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Research Paper

Target delineation error assessment for patients treated to the larynx with VMAT: a quantitative study performed at a local Maltese radiotherapy department.

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Abstract

Introduction: Target volume delineation error ($\sum_{delin}$) affects the accuracy of radiation therapy, but it is often not incorporated in studies measuring the Planning Target Volume (PTV) margin. The aim of this study was to assess the impact of $\sum_{delin}$ on the PTV margin for patients receiving treatment with Volumetric-Modulated Arc Therapy (VMAT) to the larynx in a radiotherapy department.

Methods: Six clinical oncologists were asked to delineate the Clinical Target Volume (CTV) of five patients receiving treatment to the larynx with VMAT. Van Herk's formula was used to measure the PTV margin based on target volume delineation error. All data were collected and analysed to measure the $\sum_{delin}$ and the PTV margin.

Results: The PTV margin based on $\sum_{delin}$ was 5.6 mm, 11.1 mm, and 4.5 mm, in the left-right (X), superior-inferior (Y) and anterior-posterior (Z) directions respectively. The standard deviation (SD) in the X and Z direction was 3.47 mm, and the SD in the Y direction was 6.92 mm.

Conclusion: The PTV margin calculated based on the evaluation of $\sum_{delin}$ was considerably larger than the margin currently used (5mm). If the resulting margin was implemented it would increase radiation induced side-effects.

Keywords: $\sum_{delin}$, Target volume delineation error, VMAT, Volumetric-Modulated Arc Therapy, larynx

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1. Introduction

Delivery of radiotherapy within the head and neck region requires high levels of accuracy due to the large number of organs at risk within this region (Malicki, 2012). With the introduction of Volumetric-Modulated Arc Therapy (VMAT) in radiotherapy, higher conformal doses may be applied that require higher accuracy as slight deviations from the original plan may result in mistreatment (Nyarambi, Chamunyonga & Pearce, 2015).

There are many errors and variabilities that can impact the accuracy of treatment delivery, one of the most common sources of errors is target volume delineation variability (Bernstein *et al.*, 2021). Target volume delineation error ($\sum_{delin}$) is the variability in interpreting medical images and contouring protocols resulting in variation in the contouring of the radiotherapy targets (van Herk, Osorio, & Troost, 2019). As such, there is variation in the interpretation of what is considered target resulting in different patients receiving therapeutic doses to different regions depending on this interpretation. Incorrect $\sum_{delin}$ can have a significant consequence, either lowering the probability of tumour control if part of the tumour is not contoured or unnecessary dose to normal tissue if additional areas of normal tissues are included within the target (Kristensen *et al.*, 2017).

According to The Royal College of Radiologists (2021), there are two types of variabilities: interobserver variation – variation among clinicians in delineating the target volume, and intra-observer variation – the mean of the margin outline drawn repeatedly by the same clinician.

Several studies (Bernstein *et al.*, 2021; Dewas *et al.*, 2011; Franco *et al.*, 2018) investigated differences in the delineation of tumour and normal tissues. However, the direct comparison of published data is difficult due to the use of a variety of methods to quantify the $\sum_{delin}$.

The only metric for delineation uncertainty that can be used to calculate the PTV margin is to quantify the $\sum_{delin}$ (Bernstein *et al.*, 2021). $\sum_{delin}$ occurs when the tumour is not properly contoured and this error is then carried over to the treatment phase. This error is considered a "systematic error" because it is created during the treatment planning and repeated in the same direction and magnitude in every treatment (The Royal College of Radiologists, 2021).

Although international studies have evaluated delineation variation for head and neck cancers, including the larynx, there is limited research specifically focusing on local departments. Each radiotherapy centre has unique procedures, protocols, and levels of experience, which can contribute to site-specific variations in target delineation (Lowther, Marsh, & Louwe, 2020). Therefore, it is essential to assess delineation accuracy and variability locally to determine if improvements can be made. By comparing local data to published international studies, this study aims to evaluate the interobserver variation in the delineation of laryngeal cancer at the local oncology department, where such data have not previously been collected. This comparison can help assess whether there is room for improvement in local practices and whether VMAT's dosimetric benefits are being fully utilised.

The aim of this study was to calculate $\sum_{delin}$ in patients receiving VMAT treatment to the larynx in a local radiotherapy department and assess its impact on the PTV margin size. This research will also help identify potential areas for standardisation and improvement in delineation practices, both locally and in comparison to global findings.

