients was compared. This gives an idea of the behavior of total error across time and also implies the consistency of the immobilization device over a period. This is shown in Figure 2. In head and neck region, the time trend analysis shows BL to be superior to RC where the displacement in

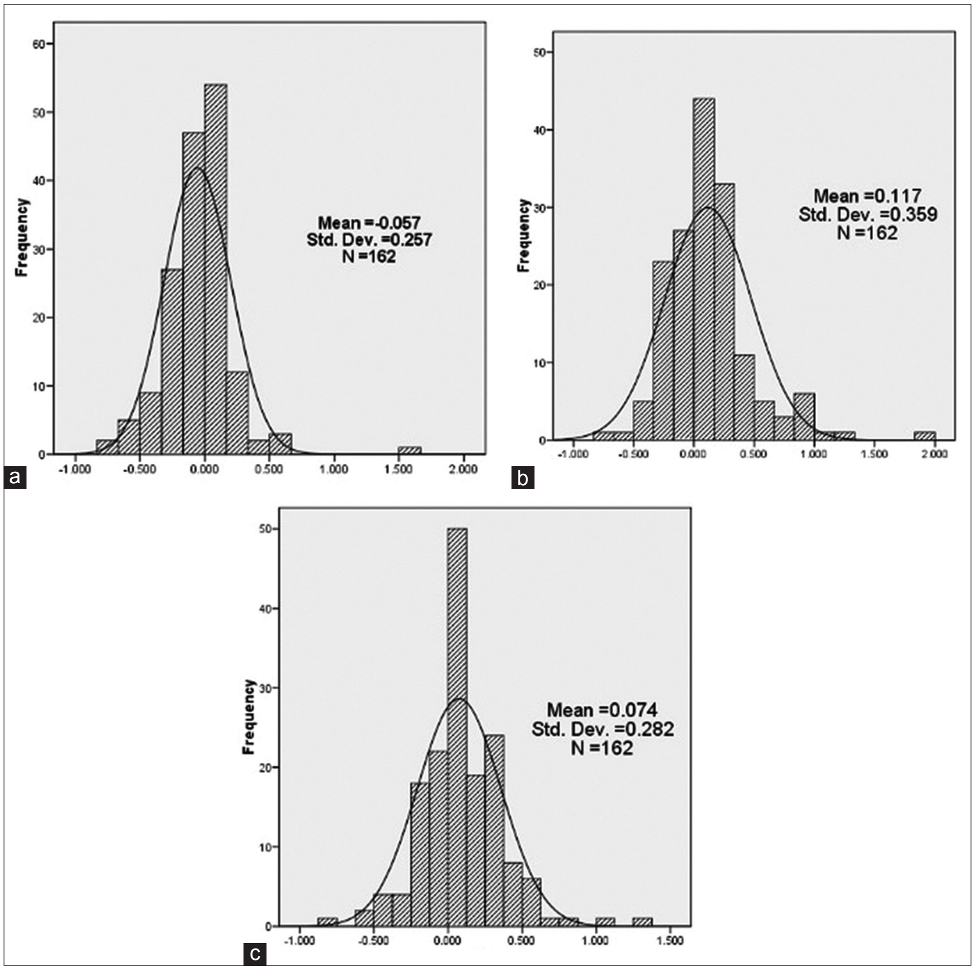

Figure 1: Distribution of total errors of all patients in mediolateral, craniocaudal and antero-posterior directions (a) Mediolateral, (b) Craniocaudal, (c) Antero-posterior

Table 3: Comparison of total error, systematic error, random error and PTV margin (Stroom's formula) in head and neck

