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PTV margin calculation for head and neck patients treated with VMAT: a systematic literature review

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Literature Review

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Head and Neck; VMAT; Planning Target Volume; PTV; Van Herk; Margin; Error; Systematic literature review

Abbreviations:
PTV, Planning Target Volume; VMAT#, Volumetric Arc Therapy; CBCT, Cone Beam Computed Tomography

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Abstract

Aim: The intent of the review was to identify different methodological approaches used to calculate the planning target volume (PTV) margin for head and neck patients treated with volumetric arc therapy (VMAT), and whether the necessary factors to calculate the margin size with the selected formula were used.
Materials and Methods: A comprehensive, systematic search of related studies was done using the Hydi search engine and different databases: MEDLINE, PubMed, CINAHL, ProQuest (Nursing and Allied Health), Scopus, ScienceDirect and tipsRO. The literature search included studies published between January 2007 and December 2020. Eligibility screening was performed by two reviewers.
Results: A total of seven studies were found. All the reviewed studies used the Van Herk formula to measure the PTV margin. None of the studies incorporated the systematic errors of target volume delineation in the PTV equation. Inter-fraction translational errors were assessed in all the studies, whilst intra-fraction errors were only included in the margin equation for two studies. The studies showed great heterogeneity in the key characteristics, aims and methods.
Findings: Since systemic errors from target volume delineation were not considered and not all studies assess intra-fraction errors, PTV margins may be underestimated. The recommendations are that studies need to determine the effect of target volume variance on PTV margins. It is also recommended to compare PTV margin results using various formulas.

Introduction

The planning target volume (PTV) concept was firstly introduced in the International Commission on Radiation Units and Measurements (ICRU) Report 50[1]. The PTV includes the clinical target volume (CTV) – which is the volume that encompasses the clinical and subclinical disease – plus a margin to account for internal movements and set-up errors[1]. According to the ICRU 83 report, PTV margin size should be calculated for each radiotherapy department, this is because set-up procedures, treatment modalities and imaging modalities are some of the department-specific factors that can influence the number of movements and set-up errors that must be accounted for in this margin. This report, however, did not specify the method to be used for margin calculation[2].

There are also several PTV margin formulas such as Van Herk, Stroom, ICRU 62 formula, Antolak, Bel, McKenzie and Parker, and the selection of the method of calculation could have an influence on the margin size[3].

A systematic literature review was conducted to identify the methodological approaches used to calculate the PTV margin in the head and neck region with volumetric arc therapy (VMAT) across published literature. To achieve this aim, the objectives of this review were to identify the formulas used to calculate the PTV margin and whether the reviewed studies considered the necessary factors to calculate the margin size with the formula used.

Methods

A systematic literature review was performed to answer the question: What methods are employed by studies to calculate the PTV margin for patients treated with VMAT to the head and neck region?

The Preferred Reporting Item for Systematic Review (PRISMA) checklist was used to guide the write-up of the systematic literature review protocol (PRISMA checklist, 2009). The following demonstrated the Population, Intervention, Comparison, Outcome and Study Design (PICOS) framework which was used to guide the literature search[4]:

Population – Patients receiving radiotherapy in the form of VMAT to the head and neck region.

Intervention – Calculation of the PTV margin.

Comparison – No comparison made

Outcomes – Identification the PTV margin formula and the factors considered.

Study Design – Quantitative studies.

A systematic search on databases in medicine and radiotherapy: MEDLINE, PubMed, CINAHL, ProQuest (Nursing and Allied Health), Scopus, tipsRO and ScienceDirect. The Hydi search engine was also used to find related studies.

Keywords were validated by two experts in the field and content validity was used to assess the validation of the keywords. There was 100% mean agreement and minor suggestions were taken on board.

The Medical Subject Headings (MeSH) thesaurus was used to search for other related words that could be used as keywords. The asterisks (*) next to the keywords identified other terms that are written in different ways and Boolean operators were also used to allow combination of words and phrases to expand the search.