2. Methods

2.1. Research design

This study had a quantitative and prospective research design. A quantitative approach was necessary since the aim was to quantify the variation in target contouring. The study had to be done prospectively since the hospital required the patient's consent to use their data, thus making it inappropriate to ask patients to provide their images once they finished treatment.

2.2. Patient selection

Patients treated for laryngeal cancer at the local oncology center between June 2021 and May 2022 were eligible for inclusion in the study. Five cases were randomly selected by the intermediary radiographer from patients' that were diagnosed with laryngeal cancer, regardless of the specific subsite (e.g., epiglottis, supraglottis, glottis, or subglottis) or lymph node involvement. Study commenced once ethical approval was obtained (UREC FORM V_15062020 8219)

2.3. Image acquisition and post-processing

All the patients had a contrast-enhanced computed tomography (CT) scan fused with a non-contrast CT scan during CT planning. Table 1 presents the specifications of the CT scanner that was used in the local department. Magnetic Resonance Imaging (MRI) diagnostic scans were also available to aid clinicians in target delineation. However, the MR images were not acquired in the radiotherapy treatment position, therefore the images were not geometrically comparable and could not be co-registered with the planning CT scan.

Table 1. CT Scanner Specifications of the Local Department						
Manufacturer	**Model**	**kV**	**mA**	**Scan rotation**	**Bore aperture**	**Slice thickness**
Canon	Aquilion LB	120	Auto mA (10–600 mA)	Helical	90 cm	2 mm

2.4. Selection of participants

All three oncology higher specialists' trainees (HSTs) and three oncologists specialised in head and neck radiotherapy at the local oncology hospital were invited to participate in this study. The participating clinicians were all considered competent in head and neck target contouring as the target delineation was done routinely as part of their normal work procedures, however all contours done by HSTs have to be peer-reviewed by an oncologist in clinical practice."

2.5. Data collection process

All six participants were asked to manually delineate the CTVs of the five selected patients. These contours were done on a Monaco® HD Treatment Planning System (TPS) (version 5.51) with which the clinicians were familiar to use in the clinical setting. In addition to the CT images, the oncologists and HSTs were also provided with a summary of the medical history to facilitate the delineation process. Since in the local oncology hospital where the study took place no specific delineation guidelines were used to delineate the target the clinicians were instructed to follow any guidelines depending on their preference.

2.6. Data analysis

The approach to evaluating CTV delineation variability was modified to account for outliers in the calculation (Lowther, Marsh, Louwe, 2020). This adjustment was implemented to ensure a more precise reflection of the delineation results achieved by the clinicians within the local department.

2.7. Ethical considerations

This study was approved by the local research ethics committee and written informed consent was obtained from all participants. The selected cases were retrieved and anonymised by an intermediary person at the radiotherapy department where the study was conducted as required by the ethical procedure established for this study

2.8. Data analysis.

All contours for each patient case were superimposed as a single structure set using the Monaco® HD TPS (version 5.51). Six perpendicular measurements were taken at specific points chosen to be visually representative of the variation around the contour on every alternating CT slice when all the clinicians' six delineated contours were visible. The contouring range was measured as the distance taken from the outer to the innermost superimposed contours in the left-right (X), superior-inferior (Y), and anterior-posterior (Z) directions. These measurements were taken on each alternating CT slice. The mean value of the measures was calculated in each direction to represent the data range of contour variation. This data was recorded and analysed using a Microsoft Excel datasheet that was previously validated and tested for reliability.

Data were analysed quantitatively using both descriptive and inferential statistics, with the results of the study being generalised to the target population.

Since the number of clinicians for each case was less than 15, the standard deviation (S) was calculated using the following equation as proposed by Tudor *et al.* (2020):

$$S = \frac{R}{d_2(N)}$$

Where R represents the data range and is calculated by measuring the distance between the inner and outermost contours in each image plane along each axis of interest at a representative point with 'average' observer variation. N represents the sample size, and d_2 is a tabled value that depends on the number of samples in the range. For a sample of six observers, the d_2 value is 2.53 (Tudor *et al.*, 2020).

The SD values from each case were combined by taking the mean value in each direction, representing the systematic error of target volume delineation.

The van Herk formula was used to calculate the PTV margin size based on $\sum_{delin}$. This formula is expressed as:

$M=2.5\Sigma + 0.7\sigma$.