Parameter	Levene's test for equality of variance		*t*-test for equality of means				
	F	Significant	Mean difference	SE of difference	*P*	95% CI of the difference	
						Lower	Upper
Total error in ML direction	10.92	0.001	−0.086	0.039	0.031	−0.1648	0.0782
Total error in CC direction	35.40	0.000	−0.0815	0.0558	0.147	−0.192	0.029
Total error in AP direction	16.34	0.000	−0.050	0.044	0.258	−0.137	0.371
Systematic error in ML direction	0.881	0.360	−0.053	0.079	0.51	0.224	0.116
Systematic error in CC direction	7.149	0.015	−0.097	0.1193	0.433	−0.359	0.165
Systematic error in AP direction	0.623	0.440	−0.055	0.075	0.469	−0.215	0.103
Random error in ML direction	11.952	0.001	<0.0005	0.031	1.00	−0.062	0.062
Random error in CC direction	8.184	0.005	<0.0005	0.036	1.00	−0.072	0.072
Random error in AP direction	11.616	0.001	<0.0005	0.035	1.000	−0.0706	0.0706
PTV margin ML	15.79	<0.001	−0.172	0.0531	0.002	−0.277	−0.067
PTV margin CC	66.182	<0.001	−0.163	0.087	0.06	−0.337	0.011
PTV margin AP	7.904	0.006	−0.099	0.057	0.08	−0.213	0.0138

PTV: Planning target volume, ML: Mediolateral, CC: Craniocaudal, AP: Antero-posterior, CI: Confidence interval, SE: Standard error any directions is maintained in a narrower range (<±0.25 cm) than RC.

DISCUSSION

Delivery of planned radiotherapy dose in a precise and accurate manner is highly important in high precision radiotherapy. A significant reduction in local tumor control results from even small (7–15%) changes in dose leading to recommendations by the ICRU suggesting accuracy in dose delivery to be ± 5%.[6] Therefore, proper positioning and immobilization is extremely important especially for precision radiotherapy. Careful verification of the setup and accurate delivery of radiation is an integral part of high precision radiotherapy in head and neck cancer because of proximity to several critical structures.

In the literature different weightage of systematic and random errors have been proposed to calculate the CTV to PTV margin to compensate the setup errors. It is important that each institute should have their own protocol based on the measurements of geometric uncertainties of treatment delivery. This study aims at exploration of set up errors that occurs with different immobilization devices in head and neck region currently in vogue using electronic portal imaging and to evaluate the accuracy and adequacy of the margin growing protocol. This data represents our experience of setup verification before cone beam CT scan was introduced in high precision radiotherapy in our institute. This may still be relevant for centers using electronic portal imaging for set up verification based on bony landmarks.

In case of head and neck radiotherapy BL (with or without the alpha cradle) was found to be the superior immobilization device than RC with statistically significant lower total, systematic and random error. The total error in ML direction was 1.00 mm versus 1.39 mm (P = 0.03), systematic error 0.09 cm versus 0.197 cm and random error 0.116 cm versus 0.258 cm (F-test, P = 0.001). CTV to PTV margin was significantly lower in BL (0.26 cm vs. 0.57 cm, P < 0.05). In CC direction, BL system had lower total error (0.075 cm vs. 0.157 cm) and a significantly less systematic error (0.116 cm vs. 0.258 cm, F = 7.149,

Table 4: Effect of additional alpha cradle with BL (in cm)

	CTV-PTV margin (cm)				
	Systematic error (∑)	Random error (σ)	ICRU 62*	Stroom's**	Van Herk's***
All patients					
ML	0.093	0.116	0.1742	0.2672	0.3137
CC	0.116	0.166	0.2322	0.3482	0.4062
AP	0.139	0.139	0.2363	0.3753	0.4448
BL only					
ML	0.163	0.140	0.261	0.424	0.505
CC	0.143	0.187	0.274	0.417	0.489
AP	0.151	0.133	0.243	0.394	0.47
With alpha cradle					
ML	0.0379	0.077	0.091	0.128	0.146
CC	0.0324	0.136	0.127	0.16	0.176
AP	0.083	0.1498	0.187	0.270	0.312

CTV-PTV margin: *ICRU (∑ +0.7×σ), **Stroom's formula (2×∑ +0.7×σ), ***Van Herk's formula (2.5×∑ +0.7×σ). CTV: Clinical target volume, PTV: Planning target volume, ML: Mediolateral, CC: Craniocaudal, AP: Antero-posterior, ICRU: International Commission of Radiation Units, BL: BrainLAB

Table 5: CTV-PTV margin: BL immobilization with and without alpha cradle

Parameter	Levene's test for equality of variance		*t*-test for equality of means				
	F	Significant	Mean difference	SE of difference	P	95% CI of the difference	
						Lower	Upper
PTV margin ML	26.709	<0.001	−0.221	0.0352	<0.001	−0.292	−0.151
PTV margin CC	49.65	<0.001	−0.1047	0.05247	0.050	−0.2097	0.0002
PTV margin AP	26.629	<0.001	0.3139	0.0528	<0.001	0.209	0.419

