Radiotherapy and Oncology 130 (2019) 82–88

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Intrafraction motion quantification and planning target volume margin determination of head-and-neck tumors using cine magnetic resonance imaging

Tom Bruijnen *, Bjorn Stemkens, Chris H.J. Terhaard, Jan J.W. Lagendijk, Cornelis P.J. Raaijmakers, Rob H.N. Tijssen

Department of Radiotherapy, University Medical Center Utrecht, the Netherlands

ARTICLE INFO

Article history:
Received 8 January 2018
Received in revised form 10 September 2018
Accepted 19 September 2018
Available online 15 October 2018

Keywords:
Intrafraction motion
Head-and-neck cancer
MRI
Radiotherapy
Margins

ABSTRACT

Purpose: To quantify intrafractional motion to determine population-based radiotherapy treatment margins for head-and-neck tumors.
Methods: Cine MR imaging was performed in 100 patients with head-and-neck cancer on a 3T scanner in a radiotherapy treatment setup. MR images were analyzed using deformable image registration (optical flow algorithm) and changes in tumor contour position were used to calculate the tumor motion. The tumor motion was used together with patient setup errors (450 patients) to calculate population-based PTV margins.
Results: Tumor motion was quantified in 84 patients (12/43/29 nasopharynx/oropharynx/larynx, 16 excluded). The mean maximum (95th percentile) tumor motion (swallowing excluded) was: 2.3 mm in superior, 2.4 mm in inferior, 1.8 mm in anterior and 1.7 mm in posterior direction. PTV margins were: 2.8 mm isotropic for nasopharyngeal tumors, 3.2 mm isotropic for oropharyngeal tumors and 4.3 mm in inferior–superior and 3.2 mm in anterior–posterior for laryngeal tumors, for our institution.
Conclusions: Intrafractional head-and-neck tumor motion was quantified and population-based PTV margins were calculated. Although the average tumor motion was small (95th percentile motion <3.0 mm), tumor motion varied considerably between patients (0.1–12.0 mm). The intrafraction motion expanded the CTV-to-PTV with 1.7 mm for laryngeal tumors, 0.6 mm for oropharyngeal tumors and 0.2 mm for nasopharyngeal tumors.

Radiotherapy is used as a primary or secondary treatment in up to 75% of patients with head-and-neck cancer [1]. Head-and-neck tumors are often in close vicinity of multiple organs at risk and therefore require highly conformal treatment plans. These treatment plans are characterized by steep dose gradients that minimize the dose to the organs at risk while maintaining an adequate tumor dose. These steep dose gradients generate effective treatment plans in theory, but rely heavily on accurate geometrical dose delivery.

To deliver the dose with high geometric accuracy, the treatment needs to be set up precisely and the intrafractional and interfractional tumor motion needs to be accounted for. Treatment setup is improved using immobilization devices such as thermoplastic masks and a personalized head support [2–4]. The residual interfractional motion is accounted for by adding an uncertainty margin that expands the clinical target, called the planning target volume (PTV), which accounts for setup errors [5,6], patient weight loss and tumor shrinkage [7,8]. Intrafractional motion is accounted for by either a personalized margin or a population-based margin that is included in the PTV. Intrafractional motion could be defined as the internal motion; that is, the result of respiration, swallowing, tongue movements and slow motions induced by organ relaxation. These movements must be accurately quantified either to determine population-based margins or personalized margins to account for the internal motion. For head-and-neck tumors this margin is not explicitly reported but generally an additional margin is used for laryngeal tumors. In our institute an additional margin of 5 mm is added to the standard PTV margin [9].

Thus far, the quantification of the intrafractional motion has primarily focused on the impact of swallowing on the accumulated dose. Swallowing-induced motion of head-and-neck tumors or surrogate structures such as the larynx was in the range of 15–29 mm [10–16]. Although the tumor motion is large, the incidence and total duration of swallowing was 1% of the irradiation time. In

* Corresponding author at: University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
E-mail address: t.bruijnen@umcutrecht.nl (T. Bruijnen).

https://doi.org/10.1016/j.radonc.2018.09.015
0167-8140/

addition, the tumor is only at the maximum position during a small part of the complete swallowing event. Therefore, the sole effect of swallowing on the accumulated tumor dose was considered small [11,12,15].

Non-swallowing induced tumor motion, on the other hand, could have a larger effect on the accumulated dose and has been investigated in three studies. Prevost et al. used video fluoroscopy in 15 patients to track platinum markers, as a surrogate for tumor motion, and concluded that the motion was insignificant for clinical practice [12]. Bradley et al. used 2D cine MRI in 11 patients to quantify intrafraction tumor motion and concluded that the tumor motion required a PTV expansion [15]. Gurney-Champion et al. used dynamic contrast enhanced MRI in 56 patients to quantify intrafractional tumor motion in 3D and concluded that the tumor motion required a PTV expansion [17].

