Radiation dose to the tongue and velopharynx predicts acoustic-articulatory changes after chemo-IMRT treatment for advanced head and neck cancer

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HEAD AND NECK

Radiation dose to the tongue and velopharynx predicts acoustic-articulatory changes after chemo-IMRT treatment for advanced head and neck cancer

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Abstract The aim of this study was to investigate to what extent changes in speech after C-IMRT treatment are related to mean doses to the tongue and velopharynx (VP). In 34 patients with advanced hypopharyngeal, nasopharyngeal, or oropharyngeal cancer, changes in speech from pretreatment to 10 weeks and 1 year posttreatment were correlated with mean doses to the base of tongue (BOT), oral cavity (OC) and tonsillar fossa/soft palate (VP). Differences in anteroposterior tongue position, dorsoventral degree of tongue to palate or pharynx constriction, grooving, strength, nasality, and laryngeal rise, were assessed by acoustic changes in three speech sounds that depend on a (post-) alveolar closure or narrowing (/t/, /s/, /z/), three with a tongue to palate/pharyngeal narrowing (/l/, /r/, /u/), and in vowel /a/ at comfortable and highest pitch. Acoustically assessed changes in tongue positioning, shape, velopharyngeal constriction, and laryngeal elevation were significantly related to mean doses to the tongue and velopharynx. The mean dose to BOT predicted changes in anteroposterior tongue positioning from pre- to 10-weeks posttreatment. From pretreatment to 1-year, mean doses to BOT, OC, and VP were related to changes in grooving, strength, laryngeal height, nasality, palatalization, and degree of pharyngeal constriction. Changes in speech are related to mean doses to the base of tongue and velopharynx. The outcome indicates that strength, motility, and the balance between agonist and antagonist muscle forces change significantly after radiotherapy.

Keywords Head and neck cancer · IMRT · Chemoradiation · Speech muscles · Acoustics · Articulation

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Introduction

In locally advanced head and neck cancer, combined chemotherapy and radiation treatment (CRT) has been associated with higher loco-regional control compared to radiation therapy alone [1]. Nonetheless, swallowing studies regularly show functional disorders such as impaired velopharyngeal closure, and reduced larynx-, hyoid, or tongue mobility [2–4]. By the use of intensity-modulated radiotherapy (IMRT) and the sparing of organs at risk such as the parotid, the side effects of this combined treatment could be reduced, without significantly compromising target coverage [5–7]. In view of functioning, the standard organs at risk (OAR) in treatment protocols these days usually include the parotid and submandibular glands,

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the larynx, and the constrictor muscles [8]. However, as Pearson et al. [9] recently pointed out, only few of the studies that focus on (swallow) functioning and the sparing of structures investigated directly the structure-to-function relationships by, e.g., evaluating outcome variables that represent the function of a certain muscle structure.

Though its significant impact on quality of life is well known, speech functioning is rarely monitored within head and neck cancer patients [10–14]. Regardless of intelligibility, minor speech deficiencies can already alter an interlocutors' social perception of a speaker [15, 16]. Two studies that assessed the patient-experienced speech problems prospectively in (C)RT patients revealed correlations between subjective speech problems and glottis and surrounding doses [17, 18]. Due to the applied patient questionnaires (HNQOL-C, UWQOL-S), the effects of laryngeal functioning (phonation) versus non-laryngeal (e.g., tongue or velopharyngeal) functioning on the subjectively assessed speech categories are difficult to disentangle. Structures involved in speech comprise the whole oral cavity, oropharynx, and larynx. Next to intrinsic laryngeal muscles, extrinsic muscles that move the larynx vertically during swallowing [9] add, together with the rotation of the cricoid, to the voluntary use of the fundamental frequency and voicing [19, 20]. Velopharyngeal functioning, which in case of weakness can cause regurgitation and swallowing problems [21], controls nasal air flow during speech and affects resonance and air pressures. Next to its role in the oral (preparatory) and oropharyngeal phase of swallowing, the tongue and its (symmetric) pliability in terms of grooving, lengthening, widening, or concaving are essential for the differentiation of articulation manners and articulation places from the lips to the hard/soft palate and pharynx. In comparison with swallowing or mastication, where timing of muscle activity is complex but sequentially repetitive, the process of speaking during conversational speech requires high variability in the sequence of muscle activities, and, with five to ten syllables per second, rather rapid fine-tuned movements.