"Σ" represents the SD for the population systematic errors, and "σ" represents the SD for the population random errors. Since $\sum_{delin}$ is purely a systematic error, there is no random error component.

The van Herk formula was considered adequate to achieve this study's goals based on a previous systematic literature review performed by this research team, evaluating the different methods to calculate PTV margins in head and neck cancer patients undergoing VMAT published by this research team (Caruana *et al.*, 2021).

3. Results

3.1. Characteristics of the patients

The characteristics of the patients are summarised in Table 2.

Table 2. Patients' Demographics

Patient' number	Sex	Age	Diagnosis	Tumour Location	Staging and/or Grading	Prescription
1	M	62	SCC	Left glottis	T1a No Mo	5500cGy @275cGy in 20#
2	M	65	SCC	Right vocal cords and anterior commissure	T3 No Mo	6600cGy @275cGy in 30#
3	F	82	SCC	Right vocal cord	T3 No Mo	5500cGy @275cGy in 20#
4	F	45	SCC	Right vocal cord	T1a No Mo	5500cGy @275cGy in 20#
5	M	81	SCC	Glottis and Subglottic involvement	T2 No Mo	5500cGy @275cGy in 20#

SCC = Squamous Cell Carcinoma

F = Female
M = Male

3.2. Delineation variability

Figure 1 shows an example of measurements that were taken for patient study 2 in the coronal plane, respectively. The coronal plane was used to measure the superior and inferior distances, whilst the axial plane was used to measure the anterior, posterior, left and right distances.