Although these studies analyzed patients with head-and-neck cancer in radiotherapy treatment setup, the extent of the quantified (non-swallowing) tumor motion varied a lot. The variation could be due to differences in imaging setup and patient population, but we believe that the different imaging methods are the main cause. In particular, the temporal resolution of the imaging method determines the sensitivity to measure fast occurring motions such as respiration. While the 3D method [17] is superior to quantify slower shifts throughout the treatment, the method lacks the temporal resolution (0.34 Hz) to accurately quantify respiratory-induced tumor motion. This hypothesis is supported by the lower respiratory-induced tumor motion found with the 3D method compared to the 2D methods by Bradley et al. That study, however, had a limited sample size (11 patients) and too short imaging window (15 s) to describe the respiratory-induced tumor motion on a population-based level.

In this study we quantify the intrafractional motion to calculate PTV margins of head-and-neck tumors in supine radiotherapy treatment position. We quantify tumor motion using 2D cine MRI and deformable image registration. We show that respiratory-induced tumor motion varies considerably among patients (larger than 10 mm) and we calculate population-based PTV margins for nasopharyngeal, oropharyngeal and laryngeal tumors.

Methods

Study population

Cine MR scans were acquired in 100 consecutive patients with head-and-neck cancer that were selected for radiotherapy treatment in our department between June 2016 and July 2017. From the 100 selected patients, 16 were excluded due to one of three reasons: image quality was insufficient for analysis (2 patients), the 2D image was not positioned correctly (7 patients), or the patient was retracted from the treatment (7 patients). The patient characteristics are described in Supplementary information I. MR scans were acquired during pretreatment imaging for which the requirement to obtain informed consent was waived by the institutional review board.

MR image acquisition

The patients underwent CT and MRI scans prior to the first week of treatment. The scans were acquired in radiotherapy treatment setup, which consisted of a custom-fit five-point thermoplastic immobilization mask and an individualized head support (Civco Radiotherapy, Reeuwijk, the Netherlands). The MRI scans were acquired on a 3T MR scanner (Ingenia, Philips, Best, the Netherlands) with two flexible surface coils and an integrated posterior coil for signal reception (Fig. 1-A).

Two 2D cine MR scans of 60 s were added to the clinical protocol, which were acquired approximately 5 and 13 min after the start of the MR examination. The time between the two cine scans was 8.8 ± 1.5 min and the range was 4–11 min. The cine MR scans were acquired in the sagittal plane because the motion in the left–right direction was found to be small [15,17]. Since the tumor position is not delineated prior to pretreatment imaging, the radiotherapy technicians used the diffusion weighted image (Fig. 1-B) along with the localizer images to estimate the slice position such that it was placed through the center of the tumor. From 84 scanned patients, 17 did not receive a second cine MR scan due to logistical reasons.

The cine MR scans were acquired using a 2D spoiled gradient echo sequence with the following sequence parameters: field of

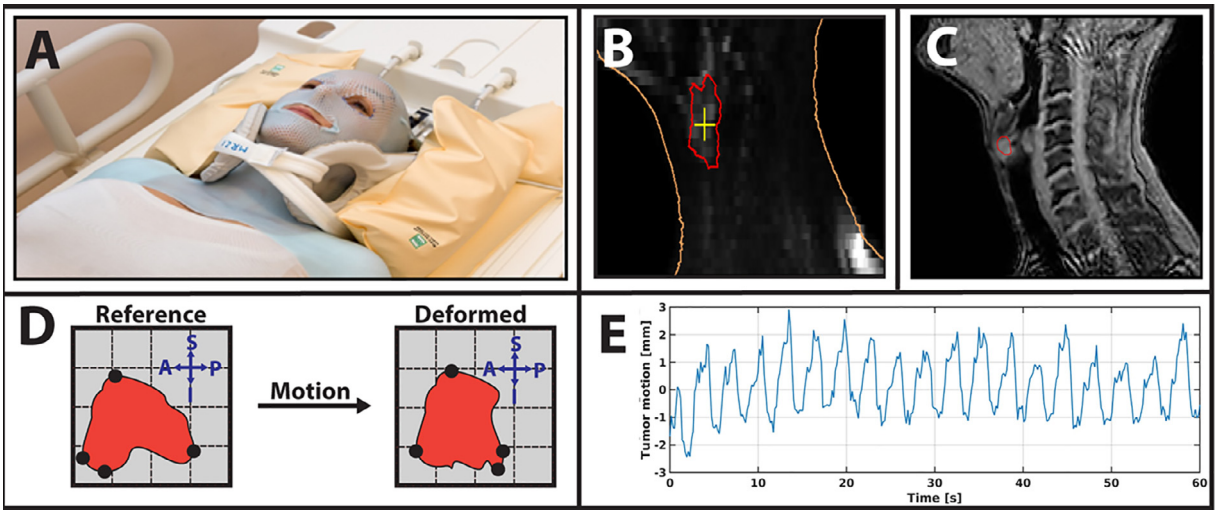

Fig. 1. Methods used to quantify the tumor motion. (A) Imaging setup including the immobilization mask, personalized head support and surface receiver coils. (B) Diffusion weighted image used to estimate tumor position. (C) RF and gradient spoiled gradient echo image from a cine MR scan. (D) Method to calculate the tumor motion by comparing maximum contour coordinates (black dots) between time-points. (E) Applying the method of (D) for each time-point yields motion profiles that can be evaluated over time.

view = 250 × 250 mm^2, slice thickness = 10 mm, flip angle = 5°, echo time = 1.45 ms and repetition time = 3.16 ms. The scans were accelerated using partial Fourier sampling of 70% and parallel imaging (R = 2.3) to increase the temporal resolution to 158 ms with 1.5 mm in-plane spatial resolution (Fig. 1-C). We did not give the patients any instructions regarding breathing patterns or swallowing behavior prior to the exam.