In a preventive swallowing exercise study conducted from 2006 to 2008 at The Netherlands Cancer Institute, "Prevention of trismus, swallowing and speech problems in patients treated with chemoradiation for advanced head and neck cancer", all patients received preventive swallowing and mouth opening exercises. Organs at risk in swallowing and mastication were delineated, and significant dose relationships were found between radiation doses to inferior constrictor and dysphagia, and mastication structures and mouth opening [22]. Acoustic analyses of the patients' speech data furthermore revealed significant tumor site-related treatment effects in articulation power and precision after chemoradiation [23].

With the present study, we aim to answer the question to what extent the acoustic-articulatory changes after chemo-IMRT treatment are related to mean doses to two important structures in articulation, the tongue and velopharynx. Hypothetically, increasing irradiation of tumor-free muscles and tissues increasingly hampers speech behavior.

Materials and methods

Subjects

Fifty-five patients with advanced stage (III, IV) head and neck squamous cell carcinoma were included between 2006 and 2008 in a randomized controlled clinical trial at the Netherlands Cancer Institution (compare [21]). For 34 of the 39 patients who were disease-free at the 1 year assessment point, speech recordings were available at three assessment points: at baseline, at 10 weeks, and at 1 year after the end of treatment (for more detail [22]). Table 1 shows the characteristics of the 34 patients.

IMRT and chemotherapy

The patients received 100 mg/m^2 cisplatin as a 40-min IV infusion on days 1, 22, and 43 over the 7 weeks of

Table 1 Characteristics of the 34 patients whose speech was analyzed at the three assessment points

	N	%
Total		100
Median age 58 (39–77)	34	
Male	27	79
T category		
T1	6	18
T2	13	38
T3	11	32
T4	4	12
N category		
N0	3	9
N1	12	35
N2	15	44
N3	4	12
Stage		
III	13	38
IV	21	62
Primary site		
Hypopharynx	13	38
Nasopharynx	6	17
Oral cavity/oropharynx	15	44

radiation course. Radiotherapy was given with 6 MV photons on a linear accelerator, up to 70 Gy in 35 fractions of 2 Gy in 7 weeks with sequential boost. An immobilization custom-made mask was used for all patients. The IMRT was calculated on the CT planning using the Pinacle treatment planning system (phill-NL). The IMRT consisted of a 5–7 angle coplanar setup with a total number of segments between 40 and 80. Ninety-five percent of the planning target volume (PTV) received 95 % of the prescribed dose [22].

MRI scan was used to determine RT-field areas and target volumes for swallowing and mastication. Target delineation was done on computed tomotherapy images in treatment position. The parotid glands were delineated to keep the mean dose below 26 Gy for the spared parotid gland in every patient. The clinical target volumes (CTVs) were expanded uniformly by 0.5 cm to yield their respective planning target volumes (PTVs), and for all delineated structures dose–volume histograms (DVHs) were calculated. The mean radiation dose was defined as the normalized mean dose for the total volume of the irradiated organ. The maximum dose allowed to the spinal cord was 50 Gy.

Regions of interest and study endpoints

Main point of interest in terms of speech was changes in tongue positioning along the anteroposterior and dorsoventral axis, laryngeal elevation, and changes in velopharyngeal functioning. In view of the available delineated structures, the base of tongue (BOT), the oral cavity (OC), and the tonsillar fossa and soft palate (VP) were most suitable for the present studies (Fig. 1a, b). Not all delineations/CT scans were available for all patients. By including the soft palate, the tonsillar fossa, and due to its adjacency to the palatoglossal and palatopharyngeal arch, the delineated VP structure roughly covered all muscles that are active in velopharyngeal closure. The delineated structure OC (oral cavity) covered the whole tongue except for the base of tongue, and thus included the intrinsic tongue muscles, the anterior and medial genioglossus. The base of tongue was the smallest of the delineated structures (BOT) and covered the posterior genioglossus, the geniohyoid, and was adjacent to suprahyoidal muscles. Since the larynx received high doses in almost all patients, it was not assessed for dose relationships.

Speech data

Speech data included a standard Dutch text, a list of words, and sustained /a/-vowels. Analysis of the speech data was conducted according to the methodology extensively described earlier [23]: Nasality as an indicator for velopharyngeal closure was assessed by band energy differences in sustained /a/ at comfortable pitch and loudness. As an indicator for changes in laryngeal elevation (compare [9, 19]), the fundamental frequency (f0, i.e., pitch) was assessed in the highest possible /a/.