The following combinations of keywords were used to search for related studies:

- Nasopharyn*/Nasal cavity
- Oropharyn*
- Laryn*/Supraglottis/Subglottis/Glottis
- Hypopharyn*
- Oral cavity/Mouth/Tongue
- Sinus*
- Thyroid
- Lymphoma
- Head and Neck
- Set-up/setup/set up
- Error/errors
- VMAT/Volumetric-Modulated Arc Therapy/Volumetric Modulated Arc Therapy/RapidArc Therapy
- PTV/Planning Target Volume

Publication period (1 January 2007 to 30 December 2020), full-text and human species filters were used to aid in the selection process. Figure 1 is a representation of the search strategy that was used on PubMed.

Only quantitative studies related to the calculation of the PTV margin for patients being treated with VMAT to the head and neck region were included. The review was also restricted to English language studies.

A dual independent literature search was done by two researchers with over 5 years of clinical experience. The reviewers performed a separate search for the literature using the same research criteria. The search was done between April and December 2020. In the first phase of the review, the literature was screened for the inclusion criteria based only on the title and abstract. For the second phase of the review, a full-text reading of the studies was performed on the eligible studies that were selected in the first phase. Disagreements with regard to data suitability were resolved by consensus between reviewers.

Meta-analysis was not performed due to the heterogeneity in the methodological, statistical and clinical sources; therefore, a narrative synthesis approach was selected[5].

Results

A total of 4341 articles were found. After removing duplicated articles and screening the studies for eligibility, a total of seven relevant studies were found. Figure 2 shows the PRISMA flow chart and Table 1 presents a summary of the study characteristics.

Methods to calculate the PTV margin

The PTV margin was calculated for all the studies in the review using the Van Herk formula. Both inter- and intra-fraction motion were measured in Bruijnen et al.[6] and Yin et al.[7] studies, whilst the other studies derived the margin by evaluating the inter-fraction errors. None of the reviewed studies assessed and included target delineation variation in the margin formula. Table 2 demonstrates the methods opted by the reviewed studies to calculate the PTV margin.

PTV margin size

There was a discrepancy in the PTV margin results of the reviewed studies; however, this was expected since the factors influencing the margin differ from department to department.

The largest discrepancy was found in Anjanappa et al.[8] and Yin et al.[7] studies. These studies analysed the margin in the nasopharyngeal region, however, Yin et al.[7] made use of cone beam computed tomography (CBCT) imaging and assessed inter- and intra-fraction errors, whilst Anjanappa et al.[8] made use of two orthogonal images and evaluated the inter-fraction errors. Intra-fractional contributes to create a larger PTV margin[9]; however, in these two studies, the smallest PTV margin result was in the study that did not evaluate intra-fraction errors. This discrepancy in the margin result could be attributed to the imaging modalities. The chosen modality has an impact on the set-up error that is detected. CBCT should be the modality of choice, since it allows for better observation of the volumes of interest[10].

Oh et al.[11] and Kukolowicz et al.[12] (post-no action level protocol) had the most similar PTV margin result. Both studies, however, varied in immobilisation devices, imaging protocols and outcomes. The similarity of results was most likely by chance. In the reviewed studies, the medial-lateral (ML) margin was not measured in the larynx and oropharynx region. Comparison of margins in the different regions of the head and neck was also not possible, since the studies did not provide data regarding the different areas.

Inter-fraction errors

The reviewed studies obtained similar results for population systematic errors with the standard deviation (SD) of the systematic errors of the reviewed studies measured to be 0·4 mm, 0·5 mm and 0·5 mm in the ML, superior-inferior (SI) and anterior-posterior (AP) direction, respectively. The SD for population random errors resulted to be slightly higher than that of the population systematic errors, with each direction (ML, SI and AP) obtaining a value of 0·6 mm.

Deb et al.[13] study obtained the highest population random error. This study treated patients without daily imaging, instead a total of 10 CBCT images were acquired for each patient. Population systematic and random errors can be corrected prior treatment with daily imaging; however, in studies where daily imaging are not performed, random error can not be compensated. For this reason, the PTV margin of Deb et al.[13] study resulted to be measured larger when compared with other studies in the review.