MR image analysis

As part of the clinical workflow, the radiation oncologist delineated the gross target volume (GTV) using the MRI and CT scans. The GTV was transferred onto a single image (reference) of the cine MR scan using a 2D-to-3D rigid normalized mutual information registration in Volumetool (an in-house built software package) [18]. The other images of the cine MR scan were then registered to the reference image using the RealTITracker [19]. The RealTITracker uses an optical flow algorithm to estimate deformable tissue motion and the algorithm returns pixel-wise deformation vector fields (DVFs). The RealTITracker has been validated for cine MR scans in multiple anatomical locations and for multiple image contrasts [20].

First, the two cine MR scans were analyzed separately to quantify the tumor motion within the one minute scan. The images were registered using the RealTITracker to obtain DVFs for the entire field-of-view. The DVFs were used to propagate the GTV to the next time-point and were used to calculate the outermost contour position of the GTV for each direction. The outermost GTV contour position was then compared to the contour positions of the reference image (Fig. 1-D). The differences in the contour positions were used to quantify the tumor motion and will be referred to as motion profiles x(t) (Fig. 1-E). To investigate whether the first and second scans showed significant systematic differences a paired t-test was performed between the motion profiles. Second, for both cine MR scans the average GTV contour positions ($\bar{x}_{cine}$) were calculated and then the difference was used to quantify the tumor shift between the scans.

To investigate the contribution of respiration to the tumor motion, the maximum tumor displacement was calculated for both the cine MR scans. In the calculation we excluded the images that were affected by swallowing motion or tongue motion. Swallowing was identified according to the definition of Matsuo et al. [21] and we discarded these frames from the analyses to calculate the maximum tumor motion. We did not discard the frames in the analysis for the PTV margin determination.

PTV margin determination

The measured tumor motion was used together with the treatment setup errors to calculate a population-based PTV (expansion from clinical target volume (CTV)). The tumor motion within and between the cine MR scans, which included swallowing motion and tongue motion, was separated into systematic errors ($\sum_{\text{motion}}$) and random errors (σ_{motion}). The different components of the systematic and random errors were added in quadrature, i.e. $\sum_{\text{motion}} = \sqrt{(\sum^2_{\text{shift}} + \sum^2_{\text{resp}})}$ and $\sigma_{\text{motion}} = \sigma_{\text{resp}}$ and $\sigma_{\text{motion}} = \sigma_{\text{resp}}$. The tumor shift between the scans was described as a linear occurring translation such that $\sum_{\text{shift}} = \text{SD}(\bar{x}_{cine1} - \bar{x}_{cine2})$, with SD as the standard deviation over the patients. The tumor motion within the scans was calculated as $\sum_{\text{resp}} = \sigma_{\text{resp}} = \sqrt{(1/\text{N}\sum(0.5\ SD(x_{cine1}) + 0.5\ SD(x_{cine2})))}$ with N is the number of patients. The $\sum_{\text{resp}}$ was used to account for the mismatch between the planning CT and the treatment setup cone beam CT [22].

The treatment setup errors were calculated from positioning verification data in 450 patients with head-and-neck cancer treated in the last two years at our institute. Note that the 100 patients selected for the cine imaging are a subgroup of the 450 patients used for the position verification data. The treatment followed an extended no action level (eNAL) protocol [23], in which imaging was performed for the first three fractions and subsequently once per week. We calculated the setup errors by registering the on board cone beam CT images to the reference CT. The images were registered in XVI using bone matching with a clipping box. All the patients received thermoplastic masks and all the registration were performed by the radiotherapy technicians. We then calculated $\sum_{\text{resp}}$ by taking the standard deviation of the mean systematic error over all the patients and σ_{setup} as the mean of all the average standard deviations over all the fractions.

The tumor motion errors and the treatment setup errors were then applied in the margin recipe of van Herk et al. (PTV = $2.5\sqrt{(\sum^2_{\text{motion}}+\sum^2_{\text{setup}})} + 0.7\sqrt{(\sigma^2_{\text{motion}}+\sigma^2_{\text{setup}})}$) to calculate the population-based PTV [24,25].