Three speech sounds that depend on a (post-) alveolar closure or narrowing by the tongue apex and blade (/t/, /s/, /z/) were assessed by differences in the spectral energy distribution of the respective sound segment before and after treatment. The dimensions of the cavity anterior to the constriction and the shape of the constriction are reflected in the location and amplitude of the spectral noise peaks. The larger the space in front of the oral narrowing or constriction, the lower is (the begin of) the spectral energy distribution. The work of Fant [24] and Stevens [25] gives a good overview of speech production and acoustics. The spectral burst energy of /t/ was assessed as an indicator of the strength of the (post-) alveolar total constriction and pressure build-up behind the constriction. /s/ was additionally assessed for grooving indicated by changes in the strength and spectral distribution of frication noise (compare [26]).

Three speech sounds that require a posterior (secondary) narrowing by elevation of the back of the tongue (/u/, /r/, Dutch velarized /l/) were assessed by formants. Dutch /l/ is produced by a primary alveolar tongue constriction with lateral openings, and a secondary uvular/velar narrowing in the posterior oral tract. Changes in the lateral opening were assessed by the first formant; the pharyngeal constriction by the second formant (compare [24]). Dutch /r/ is produced either by uvular/velar narrowing, or by an alveolar narrowing with a secondary velar/uvular narrowing. Changes in /r/ were assessed by the second formant (palatalization) and the amplitude of the third formant (pharyngeal constriction), and by the second formant of /u/ as indicator of tongue height. All sound segmentation and automatic acoustic analyses were done with Praat [27].

Statistical analyses

For differences between tumor sites at baseline, we used the Mann–Whitney *U* test. Spearman's correlations were applied to assess relationships between mean doses and changes in articulatory-acoustic measures between assessment points. For each organ at risk, dose relationships were run on the group of patients whose primary tumor site and tumor extension did not overlap with the respective organ at risk. This was to minimize the probability of an effect of baseline function deficits and tumor regression on the data, to estimate true dose effects. Statistical analyses were performed in IBM SPSS for Windows (release 21.0, IBM Corp.). For all analyses, a p value of $<=0.05$ (two tailed) was considered statistically significant.

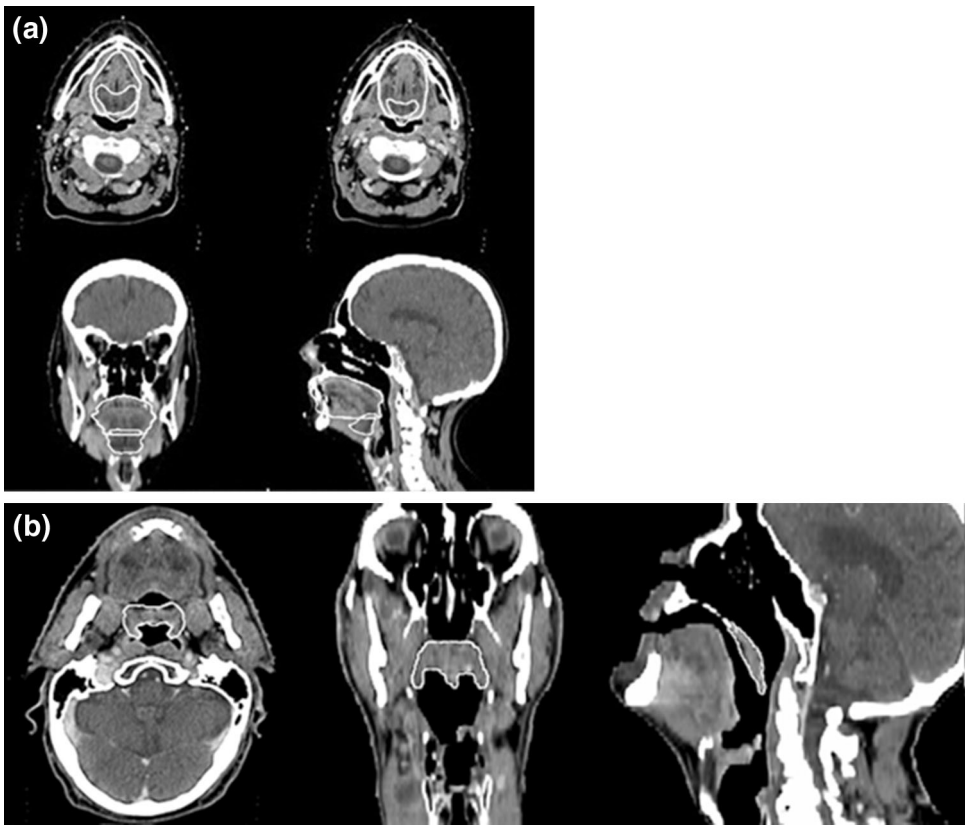

Fig. 1 **a** Example of contoured structures: transverse, coronal, and sagittal delineation of the base of tongue (BOT) and the oral cavity (OC). **b** Example of contoured velopharyngeal structure: Transverse, coronal, and sagittal delineation of the tonsillar fossa/soft palate (VP)