Rotational errors were analysed in four studies. Oh et al.[11] study compared rotational errors in different anatomical regions. The rotational error for head and neck region was below 3º and this value was small when compared with other anatomical regions. Norfadilah et al.[14] study also calculated rotational errors with

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Query	Results
Search: **(PTV OR Planning Target Volume) AND (VMAT OR Volumetric-Modulated Arc Therapy OR Volumetric Modulated Arc Therapy OR Rapid Arc Therapy) AND (set up OR setup OR set-up) AND (error or errors) AND (Hypopharyn*)** Filters: **Full text, Humans, English, from 2007 - 2020**	1
Search: **(PTV OR Planning Target Volume) AND (VMAT OR Volumetric-Modulated Arc Therapy OR Volumetric Modulated Arc Therapy OR Rapid Arc Therapy) AND (Oral cavity OR mouth OR tongue) AND (Setup OR set-up OR set up) AND (error or errors)** Filters: **Full text, Humans, English, from 2007 - 2020**	12
Search: **(PTV OR Planning Target Volume) AND VMAT OR Volumetric-Modulated Arc Therapy OR Volumetric Modulated Arc Therapy OR Rapid Arc Therapy) AND (oropharyn*) AND (set up OR setup OR set-up) AND (error OR errors)** Filters: **Full text, Humans, English, from 2007 - 2020**	15
Search: **(PTV OR Planning Target Volume) AND VMAT OR Volumetric-Modulated Arc Therapy OR Volumetric Modulated Arc Therapy OR Rapid Arc Therapy) AND (Nasopharyn* OR Nasal cavity) AND (set up OR setup OR set-up) AND (error OR errors)** Filters: **Full text, Humans, English, from 2007 - 2020**	28
Search: **(PTV OR Planning Target Volume) AND (VMAT OR Volumetric-Modulated Arc Therapy OR Volumetric Modulated Arc Therapy OR Rapid Arc Therapy) AND (Laryn* OR supraglottis OR subglottis OR glottis) AND (Setup OR set-up OR set up) AND (error OR errors)** Filters: **Full text, Humans, English, from 2007 - 2020**	12
Search: **(PTV OR Planning Target Volume) AND (VMAT OR Volumetric-Modulated Arc Therapy OR Volumetric Modulated Arc Therapy OR RapidArc Therapy) AND (Head and Neck) AND (Setup OR set-up OR set up) AND (error)** Filters: **Full text, Humans, English, from 2007 - 2020**	55
Search: **(PTV OR Planning Target Volume) AND (VMAT OR Volumetric-Modulated Arc Therapy OR Volumetric Modulated Arc Therapy OR Rapid Arc Therapy) AND (Thyroid OR Sinus* OR lymphoma) AND (Setup OR set-up OR set up) AND (error OR errors)** Filters: **Full text, Humans, English, from 2007 - 2020**	7

Figure 1. Search strategy.

the aim of comparing two tongue immobilisation devices. Average rotational errors result for headFIX® mouthpiece and syringe mouthpiece were 0·00°±0·65° and 0·34°±0·59°, respectively. In Kukolowicz et al.[12] rotations larger than one degree were seldom observed; therefore, these errors were not taken into consideration. This study, however, performed 2D imaging, therefore, rotational results from multiple perspective were not analysed. Small values of rotations were also observed in Yin et al.[7] study, with the number of fractions rarely exceeding 2° for pitch, roll and yaw directions.

Intra-fraction translational errors

Bruijnen et al.[6] measured intra-fraction errors from 2D cine magnetic resonance imaging (MRI) and deformable image registration. In this study, respiratory tumour motion, swallowing, tongue motion and set-up errors were investigated to determine the PTV margin size. When the tumour motion was incorporated into the PTV margin formula, the margin expanded by 0·6 mm for oropharyngeal tumours, 0·2 mm for nasopharyngeal tumours and 1·7 mm for laryngeal tumours[6].

In Yin et al. study[7], the intra-fraction population systematic error during the 5–9 min VMAT period ranged from 0·2 mm to 0·4 mm, and the population random error ranged from 0·5 mm to 0·6 mm.

Discussion

PTV margin equations

In radiotherapy, there is an issue on the method selected to determine the PTV margin. The Van Herk formula is a widely used strategy for PTV margin calculation, and this equation was used in all the reviewed seven studies. The reason for selecting the formula was not specified and lack of comparison of this formula against other options for head and neck was identified as a major gap in the literature.

