

Study of inter-fraction movements of tongue during radiation therapy in cases of tongue malignancy using volumetric cone beam computed tomography (CBCT) imaging

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Original Article

Abstract

Purpose: Tongue is a mobile organ in head and neck region predisposing it for geographic miss during the course of fractionated radiotherapy for tongue malignancy. This study analyses movement of tongue during the course of radiotherapy using volumetric KV-cone beam computed tomography (KV-CBCT) imaging for patients of tongue malignancy treated without using tongue bite. **Methods:** We analysed 100 KV-cone beam CTs performed on 10 patients with carcinoma of tongue undergoing fractionated radiotherapy. All the patients underwent thermoplastic mask immobilisation and CT simulation. During the course of radiotherapy, all patients underwent volumetric KV-CBCT imaging to assess the movements of tongue. Five arbitrary reference points were used to analyse the movements of tongue in 3-dimensions: 1) Point A: Tip of tongue; 2) Point B: Point over right lateral border, 4 cm posterior to the tip of tongue; 3) Point C: Point over left lateral border, 4 cm posterior to the tip of tongue; 4) Point D: Point over superior most part (dorsum) of tongue, 4 cm posterior to the tip of tongue; 5) Point E: Point over the surface of base of tongue at the level of tip of epiglottis. **Results:** Mean movements of point A: +0.21 cm (SD: 0.12) and -0.23 cm (SD: 0.14), point B: +0.14 cm (SD: 0.04) and -0.19 cm (SD: 0.1), point C: +0.12 cm (SD: 0.05) and -0.14 cm (SD: 0.06), point D: +0.15 cm (SD: 0.07) and -0.29 cm (SD: 0.22) and point E: +0.23 cm (SD: 0.15) and -0.23 cm (SD: 0.14). **Conclusion:** Organ movement is one of the great challenges encountered during radiotherapy. Tongue is one such organ in head and neck region. Concept of internal target volume (ITV) margin which takes into account the internal organ movements should be considered for tongue malignancies. ITV to PTV margin will depend on the setup accuracy, immobilization device and imaging modality utilised for setup verification. In an IGRT (Image Guided Radio Therapy) setup, a PTV margin of 0.3 to 0.5 cm from ITV would be safe.

Keywords: Inter-Fraction Movements; Tongue; CBCT; PTV Margins

Introduction

Tongue is a mobile organ in head and neck region. Hence, chances of random error pertaining to the position of tongue during the course of fractionated radiotherapy are high. PTV margin takes into account the positional and dosimetric uncertainties during the course of treatment.¹ Many institutions use immobilisation devices for tongue such as mouth bite to reduce tongue movements.² The possible problems of using tongue bite include patient discomfort and chances of secondary infections if the tongue bite is not properly sterilised.

PTV for tongue malignancy depends upon the type of immobilisation device used, image verification technology uti-

lised for checking patient setup, frequency of image verification and reproducibility of patient setup accuracy. Unlike orthogonal planar image verification techniques where only bone anatomy is matched before the treatment, KV-cone beam CT (KV-CBCT)³ with on board imager (OBI) can give soft tissue volumetric images of patient which can be used to check for internal organ match with respect to reference planning (simulation) CT images. Various studies have been conducted to analyse the internal organ movements using image guided radiotherapy (IGRT) for prostate^{4,5,6}, lung^{7,8,9}, oesophagus^{10,11}, liver^{12,13} and pancreas^{14,15}. There is a scarcity of studies and literature on volumetric 3-dimensional inter-

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nal organ movements of tongue for patients with tongue malignancy undergoing radiotherapy.

Kapanen *et al.*¹⁶ performed a study on estimation of adequate setup margins and threshold for position errors requiring attention in head and neck cancer radiotherapy based on 2-D image guidance using orthogonal kilo-voltage (kV) x-ray images. Suzuki *et al.*¹⁷ performed analysis of inter-fractional errors and intra-fractional organ motions during IMRT for head and neck tumors to define an appropriate PTV and planning organ at risk (PRV) margins based on orthogonal images.