Results

Table 2 gives an overview of the medians of the mean doses to the base of tongue, tonsillar fossa/soft palate, oral cavity, and the larynx. Mean doses to the BOT correlated positively with mean doses to OC ($r = 0.647$, $p = 0.002$) and VP ($r = 0.799$, $p < 0.001$); the correlation between VP and OC was the strongest ($r = 0.851$, $p < 0.001$). Mean doses to the larynx correlated negatively with the BOT ($r = -0.445$, $p = 0.043$), the OC ($r = -0.421$, $p = 0.026$), and the VP ($r = -0.806$, $p < 0.001$).

At baseline

The sound measures were analyzed for tumor effects before treatment. In 10 of the 34 patients (29 %), the tumor was located in, or extended into the tongue; whereas in 13 patients (38 %), the tumor was located in, or extended into the region of the tonsillar fossa or soft palate. Except for the uvular constriction in /r/, $p = 0.031$, $Z = -2{,}162$, which indicated a weaker constriction in the group with base of tongue tumors, there was no significant difference between the group with or without overlap in view of the OAR. Sound assessment in the group with tumors involving the soft palate or tonsillar fossa indicated a significantly more retracted tongue in /z/ ($p = 0.005$, $Z = -2{,}818$) and higher maximum f0 ($p = 0.038$, $Z = -2{,}073$). There was no significant difference in the highest possible maximum f0 when laryngeal versus non-laryngeal tumor sites were compared. Of all assessed measures, only measures of /z/ indicated a more retracted articulation in tumor sites that did not involve the larynx ($p = 0.011$, $Z = -2{,}552$).

Table 2 Median (range) of mean doses in Gy to the organs at risk (OAR) for the three primary tumor sites hypopharynx, nasopharynx and oropharynx/oral cavity

OAR	Mean doses in Gy		
	Hypopharynx Ca, median (range)	Nasopharynx Ca, median (range)	Oropharynx Ca, median (range)
Tonsillar fossa/soft palate	15 (7–41)	70 (69–70)	68 (41–71)
Oral cavity	11 (4–30)	49 (33–51)	34 (7–54)
Base of tongue	50 (44–58)	63 (62–65)	70 (65–71)
Larynx	68 (64–70)	45 (41–51)	55 (15–69)

From pretreatment to 10-week follow-up

Table 3 lists the significant correlations between changes from pre- to 10-week posttreatment and the mean doses to the delineated structures. In general, correlations of the OC and BOT overlapped. Acoustically assessed changes in anteroposterior position correlated mainly with doses to the OC and BOT.

From pre- to 10-week posttreatment, effects were apparent across the whole group, but stronger when patients with tumors in the respective delineated region were excluded from analysis. For measures assessing the approximation of the base of tongue to the palate or pharynx (/r/, /u/ /l/), there were no significant correlations between mean doses and assessed changes (Table 3). Considering the mean doses to the VP (range 7–71 Gy), above 40 Gy, the measures indicated a decrease in tongue height, frication, and tongue retraction, while for low mean doses, these parameters increased (example, Fig. 2). For mean doses to the OC, a less clear-cut reversal point appeared around 30 Gy. In view of the mean doses to BOT, above ca. 55 Gy, there was a decrease in tongue retraction and motility, while below 55 Gy, the measures increased (example Fig. 3). A decrease in tongue retraction was also found for the group whose tumors extended into the VP, and who had presented with a significantly more retracted tongue at baseline.

From pretreatment to 1-year follow-up

Comparing pre- versus 10-weeks, the predictability of changes in anteroposterior position decreased, while it increased for measures assessing tongue shape and sounds that are articulated more posteriorly (Table 3); there were more significant correlations for measures that assessed the posterior oral tract constellation. Higher doses to the OC correlated with decreasing frication of /s/, and high mean doses to the BOT and OC were related to decreasing strength of /t/, increased nasality, weaker pharyngeal constriction, and lowering of the highest possible f0 (less laryngeal rise). For mean doses to the OC, again, a reversal point was less clear-cut in the measures and appeared around 30 Gy. In view of mean doses to the base of tongue (range 44–71 Gy), below 55 Gy, comparable to the results from the first follow-up, there was less nasality and an increase in strength, the highest possible frequency, and tongue retraction; while above ca. 55 Gy, the measures showed weakening (compare Figs. 4, 5).