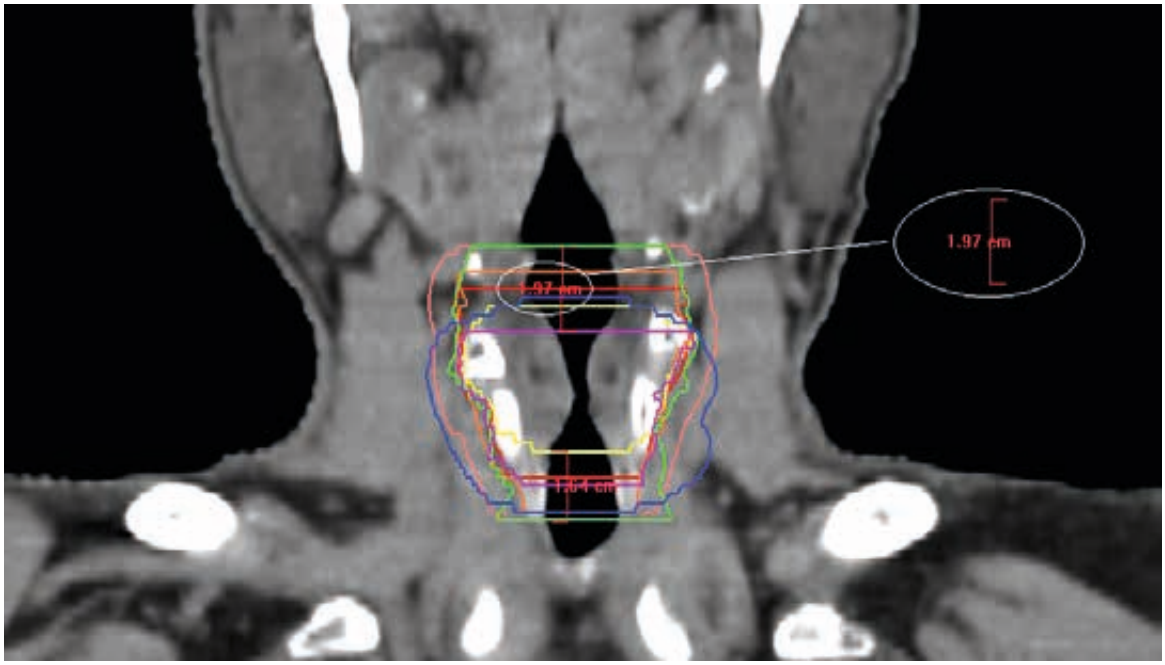
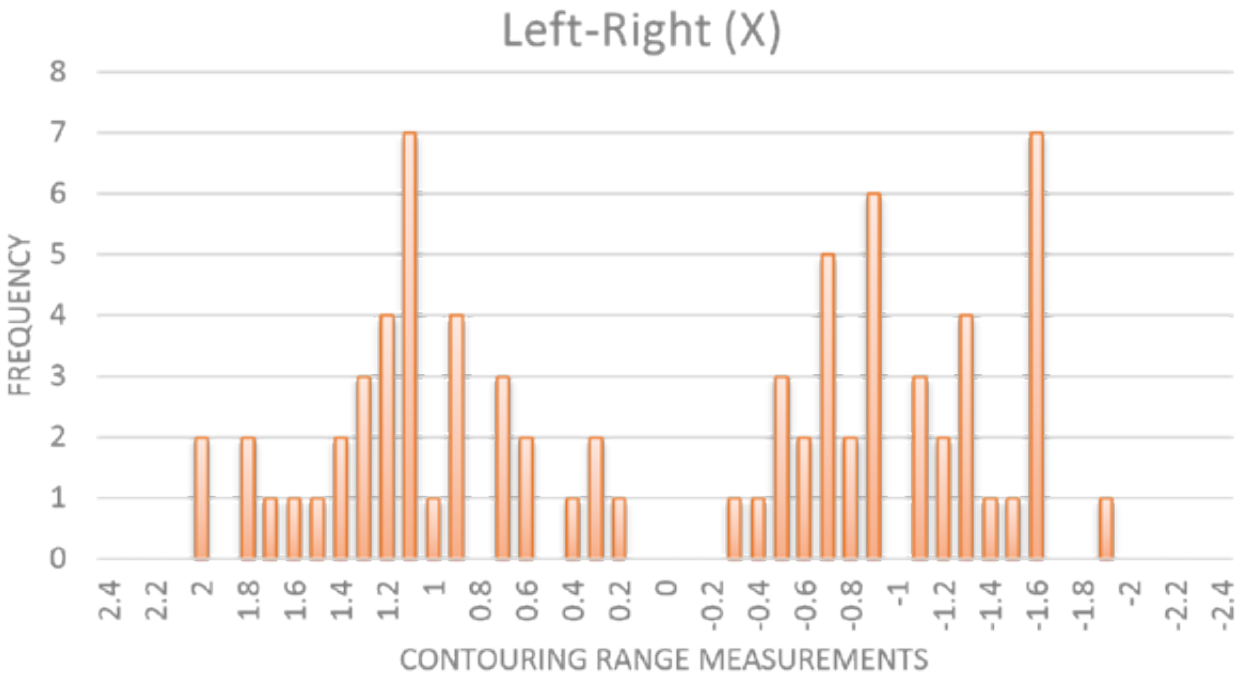
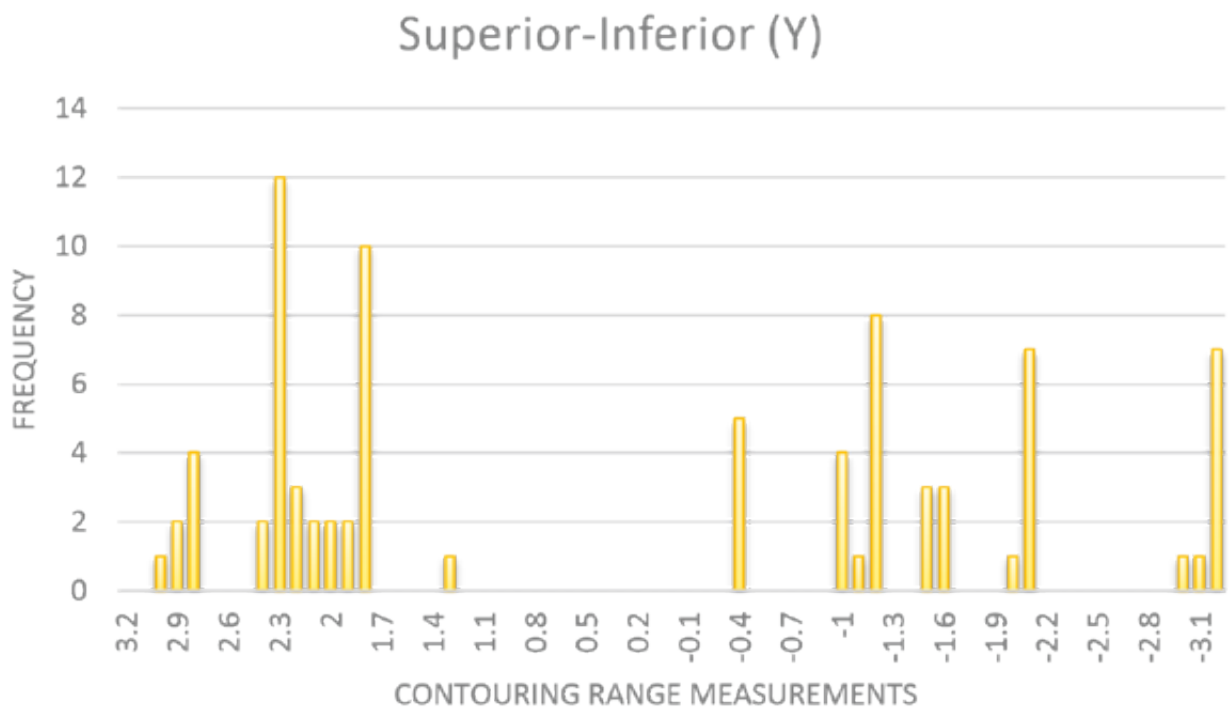