A study by Namysł-Kaletka, Tukiendorf and Wydmański[15] used three formulas; Van Herk, Stroom and ICRU, to assess PTV margin results based on set-up errors for gastric cancer patients. The margin results were compared, and the study

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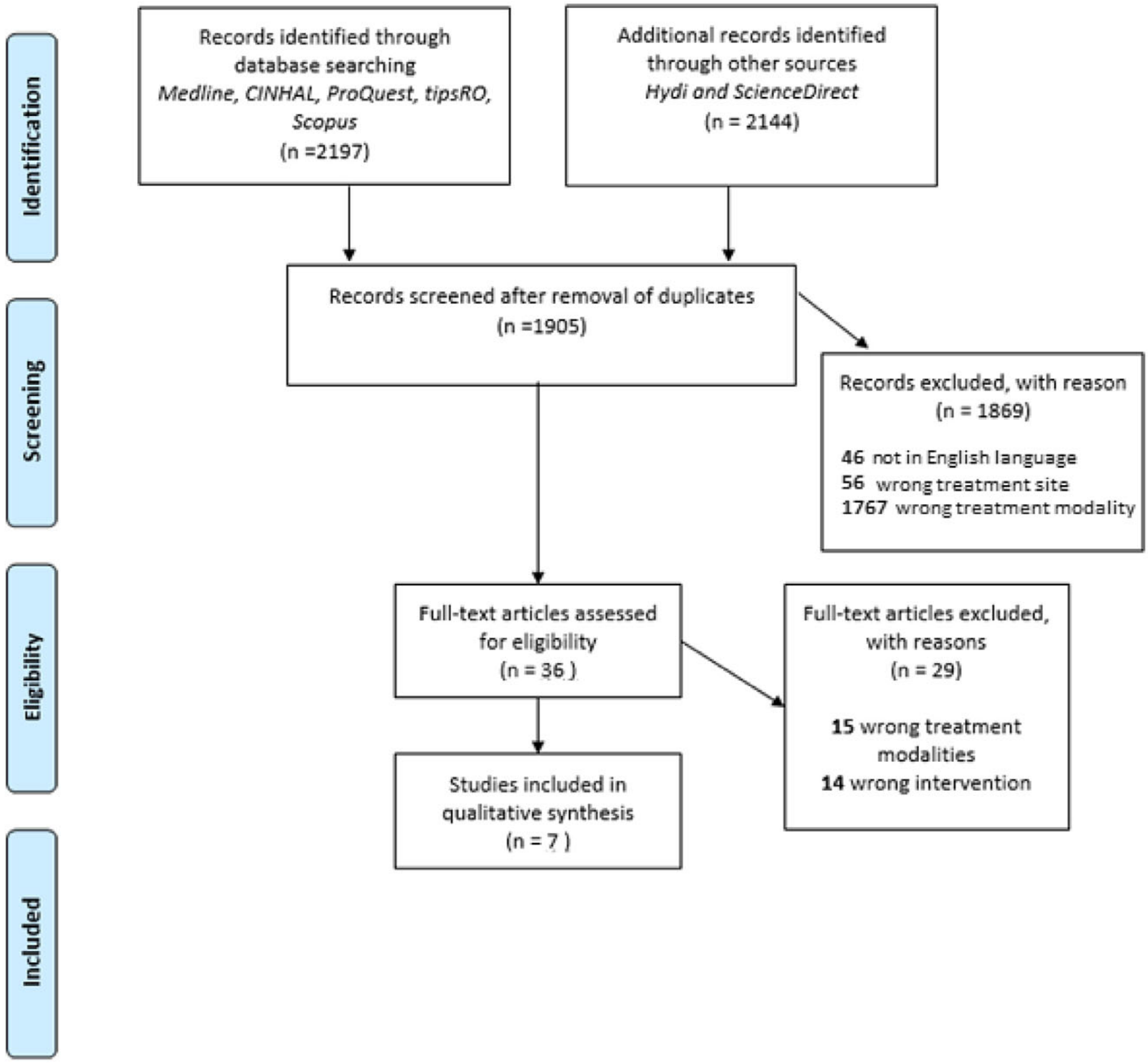

Figure 2. PRISMA 2009 flow chart *(Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses)*.

revealed that the formula being used has an impact in the PTV margin. As such, the formula should be selected carefully.