Table 3 Spearman correlations (r^2, in brackets p, sig. 2-tailed) between mean doses to the oral cavity (OC), base of tongue (BOT), and tonsillar fossa/soft palate (VP) without overlap primary tumor/metastatic lymph node and acoustic differences between baseline and follow-up (paired difference)

	OC mean dose ($N = 20$)		BOT mean dose ($N = 13$)		VP mean dose ($N = 10$)	
	Pre–10 weeks	Pre–1 year	Pre–10 weeks	Pre–1 year	Pre–10 weeks	Pre–1 year
Tongue position						
/z/	−0.543* (0.013)		−0.549 (0.052)		−0.648* (0.043)	
/t/	−0.507* (0.023)		−0.659* (0.014)	−0.599 (0.055)		
Motility						
/s/			−0.743** (0.004)			
Groove/frication						
/s/	0.424 (0.062)	0.450* (0.047)		0.505 (0.078)		
Strength						
/t/		0.442 (0.058)		0.697* (0.012)		
Highest possible f0						
/a/		0.438 (0.053)		0.621* (0.024)		
Tongue height						
/u/	−0.379 (0.051)					
Palatalization						
/r/						−0.685* (0.029)
Nasality						
/a/		0.534* (0.023)		0.629* (0.028)		

Only significant or marginally significant results are presented

* Signifies statistical significance $p < 0.05$

** Signifies statistical significance $p < 0.01$

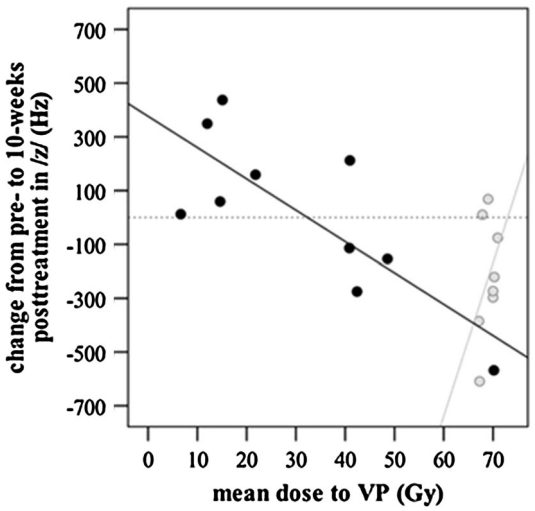

Fig. 2 Acoustic difference (*y*-axis) in /z/ between pre- and 10-week posttreatment as a function of the mean dose to the tonsillar fossa/soft palate (VP, *x*-axis). *Black dots* and linear regression: no overlap tumor extension and VP structure; in *gray* overlap

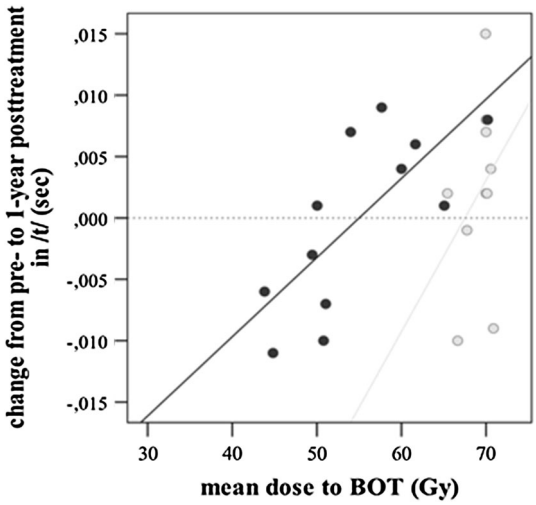

Fig. 4 Acoustic difference (*y*-axis) in /t/ between pre- and 1-year posttreatment as a function of the mean dose to the base of tongue (BOT, *x*-axis). *Black dots* and linear regression: no overlap tumor extension and BOT; in *gray*: overlap