Figure 1: A Demonstration of the Superior and Inferior Measurements of Distances taken in the Coronal Plane.

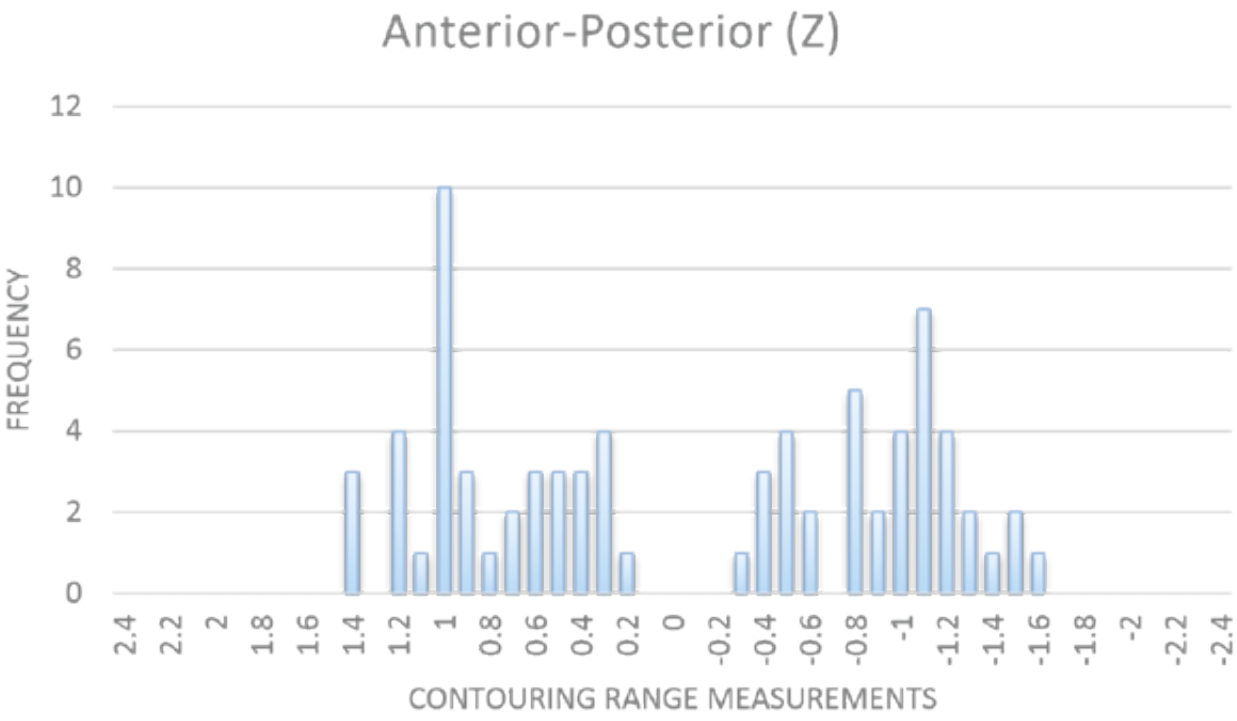
Frequency histograms were plotted to demonstrate the contouring range measurements, presented in Figure 2. a-c.