Results

Tumor motion quantification

The maximum tumor motion (swallowing excluded) was more pronounced in laryngeal tumors than in oropharyngeal and nasopharyngeal tumors (Fig. 2). Typical motion profiles for tumors that move due to respiration, swallowing or do not move at all are shown in Fig. 3. Furthermore, tumor motion was most pronounced in the superior and inferior direction and was significantly different between all directions and anatomical locations (repeated factorial ANOVA). Tumor motion varied considerably between patients and some large tumor displacements were detected (Supplementary information II). The mean maximum tumor motion was 2.3 (range: 0.3–12.0) mm in superior, 2.4 (range: 0.3–7.8) mm in inferior, 1.8 (range: 0.2–5.2) mm in anterior and 1.7 (range: 0.3–4.1) mm in posterior direction (Table. 1). The measured maximum tumor displacements of the first and second MR scans did not differ significantly ($p > 0.05$).

PTV margin determination

To determine the systematic motion errors and the random motion errors the standard deviation of the tumor motion profiles was calculated for all patients (Fig. 4). The $\sum_{\text{motion}}$ over all patients was 0.9 mm in superior, 0.7 mm in inferior, 0.6 mm in anterior and 0.6 mm in posterior direction. The standard deviation (σ_{motion}) over all the patients was 0.8 mm in superior, 0.7 mm in inferior, 0.5 mm in anterior and 0.5 mm in posterior direction. The $\sum_{\text{motion}}$ and σ_{motion} for all the directions and anatomical subsites are shown in Supplementary information III.

The systematic setup errors, calculated from positioning verification data in 450 patients, were 0.7 mm in the anterior and posterior direction and 0.7 mm in the superior and inferior direction. The random setup errors were 1.6 mm in the anterior and posterior direction and 1.4 mm in the superior and inferior direction. Note that these setup errors are institution specific and therefore require separate validation in other clinics.

The setup errors (450 patients) and the motion errors (84 patients) were used to calculate PTV margins according to the recipe of van Herk et al. (Table. 2). In general, the tumor motion expanded the CTV-PTV margin for nasopharyngeal tumors with <0.2 mm (compared to the static case). The PTV margin for oropharyngeal tumors was isotropically expanded with about 0.6 mm. The PTV margin for laryngeal tumors was expanded with 1.7 mm expansion in the superior and inferior direction and 0.7 mm expansion in the anterior and posterior direction.

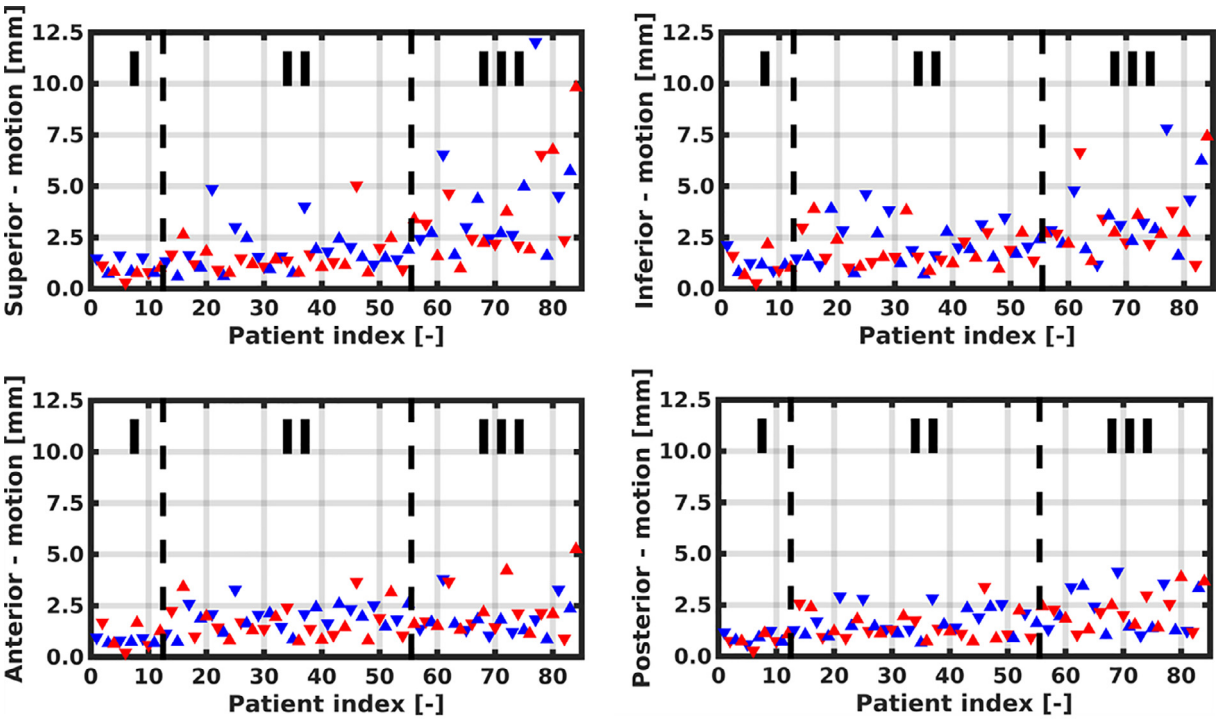

Fig. 2. Maximum (95th percentile) tumor motion (swallowing excluded) over the cine MR scans. Patients are arranged according to the anatomical position of the tumor, with I denoting the nasopharyngeal tumors, II the oropharyngeal tumors and III the laryngeal tumors. The different colors and shapes are used to distinguish neighboring points.