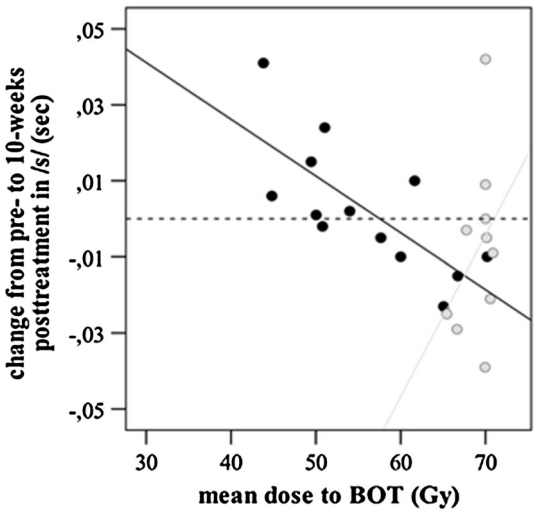

Fig. 3 Acoustic difference (*y*-axis) in /s/ between pre- and 10-week posttreatment as a function of the mean dose to the base of tongue (BOT, *x*-axis). *Black dots* and linear regression: no overlap tumor extension and tongue; in *gray*: overlap

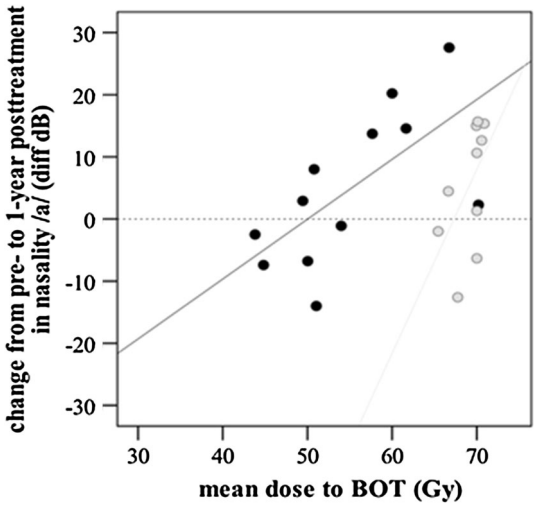

Fig. 5 Acoustic difference (*y*-axis) in nasality between pre- and 1-year posttreatment as a function of the mean dose to the base of tongue (BOT, *x*-axis). *Black dots* and linear regression: no overlap tumor extension and tongue; in *gray*: overlap

Discussion

Previous studies on the present patient group revealed dose relationships in prospective swallowing assessment and articulatory-acoustic changes after treatment by C-IMRT. The current findings built on this work and show that the assessed differences in sound quality that reflect changes in articulation (motorics) after treatment are related to mean doses to the base of tongue an velopharyngeal structures. When the individual extensions of the advanced tumors into regions of the respective OAR were accounted for, from pre- to 10-week posttreatment, there was a significant linear relationship between mean doses and measures that assessed changes in the anteroposterior tongue position. Whereas measures that assessed changes in more complex articulation such as grooving, strength, laryngeal height, nasality, palatalization and uvular constriction correlated significantly (stronger) with mean doses from pre- to 1-year posttreatment. For structures with rarely proliferating cells, such as the tongue, side effects can appear on the long term, and the increase in significant dose relationships after one year might indicate a progressive treatment effect due

to fibrosis or atrophy. In general, to prevent or decrease posttreatment deficits resulting from fibrosis and scarring after high-dose irradiation, physical therapy is advised [8]; in the present case, this would mean more fine-tuned tongue muscle-oriented exercising or stimulation.

In our data, after 1 year, high mean doses to the (base of) tongue were related to decreases in the acoustic measures that monitored laryngeal rise, nasality, and glosso-palatal/-pharyngeal constrictions. The findings in the present speech assessment coincide with decreases in oral and pharyngeal motility in swallowing studies after radiation treatment provided to the base of tongue or larynx regions [4, 28, 29]. The sensitivity of the speech data to mean doses to the BOT is also in line with the role of the genioglossus in tongue to palate pressure [30], and with the activity of almost all suprahyoidal and longitudinal pharyngeal muscles during hyolaryngeal elevation [9].

Within the tongue, fiber composition and the amount of connective tissues and fat differ, as does mobility, velocity, and presumably sensitivity to radiation or exercising. While the apex with a large amount of small type II fibers reaches the highest velocity, positioning movements of the tongue body, or e.g., rising the velum, are comparatively slow [25, 31, 32]. The styloglossi, transversus, verticalis, and longitudinal muscles work together to shape the tongue and move the tip [20, 26, 33, 34]. For /t/, studies have shown the activity of the superior longitudinal muscles, the anterior digastric, the mylohyoid, and, for the release of the (post-) alveolar constriction, activity of the inferior longitudinal muscles [35]. Next to the genioglossus, the verticalis and transversi, together with the longitudinal muscles are also known to affect central grooving [26, 35], and were covered in the delineated oral cavity, and accordingly, increasing doses to the tongue correlated with decreases in /s/ quality and strength of /t/.