With this background, we conducted a study to analyse movements of tongue during the course of radiation therapy using volumetric KV-CBCT imaging technique for patients of tongue malignancy treated without using tongue bite. The reasons for avoiding the use of tongue bite in this study were to prevent secondary infection and patient discomfort. We

also intended to see whether PTV margin of 0.5 cm for tongue is sufficient in an IGRT setting using daily cone beam CT (CBCT).

Methods and Materials

Patient characteristics

This study retrospectively analysed 100 KV-cone beam CTs performed on 10 patients with carcinoma of tongue undergoing fractionated radiotherapy. These patients included 5 post-operative cases requiring adjuvant radiotherapy^{18,19} and 5 cases requiring radical radiotherapy which were deemed surgically/medically inoperable by the surgeon. 6 cases received concurrent chemotherapy with Cisplatin under the care of Medical Oncologist. The average age of the patients was 51.5 years (range 38 years to 66 years). All the patients had ECOG 1 performance status.²⁰ Eight of them were males and two were females (**Table 1**).

TABLE 1: Patient characteristics.

S. No	Age (yrs)	Sex	ECOG PS	TNM stage	Post-operative (PO) / radical RT	Concurrent chemotherapy
1	47	Male	1	cT2 N2b M0	Radical RT	Yes
2	52	Male	1	cT2 N1 M0	Radical RT	Yes
3	55	Male	1	cT2 N2b M0	Radical RT	Yes
4	66	Female	1	cT3 N1 M0	Radical RT	Yes
5	61	Male	1	cT4 N2c M0	Radical RT	Yes
6	57	Male	1	pT2 N2b M0	PO RT	No
7	40	Female	1	pT2 N1 M0	PO RT	No
8	38	Male	1	pT2 N1 M0	PO RT	No
9	56	Male	1	pT2 N2a M0	PO RT	No
10	43	Male	1	pT2 N2b M0	PO RT	Yes

TABLE 2: Radiation dose-fractionation.

Indication	
Radical	Adjuvant (post-operative)
PTV-66: 66 Gy in 33 fractions	PTV-60: 60 Gy in 30 fractions
PTV-59.4: 59.4 Gy in 33 fractions	PTV-54: 54 Gy in 30 fractions
PTV-54: 54 Gy in 33 fractions	

Immobilization, simulation and planning

All the patients included in this study underwent Civco thermoplastic mask immobilisation with neck in neutral position resting on a neck rest. Thermoplastic mask and the neck rest were registered with the head and neck carbon fibre base plate on flat carbon fibre CT simulator table top. CT simulation was performed with 2.5 mm CT slice thickness on a GE-Discovery 16 slice CT-simulator. Tongue bite was not used for any of these patients. Moving lasers were used to put treatment isocenter using ADW work station. Images were imported in DICOM format into the Eclipse treatment planning system. Contouring of target volumes based on ICRU recommendations^{1, 21} and organs at risk (OAR) based on standard guidelines were performed. A symmetric PTV margin of 0.5 cm was used for tongue (pri-

mary) and nodal target in order to reduce chances of geographic miss. Treatment planning was performed using Eclipse version 10.0 software (Varian Medical Systems, Palo Alto, CA, United States). All the patients were treated on True Beam Linear Accelerator (Varian Medical Systems, Palo Alto, CA, United States) with volumetric modulated arc therapy (VMAT) using simultaneous integrated boost (SIB) technique.^{22, 23} All the patients were planned with two co-planar 360 degree arcs using 6 MV photon beam. Dose prescription utilised is mentioned in **Table 2**.

Setup verification and tongue movement analysis

During the course of radiation therapy, all the patients underwent daily volumetric KV-CBCT imaging to check for setup errors and assess the movements of tongue with refer-

ence to the simulation CT images. Five reference points were used to analyse the inter-fraction movements of tongue in three dimensions (**Figure 1**):

- 1) Point A: Tip of the tongue.
- 2) Point B: Point over the right lateral border, 4 cm posterior to the tip of the tongue.
- 3) Point C: Point over the left lateral border, 4 cm posterior to the tip of the tongue.
- 4) Point D: Point over the superior most part (dorsum) of tongue, 4 cm posterior to the tip of tongue.