Discussion

We quantified the 2D intrafractional tumor motion in 84 patients using cine MRI and deformable image registration. The maximum tumor motion (swallowing excluded) was small on average, with 2.8 mm in the superior–inferior direction and 2.1 mm in the anterior-posterior direction. However, we found that some laryngeal tumors showed respiratory-induced tumor motion larger than 10 mm in the superior–inferior direction. The intrafractional tumor motion (swallowing included), together with treatment setup errors, was used to calculate population-based PTV margins for nasopharyngeal, oropharyngeal and laryngeal tumors.

Head-and-neck tumor motion was quantified in three studies before: Prevost et al. used videofluoroscopy (10 Hz) to measure 2D tumor motion (swallowing excluded) in 15 patients with oropharyngeal cancer over 20 s and found mean maximum motion of 1.4 mm (range: 0.4–3.1) in superior–inferior and 1.3 mm (range: 0.4–3.4) in anterior–posterior [12]. Bradley et al. used cine MRI (6.5 Hz) to measure 2D tumor motion (swallowing excluded) in 11 patients (4 oropharyngeal and 7 laryngeal cancer), over 15 s and found mean maximum motion of 3.1 mm (range: 0.0–8.2) in superior–inferior and 1.8 mm (range: 0.0–6.0) in anterior–posterior [15]. Gurney-Champion et al. used dynamic contrast MRI (0.34 Hz) to measure 3D tumor motion in 56 patients (48 oropharyngeal and 8 laryngeal cancer) over 223 s and found 95th percentile systematic tumor motion of 0.6 mm in anterior-posterior and 1.1 mm in superior–inferior [17]. These studies did not have sufficient data to report the tumor motion separate for the anatomical subsites, however our findings indicate that the motion depends considerably on the anatomical subsite and therefore requires comparison accordingly. Here we will compare the motion reported in the aforementioned studies versus our study and discuss the resulting PTV margins. *Nasopharyngeal tumors* are in practice considered as non-moving tissue and thus no margin is added to account for the internal motion. The mean maximum tumor motion was approximately 1 mm and expanded the PTV with less than 0.2 mm. Therefore, our findings support the clinical practice of not adding a margin to account for the internal motion for nasopharyngeal tumors. *Oropharyngeal tumors* showed mean maximum motion of 2.0 mm in superior-inferior direction and 1.7 mm in anterior-posterior direction. While the average tumor motion was small, some patients had respiratory patterns that involved a structural component of tongue displacement that resulted into increased tumor motion (Video: Supplementary information IV). The tumor motion in our study slightly differed from Prevost et al. and Bradley et al. which is presumably due to the difference in imaging time and difference in patient population. However, the tumor motion reported by Gurney-Champion et al. was considerably smaller than the 95th percentile systematic motion found in our study, which was 1.5 mm in anterior–posterior and 2.0 mm in superior–inferior. The clinically used PTV for oropharyngeal tumors is typically between 3 and 5 mm depending on the availability of daily image guided radiotherapy [26]. Our findings suggest that a isotropic 0.7 mm PTV expansion is required to account for the internal motion for oropharyngeal tumors. *Laryngeal tumors* showed mean maximum motion of 3.8 mm in superior–inferior direction and 2.2 mm in anterior-posterior direction. While the average tumor motion was small, some patients had tumors that moved more than 10 mm due to respiration (Video: Supplementary information IV). The tumor motion in our study is larger than reported by Bradley et al. which was presumably due to the longer period of imaging that was considered. Our findings suggest that a 2.0 mm PTV expansion in superior-inferior and a 0.7 mm in anterior-posterior is required to account for the internal motion for laryngeal tumors. Here we want to emphasize that relatively small margins of 2.0 mm in superior-inferior are sufficient to account for the large displacements of up to 12 mm.

Tumor motion was quantified using cine MRI in combination with deformable image registration. While deformable image registration is widely used [27], a general geometric validation in the radiotherapy setting remains difficult [28]. The accuracy of deformable image registration is dependent on both the