(a)


Superior-Inferior (Y)
FREQUENCY
14
12
10
8
6
4
2
0
3.2 2.9 2.6 2.3 2 1.7 1.4 1.1 0.8 0.5 0.2 -0.1 -0.4 -0.7 -1 -1.3 -1.6 -1.9 -2.2 -2.5 -2.8 -3.1
CONTOURING RANGE MEASUREMENTS

(b)


Anterior-Posterior (Z)
FREQUENCY
12
10
8
6
4
2
0
2.4 2.2 2 1.8 1.6 1.4 1.2 1 0.8 0.6 0.4 0.2 0 -0.2 -0.4 -0.6 -0.8 -1 -1.2 -1.4 -1.6 -1.8 -2 -2.2 -2.4
CONTOURING RANGE MEASUREMENTS

(c)

Figure 2. Frequency histograms showing the distribution of contouring range measurements (cm) that were taken on each alternating CT slice for all patients in the sample. a) Left-Right (X) $\sum_{delin}$. b) Superior-Inferior (Y) $\sum_{delin}$. c) Anterior-Posterior (Z) $\sum D$.

The frequency histograms of the contouring range measurements in the X, Y, and Z axes indicated a bi-modal distribution. The left direction's mode value was 1.15 cm, whereas the right direction was -1.6 cm. The superior direction's mode value was 2.3 cm and the inferior direction's was -1.2 cm. The anterior direction's mode value was 1 cm, whereas the posterior value was -1.1 cm.

Table 3. shows the mean value of the contouring range measurements for each patient from the outer to the innermost superimposed contours, obtained at each translational axis.

Table 3. Systematic Individual Mean Values of the Contouring Range Measurements in each Translational Axis

	Left (mm)	Right (mm)	Superior (mm)	Inferior (mm)	Anterior (mm)	Posterior (mm)
Patient 1	11.9	8.3	28.2	9.6	4.5	12.4
Patient 2	8.2	10.0	19.8	16.3	8.1	5.9
Patient 3	7.6	9.9	22.3	11.6	9.4	10.6
Patient 4	4.6	6.0	21.8	4.4	3.5	5.4
Patient 5	13.9	14.6	17.0	24.0	9.5	11.4
Population means	9.2	9.8	21.8	13.2	7.0	9.1

The superior direction had the highest overall mean discrepancy variability of 21.8 mm, with patient 1 having the highest recorded average variability of 28.2 mm. The anterior direction had the smallest discrepancy overall, with a mean discrepancy variability of 7.0 mm, and with patient 4 having the smallest contouring range of 3.5 mm.

The CTVs for each of the six participating clinicians are shown in Figure 3.

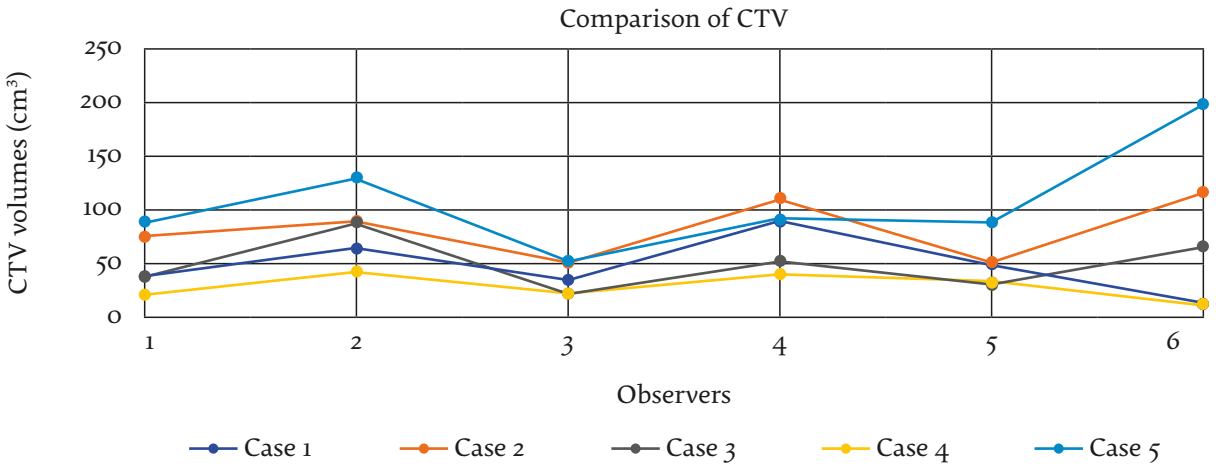


Figure 3. Graph showing the variation of the contoured clinical target volumes (cm3) obtained from the observers.

