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Original article

The impact of margin reduction on outcome and toxicity in head and neck cancer patients treated with image-guided volumetric modulated arc therapy (VMAT)

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ABSTRACT

Background and purpose: In recent decades, outcomes of patients with head and neck cancer (HNC) have improved as a result of implementing several strategies, such as chemoradiation. However, these improvements were achieved at the cost of increased toxicity. One way to reduce radiation-related toxicity is by reducing the margins.

Materials and methods: Between 2013 and 2016, 206 consecutive patients were treated with CTV-PTV margin of 5 mm and subsequently 208 patients with 3 mm margin. This study evaluates the impact of reducing clinical target volume (CTV) to planning target volume (PTV) margin on outcome and toxicity.

Results: All patients were treated with volumetric modulated arc therapy (VMAT) with daily-image guidance using cone-beam CT (CBCT). Overall acute grade 3 toxicity was significantly lower in 3 mm-group, compared to 5 mm-group (53.8% vs. 65%, respectively, $p = 0.032$). The same was true for acute grade 3 mucositis (30.8% vs. 42.2%, $p = 0.008$) and for acute grade 3 dysphagia (feeding tube-dependence) (22.1% vs. 33.5%, $p = 0.026$). The incidence of ongoing feeding tube-dependence after 3 months of radiotherapy was 11.1% and 20.4%, respectively ($p = 0.012$). The 2-year incidence of late grade $\geq$2 xerostomia was 15.8% and 19.4% ($p = 0.8$). The 2-year loco-regional control rates of patients treated in 3 mm and 5 mm-groups were 79.9% and 79.2% ($p = 1.0$). The figures for disease-free survival were 71.5% and 72.7 ($p = 0.6$) and for overall survival were 75.2% and 75.1% ($p = 0.9$).

Conclusion: Reducing the CTV-PTV margin from 5 to 3 mm combined with daily CBCT-guided VMAT reduced the severity, frequency, and duration of radiation-related toxicity without jeopardizing outcome.
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Over the last few decades, outcomes of patients with head and neck cancer (HNC) have improved as a result of implementing several strategies such as chemoradiation, altered fractionation schemes of radiotherapy, and the integration of EGFR-inhibitors [1]. However, these improvements were achieved at the cost of important toxic effects [2–4]. As a consequence of improved prognosis and the increased incidence of oropharyngeal cancer among young patients [5], patients will live longer with the burden of permanent radiation sequelae and the consequential deterioration of quality of life. Despite the tremendous gains achieved with the introduction of highly-conformal techniques such as IMRT, considerable proportion of these patients still experience troublesome acute and late side-effects [2–4]. One of the major reasons for the high rates of toxicity is the large irradiated volumes, for instance because of the use of considerable treatment margins. The gross target volume (GTV) is defined as the gross extent of the primary tumor and positive cervical lymph nodes, as demonstrated by preoperative imaging and physical examination including endoscopy. However, the clinical target volume (CTV) accounting for microscopic disease remains a source of continuous debate [6]. It should be stressed that there are different CTVs and the high-risk CTVs can be quite varying internationally. According to the Dutch Head and Neck Society, the high-risk CTV is defined as the GTV plus a margin of 10 mm, while the low-risk CTV will be generated by adding 5 mm margin to the high-dose CTV. Until 2015, the planning target volume (PTV) at our institution contained automated 5 mm 3D-expansion of CTV to account for geometric uncertainty. However, with advanced

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image-guidance during radiotherapy (daily cone-beam CT, CBCT), the size of CTV-PTV margins needed to be re-evaluated. Following a comprehensive research and clinical implementation program at our institution [7–10], the PTV margin was reduced since April 2015 from 5 to 3 mm. The purpose of the current study was to evaluate the impact of margin reduction on toxicity and outcome, by comparing the results of comparable groups of patients treated with PTV margin of 3 and 5 mm.

Materials and methods

Study population

Between April 2015 and January 2017, 208 consecutive patients with HNC were treated with curative intent in our institution with (chemo)radiation or surgery followed by adjuvant (chemo)radiation. To compare the outcome and toxicity of these patients, we identified all consecutive patients ($n = 206$) treated in the last 2 years before the introduction of smaller CTV-PTV margin. These patients were treated between April 2013 and March 2015 using a CTV-PTV margin of 5 mm.

(chemo)radiotherapy

All patients were treated with volumetric modulated arc therapy (VMAT). In case of definitive radiotherapy, the GTV of the primary tumor and the involved node(s) were delineated. The high-risk CTV was generated by adding 10 mm isotropic margin to the delineated GTV, and subsequently edited to the adjacent non-involved bone and/or air. The elective low-risk CTV was generated by adding 5 mm margin to high-risk CTV. In case of postoperative radiotherapy, no GTV but only the CTV was delineated. This CTV consists of the resection cavity which should include the pre-operative GTV seen at the pre-operative imaging which was registered to the planning CT-scan. The elective low-risk CTV of the neck was defined as level I-V in case of node-positive and level II-IV in case of node-negative neck and was delineated according to the consensus guidelines published by Grégoire et al. [11]. All patients, regardless of their N-status, were treated to both sides of the neck electively, with the exception of T1 laryngeal cancer (no elective irradiation), very-lateralized tonsillar fossa tumor and salivary gland tumors (unilateral irradiation).