The Van Herk's formula assumes that the CTV is spherical in shape, the tissue is homogeneous, conformal beam penumbra and that the number of fractions is infinite[16]. As such, the use of this formula for the PTV margin calculation should be used with caution when these assumptions do not apply.

Due to the exclusion of rotational errors and shape variation, the Van Herk's formula should be considered a lower limit for the delivery of safe radiotherapy. The formula guarantees that 90 per cent of patients receive a minimum of 95 per cent of the recommended dose in the CTV[16]. Therefore, this formula seems to be adequate for the calculation of PTV margin in head and neck patients.

PTV margin size

The studies in the review had different PTV margin size and this continues to necessitate the importance of the departments to calculate their own specific margins. Margin sizes seem to be affected by the imaging protocols and immobilisation devices.

Yin et al.[7] study demonstrated the effect of daily imaging on the margin size for nasopharyngeal patients. The resulting margin size was small when compared to other studies in the review, since the PTV margin was calculated on the set-up errors obtained after CBCT correction. Kukolowicz et al.[12] stated that daily online correction was slightly better than the NAL (no action level) protocol for patients having treatment to the head and neck region. However, the study failed to analyse rotational errors and could not assess anatomical changes since these were not visible on portal images.

Daily imaging protocols should be adhered for patients treated with a tight PTV margin, such as intensity-modulated radiotherapy or VMAT. Daily imaging aids in verifying the set-up position, identifying the location of the target, assessing tumour shrinkage and making the necessary corrections prior to each exposure[11].

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Table 1. Summary of characteristics of studies included in the narrative synthesis

Author, year and country	Study design	Head and neck region	Imaging protocol	Immobilisation device	PTV formula	PTV margin result
Yin et al., 2013 Southern China	Prospective Observational Analytical and Cross-sectional	Nasopharynx	Daily CBCT	5-point TP mask HR not specified	VHMF (inter- and intra-fraction errors)	*Total without CBCT correction*: ML = 4·1 mm SI = 3·4 mm AP = 3·5 mm *Total with CBCT correction*: ML = 1·7 mm SI = 2·2 mm AP = 2·2 MM
Oh et al., 2014 South Korea	Retrospective Observational Analytical and Cross-sectional	Not specified	Daily CBCT	5-point TP mask Individual HR	VHMF (inter-fraction error)	ML = 3·3 mm SI = 2·8 mm AP = 3·7 mm
Anjanappa et al., 2017 India	Retrospective Observational Analytical and Cross-sectional	Nasopharynx	Daily 2D KV imaging (KV images taken on alternate days were reviewed)	4-point TP mask HR not specified	VHMF (inter-fraction error)	*Clivus level:* ML = 4·0 mm SI = 3·2 mm AP = 4·4 mm *C3 level:* ML = 5·0 mm SI = 4·4 mm AP = 5·5 mm *C6 level:* ML = 6·9 mm SI = 4·4 mm AP = 6·4 mm
Norfadilah et al., 2017 Malaysia	Prospective Observational Analytical and Cross-sectional	Oral cancer	Daily CBCT	5-point TP mask Mouth Bite HR not specified	VHMF (inter-fraction error)	*HFW mouthbite*: ML = 3·1 mm SI = 2·2 mm AP = 0·8 mm *SYR*: ML = 3·8 mm SI = 6·2 mm AP = 5·1 mm
Bruijnen et al., 2018 Netherlands	Prospective Observational Analytical and Cross-sectional	Nasopharynx Oropharynx Larynx	eNAL	5-point TP mask Individual HR	VHMF (inter and intra-fraction errors)	*Nasopharynx*: S = 2·8 mm I = 2·8 mm A = 2·8 mm P = 2·8 mm *Oropharynx*: S = 3·0 mm I = 3·1 mm A = 3·0 mm P = 3·0 mm *Larynx*: S = 4·0 mm I = 3·6 mm A = 3·1 mm P = 3·1 mm *Combined:* S = 3·3 mm I = 3·2 mm A = 3·0 mm P = 3·0 mm