The mean distance between the outlines of six observers across all directions was 11.7 mm. However, there was an evident larger systematic variation in the Y direction when compared to the other directions. The population mean of the combined value of the Y direction was nearly twice as high as that obtained in the other directions, therefore as suggested by Tudor *et al.* (2020) the average range value was not considered as an

isotropic $\sum_{delin}$ and the variation for the Y direction was calculated separately from the X and Z directions.

In four out of five instances, among the group of six participants, observer number six was identified as the outlier by consistently generating either the largest or smallest CTVs when compared to the other clinicians.

The standard deviation for the X and Z directions was calculated as 8.8/2.53 = 3.47 mm. For the estimation of target delineation in the Y direction, an average value of the contouring range of both the superior and inferior directions resulted in a value of 17.5 mm. This value was divided by 2.53 and resulted in a target $\sum_{delin}$ of 6.92 mm.

These values were then inserted into van Herk's formula for calculation of PTV. Table 4 displays the PTV margin result based only on $\sum_{delin}$.

Table 4. PTV Margin Result based on $\sum_{delin}$

PTV margin (mm)	X	Y	Z
Population Systematic Errors	3.47	6.92	3.47
PTV margin	5.6	11.1	4.5

X, left–right; Y, superior–inferior; Z, anterior–posterior; PTV, Planning Target Volume

4. Discussion

When compared to the other directions, the $\sum_{delin}$ in the Y direction was more dispersed and less homogenous, indicating that the contouring range were the largest in these directions. This was also observed by Jager *et al.* (2015), where the greatest delineation volume discrepancies for the epiglottic region were observed in the Y direction (Jager *et al.*, 2015). This difficulty in defining the superior-inferior borders of the CTV is in part due to unclear boundaries in this direction in comparison with the lateral and anterior-posterior borders, which are also dependent on the tissue contrast and slice thickness of the CT. This, combined with the lack of local protocols, results in various oncologists adhering to different literature/guidelines (Freedman, 2015; Jager, 2017).

An unnecessary larger variation in delineation (in any direction) of the target would result in patients receiving unnecessary dose to normal tissues worsening radiotherapy side-effects. On the other hand, if the target is smaller than necessary, then the tumour control is compromised (Tudor *et al.*, 2020). The target should not be larger than what is necessary.

The PTV margin result, considering only the variability in CTV contouring, is of 5.6mm laterally, 11.1mm superior-inferiorly, and 4.5mm antero-posteriorly. This is a larger margin than the one currently used in the local department (Taliana *et al.*, 2020). Instead of recommendations of increasing the local CTV-PTV margin, it is recommended that the origin of this systematic error is addressed. Below are some of the recommendations to address this issue.

4.1. Imaging quality

The accuracy of delineation is hindered if imaging modalities have a low resolution (Kristensen *et al.*, 2017) and according to Mercieca, Belderbos and Van Herk (2018), observation variation is reduced when superimposing CT planning scan with MRI. Simple measures, such as intravenous and/or intracavitary contrast and reproducible imaging protocols could significantly improve imaging quality. When contouring, the use of zoom levels, simultaneous viewing in multiple planes (sagittal and coronal planes), and adequate window level and window width settings on the planning CT reduce inter-observer variability (Segedin and Petric, 2016). In this study, all patients had a contrast scan fused with a non-contrast scan during CT planning. MRI diagnostic scans were made available to assist clinicians in target delineation, though their use was at the discretion of the individual clinician. As previously mentioned, the MR images were not acquired in the radiotherapy treatment position, which prevented accurate superimposition onto the planning CT scan. Other available information was also provided to the clinicians, but its use for delineation was not formally assessed. Schmidt and Payne (2015) had reported on this, and they were of the opinion that this limited the benefits of delineating with MRI as different observers may rely on different images to perform their delineation.