5) Point E: Point over the surface of base of tongue at the level of tip of epiglottis.

Point A represents movement of tongue in antero-posterior (AP) direction, point B and C represent movements in right lateral (RL) and left lateral (LL) directions respectively, point D represents movement in supero-inferior (SI) direction and point E represents movement of base of tongue in AP direction.

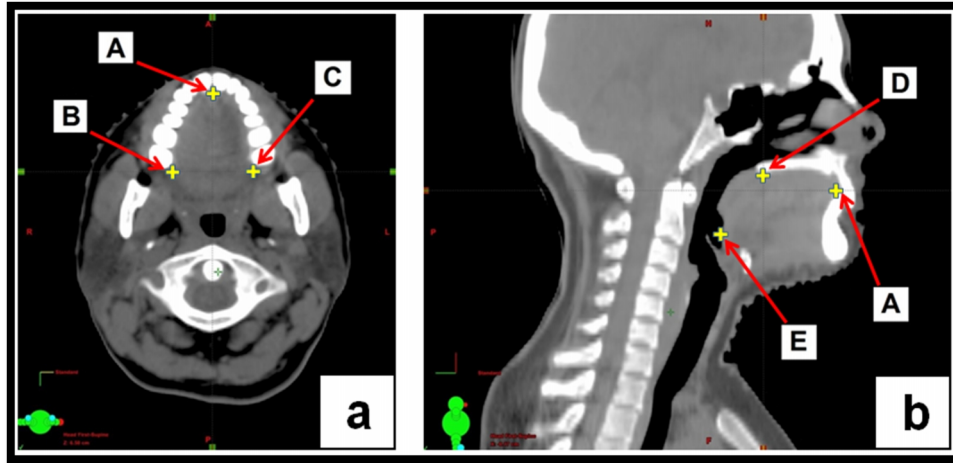


FIG. 1: Showing axial simulation CT slice at the level of tip of tongue showing reference points: A, B and C (a) and sagittal view showing reference points: A, D and E (b).



FIG. 2: Axial, sagittal and coronal simulation CT images and Cone Beam CT images overlay for image guidance before treatment using “moving window” tool.

In this study, we have taken 5 arbitrary reference points related to the tongue in such a way that they could be easily localized on KV-CBCT so that good localization reproducibility can be maintained. The quality of KV-CBCT image performed on True Beam Linear Accelerator is close to diagnostic CT and tongue is very nicely discernible on KV-CBCT images.

Daily treatment was performed by matching the bones on KV-cone beam CT with the simulation CT (**Figure 2**). 100 consecutive bone matched cone beam CTs were analysed for 10 patients to determine the 3-dimensional variation in the position of tongue (residual positioning error) using the 5 anatomical reference points. Movement of reference point towards the PTV (outward movement) was given +ve sign and movement in the opposite direction (inward movement) was given -ve sign. Nil variation of the reference point was denoted by a value of zero (0) shift. The main objective of this study is to find the residual movements of tongue (inter-fraction) after bone based registration is done so as to derive a safe PTV margin for tongue. And for this very reason, 5 reference points located on the surface of tongue which are easily discernible are reasonable to assess the tongue movements in 3 dimensions.

Patients were instructed to keep the tongue still during pre-treatment CBCT and while the treatment is going on, in

order to avoid intra-fraction movements. Tongue movements are voluntary and hence if patient keeps it still during CBCT and treatment, intra-fraction movement is negligible.

Statistical analysis

“Student’s t-test” was performed using SAS (Statistical Analysis Software) version 9.3 for determination of *p*-values.