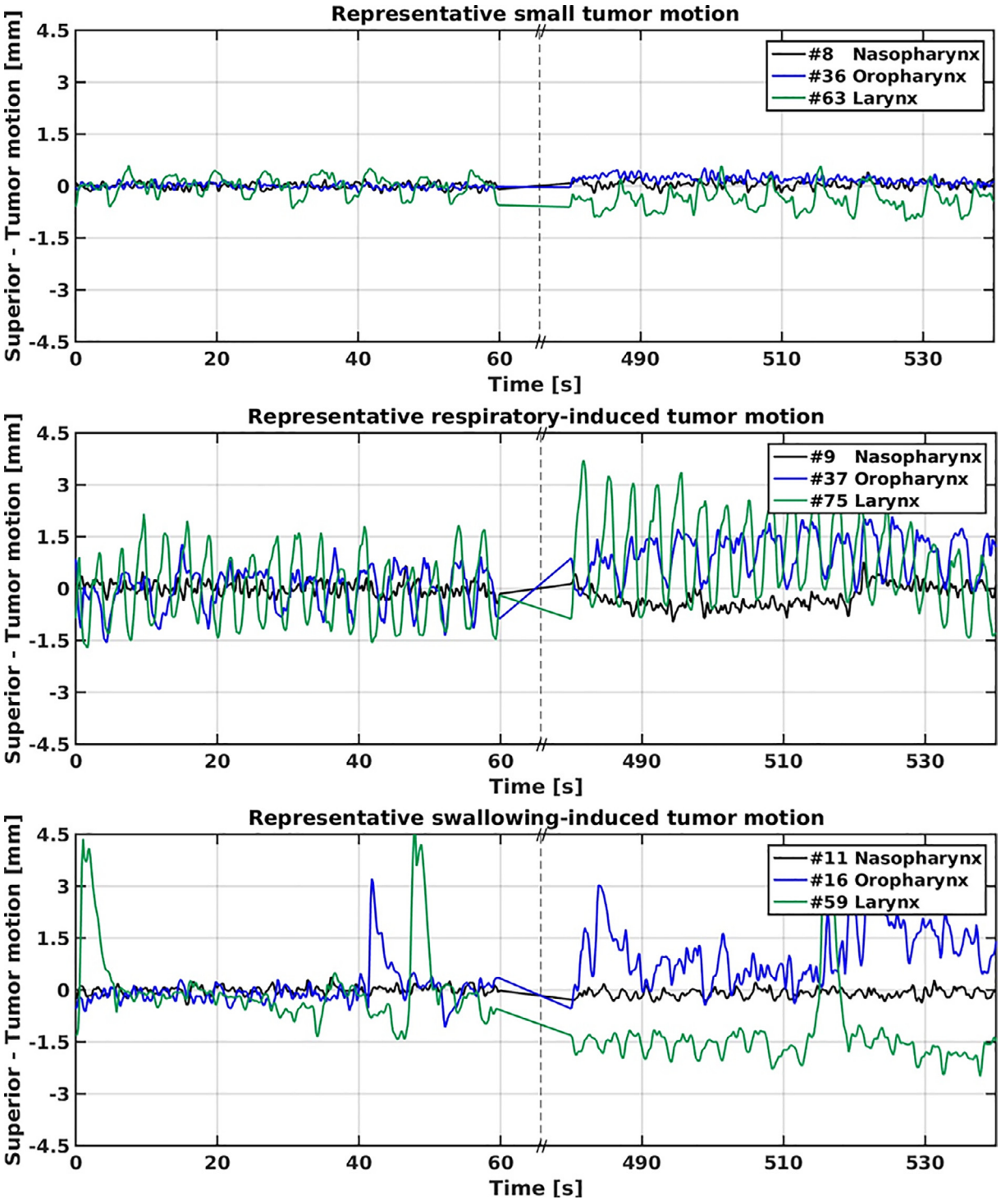

Fig. 3. Examples of motion in the superior direction for tumors that showed almost no motion, for tumors that showed respiratory-induced motion and tumors that showed swallowing-induced motion. The graphs have a break on the horizontal axis to differentiate the data from the two different cine MR scans.

Table 1
Mean maximum (95th percentile) tumor motion over the cine scans.

Mean max motion	Superior [mm]	Inferior [mm]	Anterior [mm]	Posterior [mm]
Nasopharynx (n = 12)	1.0	1.2	0.9	0.8
Oropharynx (n = 43)	1.7	2.1	1.8	1.6
Larynx (n = 29)	3.8	3.3	2.0	2.2
Combined (n = 84)	2.3	2.4	1.8	1.7