CTV: Clinical target volume, PTV: Planning target volume, ML: Mediolateral, CC: Craniocaudal, AP: Antero-posterior, CI: Confidence interval, SE: Standard error, BL: BrainLAB

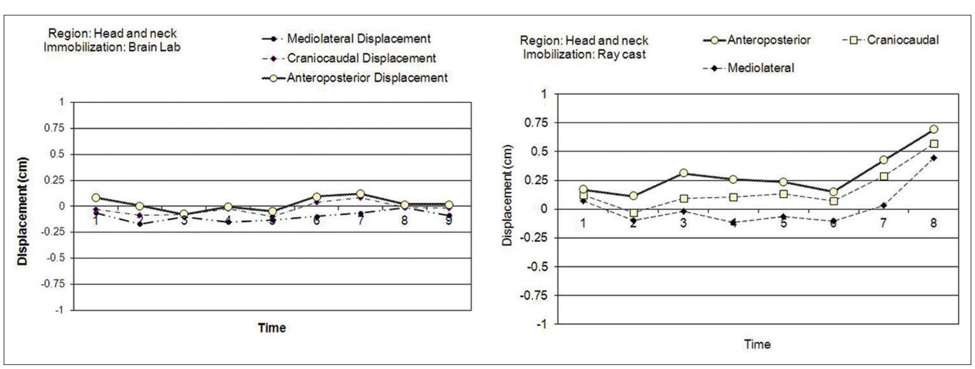

Figure 2: Time trend analysis over the entire treatment period

P = 0.015). CTV to PTV margin was less in BL than RC in CC direction (0.34 cm vs. 0.92 cm, P = 0.06). Similarly in AP direction, total, systematic and random errors were less in BL than RC. CTV to PTV margin calculated was also less with BL (0.37 cm vs. 0.57 cm, P = 0.08, NS). Time trend analysis showed BL to be superior to RC where the displacement in all directions is maintained within a narrower range (<±0.25 cm) than RC (0.75–0.25 cm).

The setup errors of various immobilization devices have been compared in the literature. One randomized trial has compared the accuracy of two types of thermoplastic masks which did not show statistically significant differences between the groups (head mask [HM] or head shoulder mask [HSM]) in terms of reproducibility. Patients using HSM experienced significantly more claustrophobia (P = 0.023). Patients allocated to HSM receiving >60 Gy were found to have more skin reactions. The smaller HM reduced feelings of claustrophobia, as well as skin reactions, for patients receiving >60 Gy. The smaller mask did not compromise the reproducibility of the setup.[8] In a study, comparing the Vogel-Bel-Hohner head fixation device and thermoplastic mask Sweeney *et al.*, observed that repositioning accuracy in various immobilization devices in head and neck could range between 0.6 and 3.5 mm.[9] Hurkmans *et al.*, reported EIPD based systematic and random errors between 1.5 and 2mm in head and neck region.[2] Jensen *et al.* compared Scotchcast and thermoplastic head and shoulder immobilization system and found that both the immobilization device had errors of 2.1 mm (Scotchcast) and 2.9 mm (thermoplastic masks) in 6 degrees of freedom (DOF) and 3.9–3.0 mm in 3 DOF respectively.[10] Georg *et al.* compared head fixation alone and head with neck fixation in BL immobilization systems. He found that the repositioning variations of systematic error was same in both the mask, but the random error was slightly more in the head with neck fixation compared with head fixation BL system.[11]

CONCLUSION

EPID is an effective tool for determination of total, systematic and random errors of different immobilization devices. Total, systematic, random errors and CTV to PTV margin of various immobilization devices varies with directions. In head and neck region, when EPID based verification is used, for BL margins ranged from 2.6 to 3.7 mm. With the addition of alpha cradle margins reduced to from 0.76 to 2.1 mm. For RC in the PTV margin was 5.7–9.2 mm. Therefore, a margin of 3 mm for BL and 5–10 mm for RC with online correction in head and neck is adequate.

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Conflicts of interest

There are no conflicts of interest.

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