Results

100 bone matched KV-CBCTs were analysed to determine movements of tongue in 3 dimensions represented by 5 reference points (**Table 3, Figure 3**). Mean movements of point A representing movements of tip of tongue in AP direction were +0.214 cm (SD: 0.124) and -0.234 (SD: 0.145), point B representing right lateral border of tongue movements in RL (right lateral) direction were +0.14 cm (SD: 0.045) and -0.19 cm (SD: 0.1), point C representing left lateral border of tongue movements in LL (left lateral) direction were +0.121 cm (SD: 0.051) and -0.146 cm (SD: 0.06), point D representing dorsum of tongue movements in SI (supero-inferior) direction were +0.155 cm (SD: 0.071) and -0.291 cm (SD: 0.222) and point E representing base of tongue movements in AP direction were +0.236 cm (SD: 0.152) and -0.236 cm (SD: 0.14).

TABLE 3: Movements of 5 reference points as analysed on 100 CBCTs.

Point location	Average movement (SD) = (all +ve) + (all -ve) + (all zero) divided by 100.	Average absolute movement (SD) = All absolute values (neglecting +ve or -ve sign) divided by 100.	Average +ve movement (SD)	Average -ve movement (SD)	Range of movement	Frequency of all absolute readings (irrespective of +ve or -ve sign)					
						<1 mm (%)	1-2 mm (%)	2-3 mm (%)	3-4 mm (%)	4-5 mm (%)	>5 mm (%)
A	0.029 cm (0.201)	0.137 cm (0.149)	0.214 cm (0.124)	(-)0.234 cm (0.145)	(+)0.5 to (-)0.7 cm	55%	20%	9%	11%	4%	1%
B	0.022 cm (0.106)	0.064 cm (0.087)	0.14 cm (0.045)	(-)0.19 cm (0.1)	(+)0.22 to (-)0.39 cm	74%	16%	8%	2%	0%	0%
C	(-)0.020 cm (0.1)	0.064 cm (0.079)	0.121 cm (0.051)	(-)0.146 cm (0.060)	(+)0.3 to (-)0.34 cm	78%	16%	5%	1%	0%	0%
D	(-)0.019 cm (0.225)	0.149 cm (0.169)	0.155 cm (0.071)	(-)0.291 cm (0.222)	(+)0.38 to (-)0.8 cm	56%	22%	10%	4%	3%	5%
E	0.047 cm (0.248)	0.194 cm (0.161)	0.236 cm (0.152)	(-)0.236 cm (0.140)	(+)0.9 to (-)0.52 cm	36%	28%	15%	11%	8%	2%
P-value	-	0.0087	0.0014	0.0008	-	0.0014	0.0008	0.0045	0.0562	0.1132	0.1596

TABLE 4: Frequency of displacement of 5 reference points for various ranges of movement.

	Point location	A	B	C	D	E	P-Value
MOVEMENTS WITH +ve SIGN	Total number of +ve readings out of 100 readings	39	31	18	42	51	0.0029
	Frequency of reading for range 1-2 mm movement (%)	25 (25/39×100=64.1%)	26 (26/31×100=83.8%)	17 (17/18×100=94.4%)	32 (32/42×100=76.1%)	29 (29/51×100=56.8%)	0.0005
	Frequency of reading for range 2-3 mm movement (%)	4 (4/39×100=10.25%)	5 (5/31×100=16.1%)	1 (1/18×100=5.55%)	8 (8/42×100=19.0%)	10 (10/51×100=19.6%)	0.0234
	Frequency of reading for range 3-4 mm movement (%)	6 (6/39×100=15.38%)	0	0	2 (2/42×100=4.76%)	6 (6/51×100=11.76%)	0.1079
	Frequency of reading for range 4-5 mm movement (%)	4 (4/39×100=10.25%)	0	0	0	5 (5/51×100=9.8%)	0.1813
	Frequency of reading for range >5 mm movement (%)	0	0	0	0	1 (1/51×100=1.96%)	0.3739
	Total number of -ve readings out of 100 readings	23	11	29	29	31	0.0025
MOVEMENTS WITH -ve SIGN	Frequency of reading for range 1-2 mm movement (%)	14 (14/23×100=60.8%)	8 (8/11×100=72.7%)	25 (25/29×100=86.2%)	17 (17/29×100=58.6%)	17 (17/31×100=54.8%)	0.0041
	Frequency of reading for range 2-3 mm movement (%)	2 (2/23×100=8.69%)	1 (1/11×100=9.09%)	3 (3/29×100=10.3%)	2 (2/29×100=6.89%)	5 (5/31×100=16.1%)	0.0186
	Frequency of reading for range 3-4 mm movement (%)	6 (6/23×100=26.0%)	2 (2/11×100=18.1%)	1 (1/29×100=3.44%)	2 (2/29×100=6.89%)	5 (5/31×100=16.1%)	0.0299
	Frequency of reading for range 4-5 mm movement (%)	0	0	0	3 (3/29×100=10.34%)	3 (3/31×100=9.67%)	0.1778
	Frequency of reading for range >5 mm movement (%)	1 (1/23×100=4.34%)	0	0	5 (5/29×100=17.24%)	1 (1/31×100=3.22%)	0.2056
	Frequency of nil movements out of 100 readings	38	58	53	29	18	0.0061