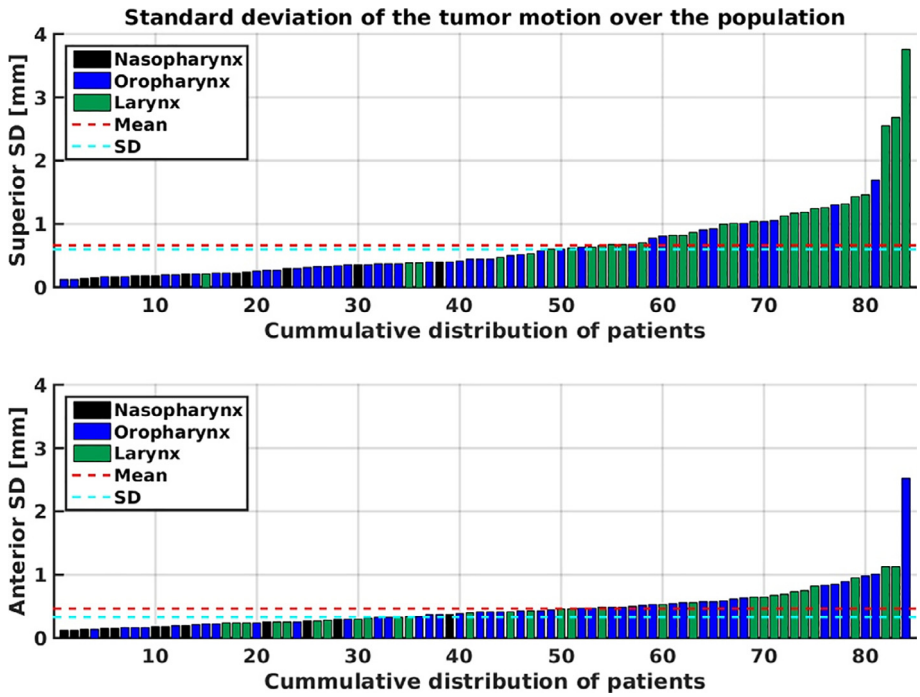

Fig. 4. Sorted distribution of the standard deviation of the tumor motion profiles and colored by the anatomical location.

Table 2
PTV margins calculated with the quantified tumor motion.

PTV margin (IMRT)	Superior [mm]	Inferior [mm]	Anterior [mm]	Posterior [mm]
Nasopharynx (n = 12)	2.8	2.8	2.8	2.8
Oropharynx (n = 43)	3.1	3.2	3.2	3.1
Larynx (n = 29)	4.3	3.8	3.2	3.2
Combined (n = 84)	3.5	3.4	3.1	3.1

parametrization of the algorithm and the contrast of the images. In this work we validated the deformable image registration algorithm by tracking local landmarks (epiglottis, posterior oral cavity) in a small number of patients and adjusted the parametrization such that the best match was obtained. In addition, we subtracted the deformation vector field from each image and inspected the residual motion to ensure that the registration fully resolved the motion around the tumor. Deformable image registration was used to quantify tumor with sub-voxel precision. Sub-voxel precision of the specific algorithm used in this work was demonstrated to detect deformations at approximately 1/3 of the pixel size [29].

Tumor motion was quantified over a 8 min period approximately 5 and 13 min after the patient entered the MR scanner. While these times correspond with typical step-and-shoot intensity modulated radiotherapy (IMRT) treatment at our institute, typical volumetric modulated arc therapy treatment times are approximately half [30]. For the volumetric modulated arc therapy (VMAT) treatment times we calculated the PTV margins by halving the tumor shift between the two cine MR scans (Supplementary information V). Note that VMAT and hypofractionation will counterbalance the assumption that swallowing has a relatively low contribution to total accumulated dose. However, ultimately it is the percentage of time per fraction that the person is swallowing which is important, which does not differ between VMAT or IMRT.

The motion analysis provides a representative overview of the tumor motion in a large group of patients with head-and-neck cancer, however the analysis has some inherent limitations: (1) Left–right (through-plane) motion can affect the image registration, however previous studies reported the motion to be small compared to slice thickness of 10 mm used in our acquisition [17]. (2) The tumor motion between the two cine MR scans was processed as a linear trend. This assumption is not completely valid but it is the most reasonable approach for the presented data [24]. (3) The persistence of the tumor motion over a prolonged period of treatment is unclear. For example, swallowing incidence is known to vary over the course of the treatment [11].

Intrafractional tumor motion was quantified in 84 patients using cine MRI with deformable image registration and population-based PTV margins were calculated for patients with head-and-neck tumors. Although the average tumor motion was small (95th percentile motion <3.0 mm), tumor motion varied considerably between patients (0.1–12.0 mm). Incorporating the tumor motion in the margin recipe expanded the CTV to PTV with 0.2 mm for nasopharyngeal tumors, with 0.6 mm for oropharyngeal tumors and with 1.7 mm for laryngeal tumors.

Conflict of interest

None.

Acknowledgements

This work is part of the research programme HTSM with project number 15354, which is financed by the Netherlands Organisation for Scientific Research (NWO) and Philips Healthcare (Best, the Netherlands).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.09.015.

References

[1] Ratko T, Douglas GW, De Souza J, Belinson SE, Aronson N. Radiotherapy treatments for head and neck cancer update. Eff Heal Care Progr Comp Eff Rev 2014;144.

[2] Houweling AC, van der Meer S, van der Wal E, Terhaard CHJ, Raaijmakers CPJ. Improved immobilization using an individual head support in head and neck cancer patients. Radiother Oncol 2010;96:100–3.

[3] Nakata A, Tateoka K, Fujimoto K, et al. The reproducibility of patient setup for head and neck cancers treated with image-guided and intensity-modulated radiation therapies using thermoplastic immobilization device. Int J Med Physics, Clin Eng Radiat Oncol 2013;2:117–24.

[4] Astreinidou E, Bel A, Raaijmakers CPJ, Terhaard CHJ, Lagendijk JJW. Adequate margins for random setup uncertainties in head-and-neck IMRT. Int J Radiat Oncol Biol Phys 2005;61:938–44.

[5] Schubert LK, Westerly DC, Tomé WA, et al. A comprehensive assessment by tumor site of patient setup using daily MVCT imaging from more than 3,800 helical tomotherapy treatments. Int J Radiat Oncol Biol Phys 2009;73:1260–9.