Table 1. (*Continued*)

Deb et al., 2019 India	Retrospective Observational Analytical and Cross-sectional	Not specified	Daily imaging (eNAL for CBCT and remaining days with 2D PI)	TP mask with shoulder retraction Standard HR	VHMF (inter-fraction error)	ML = 5·6 mm SI = 6·1 mm AP = 4·7 mm
Kukolowicz et al., 2020 Poland	Retrospective Observational Case-control	Nasopharynx and larynx	Daily EPID	5-point TP mask Standard HR	VHMF (inter-fractional error)	*Prior NAL protocol:* AP = 4·0 mm SI = 6·0 mm ML = 4·0 mm *NAL protocol:* AP = 3·0 mm SI = 2·2 mm ML = 3·0 mm

N = sample number; S = superior; I = inferior; A = anterior; P = posterior; ML = medial-lateral; SI = superior-inferior; AP = snterior-posterior; C3 = cervical spine level 3; C6 = cervical spine level 6; TP = thermoplastic; HR = head rest; HFW = HeadFIX® mouthpiece; SYR = 10 mL/cc syringe barrel; EPID = electronic portal imaging device; CBCT = cone beam computed tomography; PI = portal imaging; eNAL = extended no action level protocol (imaging on first three fractions, followed with once weekly imaging); NAL = no action level protocol (imaging on first three fractions); VHMF = Van Herk's margin formula.

Norfadilah et al.[14] study assessed the impact of variation in tongue immobilisation on the margin size, and the results were indicative that immobilisation devices influence the PTV margin size.

According to Anjanappa et al.[8] study, the lower neck region requires a larger PTV margin in the ML and AP direction. Another similar result was obtained in Cheo et al.[17] study, where the set-up errors were evaluated in different levels of the neck and the largest displacement was found to be in the ML direction (6·52 mm). As compared to the SI direction, the PTV margin findings in the other reviewed studies do not appear to indicate any substantial difference in the margin size of the ML and AP direction. Anjanappa et al.[8] suggestion of increasing the margin size in the ML and AP direction should therefore not be considered for all clinical situations.

Inter-fraction and intra-fraction errors

All the studies in the review analysed inter-fraction errors; therefore, the method of calculating the margin varied solely on whether intra-fraction error was being assessed. Van Herk et al. suggested to include target volume delineation variation and intra-fractional errors in the margin estimation, as well as including the SD of these errors in quadrature[18].

The systematic literature found that inter-fraction errors were generally higher than intra-fraction errors, which indicates that maintaining the position during treatment leads to less errors than reproducing the set-up between treatments.

Population-based margins should account for internal motion, therefore intra-fraction movements should be quantified[6]. Bruijnen et al.[6] and Yin et al.[7] were the only studies that analysed both intra-fraction errors and inter-fraction errors. Intra-fraction error is related to internal organ motion and patient movement during treatment, therefore it is a random error[19].

In Bruijnen et al.[6] study, when the tumour motion was incorporated into the PTV margin formula, the margin expanded mostly in the laryngeal region. This indicates that this region is subjected to greater tumour motion due to swallowing[6]. These results were similar to a study by Gurney-Champion et al.[20] where the tumour motion analysed with MRI imaging was found to be significantly larger in the larynx and hypopharynx when compared to oropharynx.

In Yin et al.[7] study, intra-fraction errors were assessed via CBCT images. The study focused on patients receiving treatment to the nasopharynx and intra-fraction errors were based on patient movement during treatment.

Few studies obtained intra-fraction results on patients treated with VMAT and the need to calculate this error was raised by Yin et al.[7]. There was no significant correlation between treatment delivery time and intra-fraction errors. This study had some limitations since there was a limited data for analysis and statistically significant results could not be obtained due to the narrow range of treatment time. These results are contradictive to Hoogeman et al.[21], who stated that with an increment in time, intra-fraction systematic errors increase.