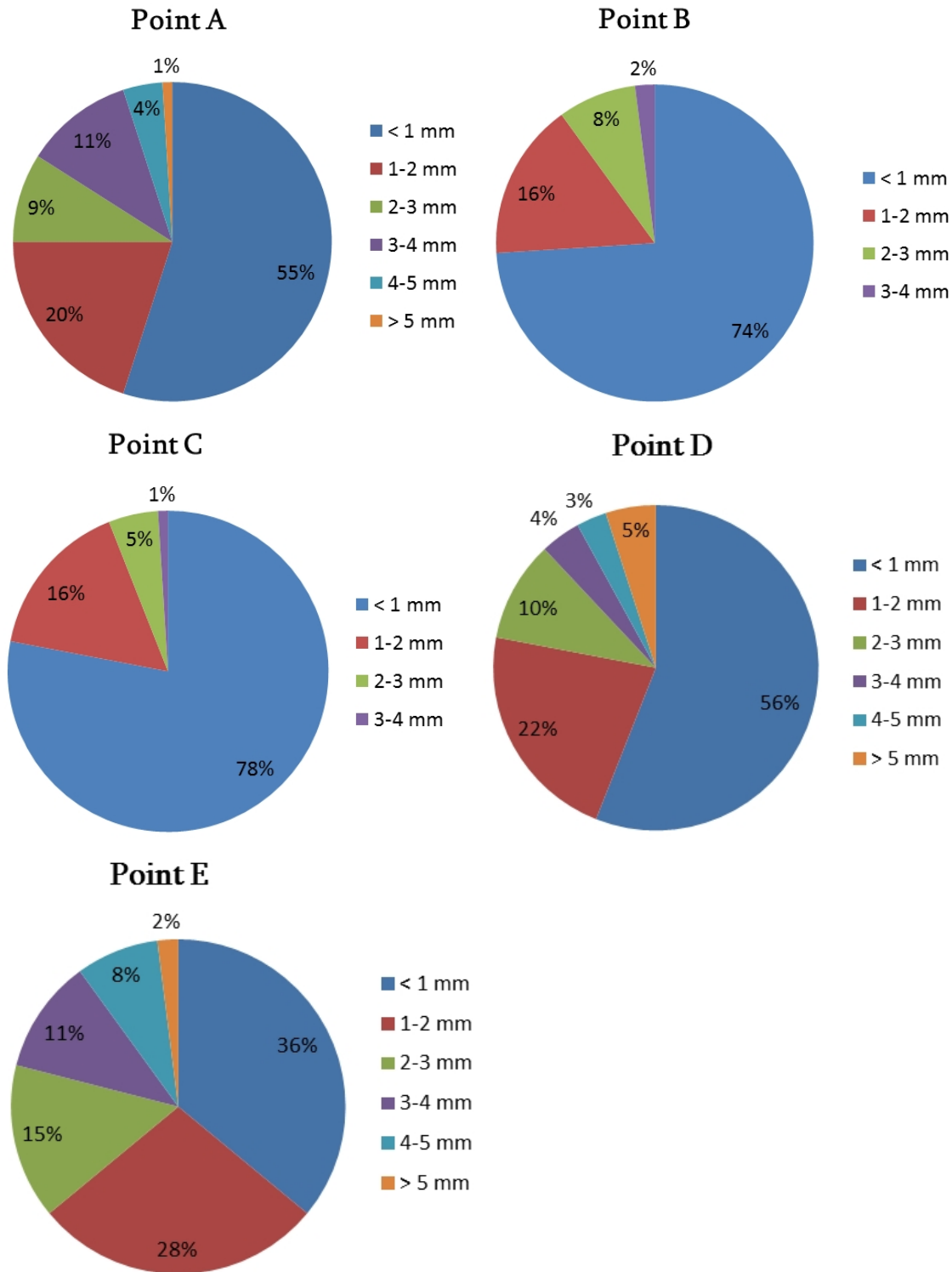


FIG. 3: Pie chart description of the movements of 5 reference points as analysed on 100 CBCTs.