[6] Kwa SLS, Al-Mamgani A, Osman SOS, Gangsaas A, Levendag PC, Heijmen BJM. Inter- and intrafraction target motion in highly focused single vocal cord irradiation of t1a larynx cancer patients. Int J Radiat Oncol Biol Phys 2015;93:190–5.

[7] Castadot P, Geets X, Lee JA, Christian N, Grégoire V. Assessment by a deformable registration method of the volumetric and positional changes of target volumes and organs at risk in pharyngo-laryngeal tumors treated with concomitant chemo-radiation. Radiother Oncol 2010;95:209–17.

[8] International Commission on Radiation Units and Measurements (ICRU). Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT) – Report 83. J ICRU. 2010;10(2):1-58.

[9] Vugts CAJM, Terhaard CHJ, Philippens MEP, Pameijer FA, Kasperts N, Raaijmakers CPJ. Consequences of tumor planning target volume reduction in treatment of T2–T4 laryngeal cancer. Radiat Oncol 2014;9:195.

[10] Leonard RJ, Kendall KA, McKenzie S, Gonçalves MI, Walker A. Structural displacements in normal swallowing: a videofluoroscopic study. Dysphagia 2000;15:146–52.

[11] Van Asselen B, Raaijmakers CPJ, Lagendijk JJW, Terhaard CHJ. Intrafraction motions of the larynx during radiotherapy. Int J Radiat Oncol Biol Phys 2003;56:384–90.

[12] Prévost JB, de Boer H, Pöll J, Voet P, Levendag P. Analysis of the motion of oropharyngeal tumors and consequences in planning target volume determination. Radiother Oncol 2008;87:268–73.

[13] Dantas RO, Kern MK, Massey BT, et al. Effect of swallowed bolus variables on oral and pharyngeal phases of swallowing. Am J Physiol 1990;258:G675–81.

[14] Jacob P, Kahrilas PJ, Logemann JA, Shah V, Ha T. Upper esophageal sphincter opening and modulation during swallowing. Gastroenterology 1989;97:1469–78.

[15] Bradley JA, Paulson ES, Ahunbay E, Schultz C, Li XA, Wang D. Dynamic MRI analysis of tumor and organ motion during rest and deglutition and margin assessment for radiotherapy of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2011;81:803–12.

[16] Hamlet S, Ezzell G, Aref A. Larynx motion associated with swallowing during radiation therapy. Int J Radiat Oncol Biol Phys 1994;28:467–70.

[17] Gurney-Champion OJ, McQuaid D, Dunlop A, et al. MRI-based assessment of 3D intrafractional motion of head and neck cancer for radiation therapy. Int. J Radiat Oncol 2017.

[18] Bol GH, Kotte ANTJ, van der Heide UA, Lagendijk JJW. Simultaneous multi-modality ROI delineation in clinical practice. Comput Methods Programs Biomed 2009;96:133–40.

[19] Zachiu C, Denis de Senneville B, Moonen C, Ries M. A framework for the correction of slow physiological drifts during MR-guided HIFU therapies: Proof of concept. Med Phys 2015;42:4137.

[20] Zachiu C, Papadakis N, Ries M, Moonen C, Denis de Senneville B. An improved optical flow tracking technique for real-time MR-guided beam therapies in moving organs. Phys Med Biol 2015;60:9003–29.

[21] Matsuo K, Palmer J. Anatomy and physiology of feeding and swallowing - normal and abnormal. Phys Med Rehabil Clin N Am 2008;19:691–707.

[22] Wolthaus JWH, Sonke J-J, van Herk M, et al. Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Int J Radiat Oncol Biol Phys 2008;70:1229–38.

[23] de Boer HCJ, Heijmen BJM. eNAL: an extension of the NAL setup correction protocol for effective use of weekly follow-up measurements. Int J Radiat Oncol Biol Phys 2007;67:1586–95.

[24] van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol 2004;14:52–64.

[25] van Herk M, Remeijer P, Rasch C, Lebesque J. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. 2000;47(4):1121–1135.

[26] Chen AM, Farwell DG, Luu Q, Donald PJ, Perks J, Purdy JA. Evaluation of the planning target volume in the treatment of head and neck cancer with intensity-modulated radiotherapy: What is the appropriate expansion margin in the setting of daily image guidance? Int J Radiat Oncol Biol Phys 2011;81:943–9.

[27] Oliveira FPM, Tavares JMRS. Medical image registration: a review. Comput Methods Biomech Biomed Eng 2014;17:73–93.

[28] Schultheiss TE, Tomé WA, Orton CG. It is not appropriate to “deform” dose along with deformable image registration in adaptive radiotherapy. Med Phys 2012;39:6531–3.

[29] Glitzner M, De Senneville BD, Lagendijk JJW, Raaymakers BW, Crijns SPM. On-line 3D motion estimation using low resolution MRI. Phys Med Biol 2015;60:N301–10.

[30] Bertelsen A, Hansen CR, Johansen J, Brink C. Single arc volumetric modulated arc therapy of head and neck cancer. Radiother Oncol 2010;95:142–8.