Treatment protocols these days usually include the larynx, the constrictor muscles, and the parotid and submandibular glands. Next to covering the tongue, and thereby a structure that is crucial for speech, swallowing, and chewing, the delineated oral cavity also plays an important role in xerostomia, mucositis and taste loss [5, 28, 29]. Due to their role in swallowing and speech, both the tongue and the velopharyngeal structure might as well be considered as the organs at risk in treatment planning.

In the head and neck region, in view of structures needed for speech functioning or swallowing, there are comparatively few skeletal muscle attachments, and many, often antagonistic, muscles intersect and act synergistically [36]. Almost all our correlations revealed a turning point, i.e., in the low dose area, the articulatory pattern of change contrasted with the pattern at high doses from pretreatment to posttreatment (e.g., tongue or larynx heightening versus lowering). The contrasting dose-related patterns might reflect the sensitivity of articulation precision towards a (radiation-induced) imbalance between antagonistic muscle forces.

While for swallowing, the whole velopharyngeal process is active to reach a complete closure in the oral tract, in articulation, the posterior pharyngeal wall is rather steady [37], and the passage to the nostrils can be sealed while the tongue is fronted (e.g., for /t/, /s/) or in a low position (e.g., /a/), and thus the pharyngeal passage is open. On MRI across various speech sounds, a small nasopharyngeal area opening and the strongest reduction in length of the levator palatini was seen during anterior fricative (i.e., /s/, /z/) production [38]. In our data, though the mean dose to the VP (coincidently) affected /z/ significantly, there were few dose–effect relationships considering VP. There was a lack of data in view of higher VP mean doses in patients whose tumor extension did not involve the soft palate or tonsillar fossa. Additionally, the delineated structure VP involved not only palatal elevators and tensors, but was also adjacent to palatal or pharyngeal depressor muscles, which probably hampered a disentanglement of mean dose effects on palatal elevation versus lowering musculature.

In view of the latter, articulation functioning is a highly variable, fine-tuned process, and the delineated OAR—except for BOT—are quite rough. Another drawback of the present study is the lack of data regarding the delineation of the assessed organs at risk. Difficult to single out are effects of individuality of anatomy, tumor location, tumor extent, and unilateral treatment. Also, the effect of radiation on innervations of, e.g., the hypoglossal nerve or the pharyngeal branch that were covered in the delineated regions, are yet unknown, and the tongue's adaptation and compensatory behavior in speech in view of asymmetric changes in muscles and tissues needs to be investigated as well. Nonetheless, the data showed that speech analyses can offer an effortless non-invasive way to assess radiation-induced toxicity affecting muscle functioning in more detail.

Conclusion

Overall, the present speech data show changes dependent on radiation doses to the tongue and velopharynx. This indicates that the balance in the complex mesh of muscle protagonists and antagonists has changed significantly after treatment and has an important influence on articulation. Especially radiotherapy doses to the base of tongue had manifold non-local functional effects on voice and speech. However, more data and finer delineation of OAR are needed to support the effects on muscle functioning and more precisely show dose–effect relationships.