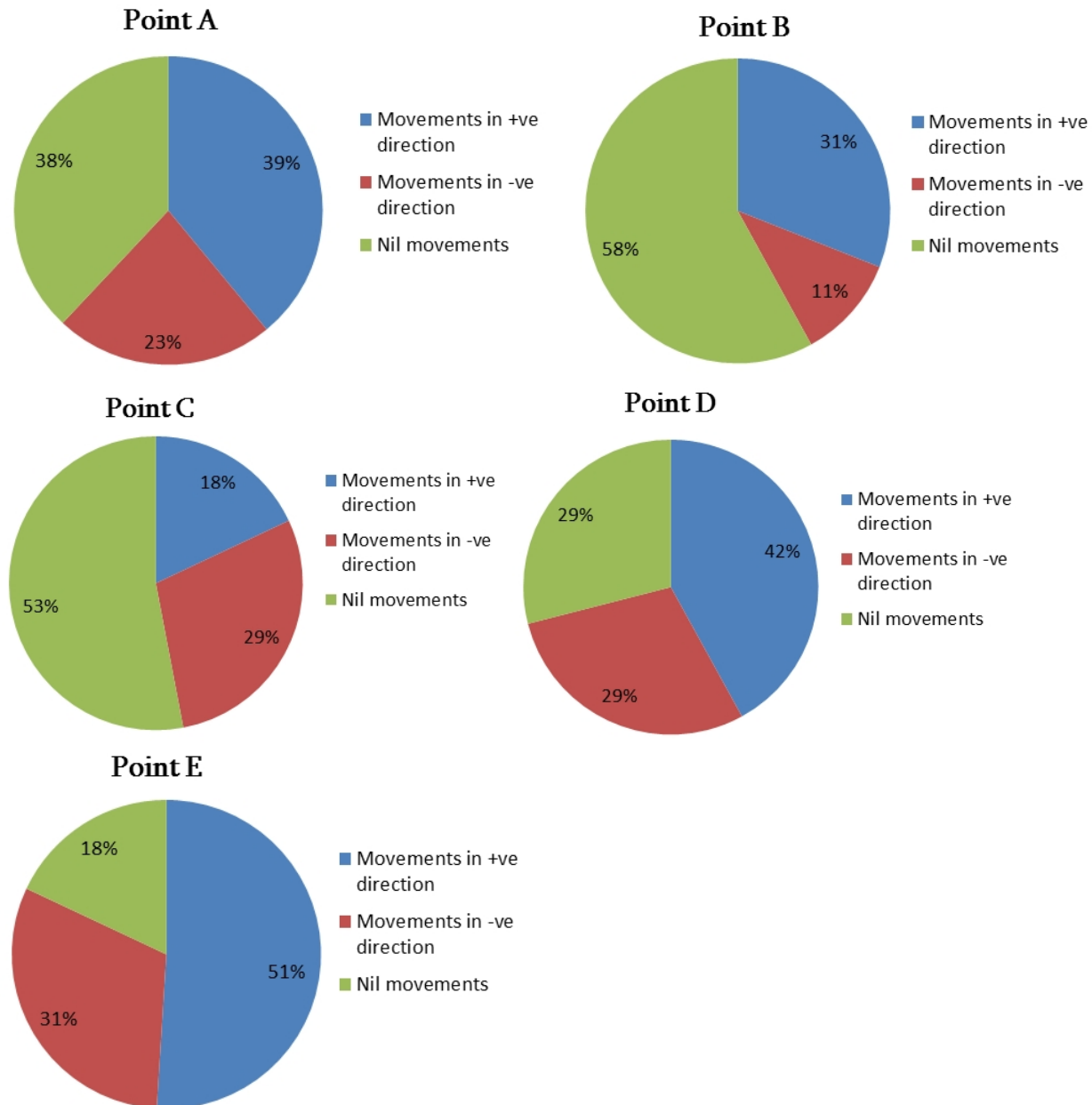


FIG. 4: Pie chart description of frequency of displacement of 5 reference points as analysed on 100 CBCTs.

Out of 100 KV-CBCTs analysed for each point (**Table 4, Figure 4**), point A showed movements in positive direction 39 times, negative direction 23 times and nil movements 38 times. Point B showed movements in positive direction 31 times, negative direction 11 times and nil movements 58 times. Point C showed movements in positive direction 18 times, negative direction 29 times and nil movements 53 times. Point D showed movements in positive direction 42 times, negative direction 29 times and nil movements 29 times. Point E showed movements in positive direction 51 times, negative direction 31 times and nil movements 18 times. **Table 4** shows frequency of 5 reference point displacements for various ranges of movements. Maximum

range of movements were noticed for point A with a range of +0.5 cm to -0.7 cm, point D with a range of +0.38 to -0.8 and point E showing range of +0.9 cm to -0.52 cm (**Table 3**). Points B and C rarely showed movements more than 0.3 cm. Displacement of more than +0.5 cm (PTV margin) carries risk of target geometric miss meriting immediate attention. In this study, only once we noticed a reading (+0.9 cm for point E) showing a displacement value of more than +0.5 cm. However displacement of more than 0.5 cm in negative direction (inward displacement) represented by -ve sign was noticed once for point A, 5 times for point D and once for point E. Since the displacement is in -ve direction, there is no risk of target geometric miss. It was noticed that tongue

shows asymmetric movements in different directions represented by 5 reference points. The variation of differential average positive movements for 5 reference points as mentioned in **Table 3** showed a statistically significant *p*-value of 0.0014. Hence, asymmetric margins from CTV tongue should be considered to generate an internal target volume (ITV) tongue in order to avoid chances of geographic miss due to internal movements