4.2. Standardised protocols/guidelines

International guidelines, such as those of the Radiation Therapy Oncology Group, Danish Head and Neck Cancer Group, European Organisation for Research and Treatment of Cancer and guidelines written by Grégoire *et al.* (2018) may be used by clinicians for CTV delineation. Studies have shown that the introduction of site-specific anatomical atlases could reduce variability between observers in various tumour sites (Kim *et al.*, 2019). There was no specific guideline which clinicians could follow, when different or ambiguous guidelines are used for target volume delineation, this will have a significant impact on the consistency of delineated structures (Mercieca, Belderbos and Van Herk, 2018). According to Tudor *et al.* (2020), outliers should not be considered when measuring the range measurement of contouring because these contours would be inconsistent with clinical protocols, and one should not attempt to correct for major differences in opinion of the target volume. For this study, outliers were still considered as the department did not follow a specific clinical protocol regarding target delineation of the CTV volume for laryngeal cancer and all participants performed head and neck contouring in clinical practice.

Since one of the clinicians was an outlier and was still considered, the margin size may have been larger than necessary for most patients, because the other clinicians' delineations were closer to each other. This could have also been the reason for the large $\sum_{delin}$ obtained in this study.

Another reason for the large variability could be attributed to the consideration of organ motion in the CTV delineation instead of considering organ motion as part of the PTV delineation error. According to *ICRU Reports 50 and 62*, set-up and organ motion errors should be integrated into the treatment planning procedure by taking a margin around the CTV, consequently defining the PTV. However, the Northern Association of Clinical Physics recommendation was to create a separate margin for set-up errors and organ motion (Van Herk, 2003). These different thoughts result in the lack of standardisation of margin calculation

4.3. Specialised training

Having a diverse group of clinicians with varying roles and experiences was an accurate representation of the local department, however during the clinical settings the contours performed by HSTs would have been checked by the clinical oncologists. The HSTs in the local department rotate according to different treatment areas and this may cause inconsistencies in target delineation (Tudor *et al.*, 2020).

Some publications have addressed the issue of training in target delineation, for example, Schimek-Jasch *et al.* (2015) reported that after a teaching session at a study group meeting, there was an improvement in overall inter-observer agreement, as evidenced by a reduction in target volumes. Khoo *et al.* (2012) obtained similar results and were of the opinion that a well-structured education programme reduced both inter – and intra-observer prostate contouring variations. In contrast, Dewas *et al.* (2011) reported no improvement among clinicians following a teaching course and believed that the reason for this could have been the high standard of the initial delineations. Furthermore, the authors had noted that several clinicians had discussed with each other to reach an agreement about the volumes that needed to be treated within their groups. This could have explained the homogeneity and high quality of the contours reported by Dewas *et al.* (2011), and shows the importance of having target delineation checked by other clinicians who are experts in the field.

This study has several limitations that must be acknowledged. The diversity of the cases, ranging from T1a to T3 tumor staging, may have contributed to some of the observed variations. Additionally, intra-observer variation was not assessed, as the study focused primarily on inter-observer variability among experienced clinicians, which we considered more relevant to our objectives. However, evaluating intra-observer consistency could offer valuable insights into the reproducibility of delineation practices and should be explored in future research. Another limitation is the small sample size, with only five cases included, which restricts the generalisability of the findings. This decision was made to minimise the risk of attrition among participating oncologists if the case load were increased. Future studies should aim to replicate this research with a larger sample. Furthermore, as previously mentioned, the impact of the oncologists' experience on contouring was not evaluated. It is recommended that future studies assess whether seniority or experience influences variability in contouring.

Another recommendation for future studies is to evaluate if training, local protocols, or improvements in imaging would improve the variability and reduce the

PTV margin. The results of such future studies could be compared with the current research findings.

5. Conclusion

The results obtained from this study clearly indicate that $\sum_{delin}$ may have a considerable impact on the PTV margin, particularly in the superior direction. Therefore, it is crucial to reduce the variability associated with $\sum_{delin}$ to achieve better treatment outcomes and radiotherapy-induced toxicities.

In this study all clinicians who contour the head and neck region, irrespective of experience, participated in the study, however in clinical practice the contours performed by HSTs would have been checked by the most experienced clinical oncologists. This could have been one of the reasons of the resulting large PTV margin.

Several recommendations can help minimise target $\sum_{delin}$. It is recommended that clinical contouring protocols are implemented locally as this will reduce the impact of target $\sum_{delin}$. It is also advised that clinicians receive contouring training and follow published contouring guidelines. Further studies to measure target $\sum_{delin}$ for assessing PTV margin are also recommended as most studies that assessed $\sum_{delin}$ were not done with the scope of measuring the delineation variability to calculate the PTV margin size.

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