Van Herk's formula does not consider rotational errors[18]. Four studies from the review still investigated the rotational set-up errors on their population sample. In high-precision treatments, it is important that rotational errors are not ignored, especially when the distance from the isocentre to the target is large or when the tumour has a non-spherical shape[22]. In most clinical

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Table 2. PTV margin methods

Study	Target delineation	Intra-fraction error	Inter-fraction errors	PTV formula
Oh et al. (2014)	x	x	✓	$PTV = 2{\cdot}5\Sigma + 0{\cdot}7\sigma$
Bruijnen et al. (2018)	x	✓	✓	$PTV = 2{\cdot}5\sqrt{(\Sigma motion^2 + \Sigma setup^2)} + 0{\cdot}7\sqrt{(\sigma motion^2 + \sigma setup^2)}$
Yin et al. (2013)	x	✓	✓	$PTV = 2{\cdot}5\sqrt{(\Sigma inter\text{-}fraction^2 + \Sigma intra\text{-}fraction^2)} + 0{\cdot}7\sqrt{(\sigma inter\text{-}fraction^2 + \sigma intra\text{-}fraction^2)}$
Norfadilah et al. (2017)	x	x	✓	$PTV = 2{\cdot}5\Sigma + 0{\cdot}7\sigma$
Deb et al. (2019)	x	x	✓	$PTV = 2{\cdot}5\Sigma + 0{\cdot}7\sigma$
Anjanappa et al. (2017)	x	x	✓	$PTV = 2{\cdot}5\Sigma + 0{\cdot}7\sigma$
Kukolowicz et al. (2020)	x	x	✓	$PTV = 2{\cdot}5\Sigma + 0{\cdot}7\sigma$

departments, these errors are not corrected due to couch limitations[23]. Rotational errors were minimal in the four studies.

Target volume delineation

Calculation of the PTV margin should incorporate the systematic errors obtained from target volume delineation[7,8]. Even though target volume delineation might have the largest impact in margin size since it is fixed throughout the treatment[24], none of the studies in the review evaluated this factor. This type of systematic error is commonly ignored in studies that investigate PTV margin calculation[24] leading to a potential underdosage to the tumour. This is important for all head and neck locations, but more so for the oropharyngeal cancer since interobserver variability in target delineation is greater in this region[25].

Limitation

The researchers ran a thorough search and all the body of evidence found was analysed and discussed; however, the availability of data on PTV margin calculation to the head and neck region was limited and this resulted in a small sample of studies. This could have limited the findings of significant relationships.

Also, some studies were not reliable since they obtained a weak quality evaluation after been analysed by the Joanna Briggs Institute tool, as such, the researchers were careful in drawing conclusions from these publications.

Since the review relied on pre-existing data, the obtained results were dependent on the methodology of the studies. Self-reported data bias could be introduced from relying on pre-existing data. The studies were also limited to the English language; therefore, 46 non-English language studies were excluded in the first phase of the review, this resulted in the review to be susceptible to reporting bias and language bias[26].

Comparison of study results was limited due to the studies being heterogenous in terms of the key characteristics of the studies and methodology design.

Although the findings of this study should be interpreted with caution, this review represents a comprehensive examination of studies that analysed PTV margin to the head and neck region with VMAT.

Conclusion

The Van Herk formula was used in all the studies in the review and none of the studies made use of other PTV margin formula. This margin seems adequate to calculate the PTV margin for head and neck patients treated with VMAT.

Most studies only included inter-fraction errors into the van Herk formula. However, PTV margin should incorporate target volume delineation, intra-fraction errors and inter-fraction set-up errors to ensure a well-defined margin.

The result indicated that tumours in the laryngeal region where more susceptible to motion when compared to those found in the nasopharynx and oropharynx.

Inter-fraction translational errors were assessed in all the studies from set-up errors that were registered by the imaging software. The SD of population random errors was found to be a little bit higher than that of population systematic errors. The systematic and random errors of set-up rotational errors were not considered in most studies, and the obtained values were not included in the PTV formula since this formula assumes that the CTV is spherical and, therefore, is unaffected by rotation.

The findings of the review where in line with other studies that stated that different anatomical regions, immobilisation devices, imaging frequency, treatment modality, set-up procedures and patient collaboration influence the size of the PTV margin.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1460396921000546.

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