of tongue. Coverage of 95% of tongue mobility would therefore require an asymmetric ITV margin of 0.338 cm anteriorly, 0.185 cm in right lateral direction, 0.172 cm in left lateral direction, 0.226 cm in superior direction and 0.388 cm in posterior direction. ITV can be further expanded to generate a PTV to account for daily setup errors and dosimetric uncertainties.

Discussion

Organ motion is one of the great challenges encountered during the course of radiotherapy. Tongue is one such organ in head and neck region which is prone for internal movements, increasing probability of geographical miss.

It is very important for the scientific community to address the issue of tongue movements as not much work has been done so far and majority of head and neck cancers are tongue primaries. Although it is a good approach to study organ movement during fractionated radiotherapy using implanted radio-opaque fiducial markers (like prostate, liver and pancreas), it is not feasible to implant fiducials in tongue for such study. Hence good quality KV-CBCT is a reasonable approach towards this direction for tongue movements.

Concept of internal target volume (ITV) margin takes into account the organ movements in all directions such that the clinical target volume (CTV) is always encompassed by the ITV contour.²¹ Similar to studies performed for inter-fraction organ motion assessment of prostate^{4,5,6} and oesophagus,^{10,11} this study aimed to assess inter-fraction tongue movements during radiotherapy in order to find out an adequate ITV margin for tongue. ITV to PTV margin will depend on the setup accuracy, immobilization device and imaging modality utilised for patient setup verification. It may vary from institution to institution. In an IGRT setup, a PTV margin of 0.3 to 0.5 cm from ITV would be safe.^{17,24} Movements with +ve sign (displacement towards PTV) needs more attention as it increases chances of geographic miss. To our knowledge, this is the first manuscript to report internal organ motion of tongue in cases of tongue malignancy undergoing radiotherapy.