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References

1. Pignon JP et al (2000) Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet 355(9208):949–955
2. Kotz T et al (1999) Pharyngeal transport dysfunction consequent to an organ-sparing protocol. Arch Otolaryngol Head Neck Surg 125(4):410–413
3. Lazarus C (2009) Effects of Chemoradiotherapy on tongue function in patients with head and neck cancer. Perspect Swallow Swallow Disord (Dysphagia) 18(2):55–60
4. Logemann JA et al (2008) Swallowing disorders in the first year after radiation and chemoradiation. Head Neck 30(2):148–158
5. Wang X, Hu C, Eisbruch A (2011) Organ-sparing radiation therapy for head and neck cancer. Nat Rev Clin Oncol 8(11):639–648
6. Marta GN et al (2014) Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol 110(1):9–15
7. Chen AM et al (2012) Intensity-modulated radiotherapy is associated with improved global quality of life among long-term survivors of head-and-neck cancer. Int J Radiat Oncol Biol Phys 84(1):170–175
8. Thomson D et al (2014) Evaluation of an automatic segmentation algorithm for definition of head and neck organs at risk. Radiat Oncol 9(1):173
9. Pearson WG Jr et al (2013) Evaluating swallowing muscles essential for hyolaryngeal elevation by using muscle functional magnetic resonance imaging. Int J Radiat Oncol Biol Phys 85(3):735–740
10. Givens DJ et al (2009) Adverse events associated with concurrent chemoradiation therapy in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 135(12):1209–1217
11. Schuster M, Stelzle F (2012) Outcome measurements after oral cancer treatment: speech and speech-related aspects-an overview. Oral Maxillofac Surg 16(3):291–308
12. Verdonck-de Leeuw IM et al (2014) The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: a prospective cohort study. Radiother Oncol 110(3):422–428
13. Jacobi I et al (2010) Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol 267:1495–1505
14. Lazarus CL et al (2014) Functional outcomes and quality of life after chemoradiotherapy: baseline and 3 and 6 months post-treatment. Dysphagia 29(3):365–375
15. Kissane DW et al (2013) Preliminary evaluation of the reliability and validity of the Shame and Stigma Scale in head and neck cancer. Head Neck 35(2):172–183
16. Lallh AK, Rochet AP (2000) The effect of information on listeners' attitudes toward speakers with voice or resonance disorders. J Speech Lang Hear Res 43(3):782–795
17. Vainshtein JM et al (2014) Patient-reported voice and speech outcomes after whole-neck intensity modulated radiation therapy and chemotherapy for oropharyngeal cancer: prospective longitudinal study. Int J Radiat Oncol Biol Phys 89(5):973–980
18. Dornfeld K et al (2007) Radiation doses to structures within and adjacent to the larynx are correlated with long-term diet- and speech-related quality of life. Int J Radiat Oncol Biol Phys 68(3):750–757
19. Honda K, Masaki S, Shimada Y (2000) Observation of laryngeal control for voicing and pitch change by magnetic resonance imaging technique. In: Conference on Spoken Language Processing. Beijing, China: ICSLP
20. Raphael LJ, Borden GJ, Harris KS (2006) Speech science primer-physiology, acoustics, and perception of speech (eds). LJ Raphael, GJ Borden, KS Harris, vol 5, Lippincott Williams & Wilkins
21. Shaker R et al (1990) Coordination of deglutitive glottic closure with oropharyngeal swallowing. Gastroenterology 98(6):1478–1484
22. van der Molen L et al (2013) Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol 106(3):364–369
23. Jacobi I et al (2013) Acoustic analysis of changes in articulation proficiency in patients with advanced head and neck cancer treated with chemoradiotherapy. Ann Otol Rhinol Laryngol 122(12):754–762
24. Fant G (1970) Acoustic theory of speech production (With calculations based on X-ray studies of Russion articulations). Mouton & Co. N.V, The Hague
25. Stevens KN (2000) Acoustic phonetics. MIT Press, Cambridge
26. Stone M, Lundberg A (1996) Three-dimensional tongue surface shapes of English consonants and vowels. J Acoust Soc Am 99(6):3728–3737
27. Boersma P, Weenink D (2013) Praat: doing phonetics by computer (version 5.3.53) [Computer program], http://www.praat.org
28. Kumar R et al (2014) Radiation dose to the floor of mouth muscles predicts swallowing complications following chemoradiation in oropharyngeal squamous cell carcinoma. Oral Oncol 50(1):65–70
29. Schwartz DL et al (2010) Candidate dosimetric predictors of long-term swallowing dysfunction after oropharyngeal intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 78(5):1356–1365
30. Palmer PM et al (2008) Quantitative contributions of the muscles of the tongue, floor-of-mouth, jaw, and velum to tongue-to-palate pressure generation. J Speech Lang Hear Res 51(4):828–835
31. Stal P et al (2003) Fibre composition of human intrinsic tongue muscles. Cells Tissues Organs 173(3):147–161
32. Miller JL, Watkin KL, Chen MF (2002) Muscle, adipose, and connective tissue variations in intrinsic musculature of the adult human tongue. J Speech Lang Hear Res 45(1):51–65
33. Stone M et al (2001) Modeling tongue surface contours from Cine-MRI images. J Speech Lang Hear Res 44(5):1026–1040
34. Stone M et al (2001) Modeling the motion of the internal tongue from tagged cine-MRI images. J Acoust Soc Am 109(6):2974–2982
35. Marchal A (2009) From speech physiology to linguistic phonetics. Wiley-ISTE; 1 edn (September 22, 2009)
36. Takemoto H (2001) Morphological analyses of the human tongue musculature for three-dimensional modeling. J Speech Lang Hear Res 44(1):95–107
37. Magen HS et al (2003) Posterior pharyngeal wall position in the production of speech. J Speech Lang Hear Res 46(1):241–251
38. Ettema SL et al (2002) Magnetic resonance imaging of the levator veli palatini muscle during speech. Cleft Palate Craniofac J 39(2):130–144