Our data indicates that tongue is prone for asymmetric movements in different directions especially when mouth bites are not used. There are no studies available which have compared internal organ motion of tongue “with” versus “without” the use of tongue bite. Asselen *et al.*²⁵ studied intrafraction laryngeal movements for 10 laryngeal cancer

patients on radiotherapy using amorphous silicon flat panel imager. They used tip of epiglottis as an anatomical landmark to quantify the movements. The reported deviation of tip of epiglottis (peak to peak) ranged 0.63-0.7 mm in AP direction and 0.3-11.5 mm in cranio-caudal direction. The maximum degree of laryngeal movement due to swallowing was reported to be >20 mm in cranio-caudal direction but the incidence of this event was quite low (only 0.45% of irradiation time). Therefore it was concluded that swallowing induced laryngeal movements does not warrant any change of PTV margins or need for any internal margin.

Suzuki *et al.*¹⁷ studied inter-fractional setup errors and intra-fractional organ motion using x-ray simulator on 22 head and neck patients to quantify adequate PTV margin and planning organ at risk volume (PRV) margin. They concluded that 0.5 cm PTV margin and 0.3 cm PRV margin is adequate in head and neck IMRT. Zhang *et al.*² have performed analysis of setup uncertainties using multiple regions-of-interest in head and neck cancer using CT-on-rails.

KV-Cone Beam CT is an excellent tool for organ movement study for patients on fractionated radiotherapy with IGRT. CBCT was first introduced by Jaffray *et al.*³ which deeply impacted the quality of IGRT. Qi *et al.*²⁶ studied 3 CT based on board image guidance modalities (MV-CBCT, KV-CBCT and MV-Fan Beam CT) for assessment of setup errors in head and neck IMRT. They concluded that larger margins of 6.9 mm to 8.9 mm may be appropriate for MV-FBCT and MV-CBCT respectively compared to a smaller margin of 5.6 mm for KV-CBCT. The limitations of our study include:

- 1) Treatment without tongue bite may increase dose to palate.
- 2) Uncooperative patients are not suitable as they may not be able to avoid voluntary tongue movements during imaging and treatment.
- 3) Presence of metallic dental prosthesis/filling may introduce artefact and hamper identification-localization of tongue reference points.
- 4) Bulky exophytic growth over the tongue surface if overlaps with the region of reference points, may give additional shift of reference point due to significant tumor regression during treatment.

Although a small number of patient population limits our study, a total of 100 KV-CBCTs were evaluated for 5 reference points (500 readings). This study supports the use of a relatively larger (0.5-0.7 cm in anterior, posterior and superior direction) and asymmetric PTV margins for tongue malignancy as compared to other anatomical sites in head and neck malignancies especially in view of potential inter-fraction mobility of tongue during radiotherapy. Margins of 0.5 cm towards left and right lateral direction can be considered safe. Application of an ITV concept²¹ can be considered, wherein an asymmetric margin of 0.338 (≈ 0.4 cm) anteriorly, 0.185 cm (≈ 0.2 cm) in right lateral direction,

0.172 cm (\approx 0.2 cm) in left lateral direction, 0.226 cm (\approx 0.3 cm) in superior direction and 0.388 cm (\approx 0.4 cm) in posterior direction. PTV expansion of 0.3 cm from ITV can be safe in an IGRT setting with KV-CBCT.^{17,24}

Conclusion

Organ movement is one of the great challenges encountered during radiotherapy. Tongue is one such organ in head and neck region. Tongue is prone for asymmetric movements in 3 dimensions. Concept of internal target volume (ITV) margin which takes into account the internal organ movements should be considered for tongue malignancies. ITV to PTV margin will depend on the setup accuracy, immobilization device and imaging modality utilised for setup verification. In an IGRT setup, a PTV margin of 0.3 cm from ITV would be safe.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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