The radiation dose to the high-risk PTV was 70 Gy and to the elective low-risk PTV was 46 Gy in 23 fractions in case of sequential and to 54.25 Gy in 35 fractions in case of concomitant boost. The radiation was given in 2 Gy per fraction, 6 fractions a week in case of radiotherapy alone and 5 fractions a week in case of chemo-radiation. In case of postoperative radiotherapy, the high-risk PTV receives 66 Gy (2 Gy per fraction, range 66–70 Gy). Concomitant cisplatin (100 mg/m^2 on days 1, 22, and 43 of radiotherapy) was added to the radiotherapy in patients with locoregional-advanced disease in primary setting (T3-4 and/or N2c, N3 or extra-capsular extension) and those with positive resection margins and/or extra-capsular extension in adjuvant setting. Patient who were unfit for cisplatin received weekly cetuximab.

Daily online set-up corrections were performed for all patients based on CBCT (Elekta Synergy, Crawley, UK) using a multiple region-of-interest registration method [7–9]. Residual misalignments and anatomical changes were flagged by the radiation therapists and evaluated by the radiation oncologist for the need of adaptive replanning [10].

Follow-up

During treatment patients were seen twice weekly at the out-patients clinic in order to monitor the acute toxicities. After completion of treatment, patients were seen every 2 weeks until the acute toxicity had subsided. Thereafter, patients were followed up 3-monthly for the first year, 4-monthly for the second year and 6-monthly thereafter.

End points

Acute ($\leq$90 days after treatment) and late (>90 days after treatment) toxicities were reported using Common Terminology Criteria for Adverse Events, version 4.0 [12]. At our department, toxicity registration is an obligate part of our Electronic Medical Record. The toxicity was registered by the radiation oncologist at each visit of patient to the out-patient clinic. The radiation oncologist registered the start and end dates and the grade of any radiation-related toxicity. During the data collection for the current study, the registered dates and grades of all toxicities were checked for consistency with the reported toxicity (type, timing and grading) in the written free text in patient's chart. Disease progression was assessed by clinical examination at each visit, including flexible endoscopy and in case of clinical suspicion MRI or CT-scan, FDG-PET and, when indicated, examination under anesthesia were done.

Statistical analysis

With two groups of $\approx$200 patients, we had the statistical power (alpha = 0.05, beta = 0.3) to identify relative risk reductions of at least 40% in case of toxicity risks in the reference group of $\approx$25% (i.e. absolute reductions of $\geq$6%), and to identify relative risks reductions of at least 30% in case of reference group risks of $\approx$40% (absolute reductions of $\geq$12%). Because of differences in median and maximum follow-up between the cohorts, follow-up was maximized at 26 months, and events after 26 months were consequently not taken into account in the statistical analyses. Baseline distributions and the proportion of patients with acute toxicity events of interest within each cohort were compared by $\chi 2$ testing. Cumulative incidences of late toxicity and oncologic outcomes (loco-regional control (LRC), disease-free survival (DFS), overall survival (OS)) were estimated with the Kaplan–Meier method, with time calculated from the first radiotherapy fraction. The log-rank test was used to compare the cohorts. Adjusted p-values were calculated using regression models, adjusting for other potential relevant variables. For this purpose, the following variables were considered for each toxicity endpoint: T-stage (T3/4 vs. T1/2), bilateral irradiation (yes vs. no), systemic therapy (yes vs. no), accelerated radiotherapy (yes vs. no), postoperative radiotherapy (yes vs. no), radiation dose (70 vs. 66 Gy), and tumor subsite. Tumor subsite was added as a category variable with oropharynx as the reference (the largest subsite). Using stepwise forward method, variables with $p < 0.2$ were selected and added to the final multivariable model with margin group. In case a variable was relevant for either the Grade $\geq$2 or Grade 3 endpoint it was included. For comparison of tumor control endpoints, hazard ratios (with 5 mm as the reference group) and corresponding 90% CIs were calculated using the Cox proportional hazard model. Statistical analyses were conducted using SPSS software (version 24, IBM Corporation, Armonk, NY). Tests with $p < 0.05$ were considered as significant.

Results

Table 1 shows patients' demographics. Follow-up time for patients treated in 3 mm group was significantly shorter (17.2 vs. 34.9 months, respectively, $p < 0.001$) because the use of 3 mm margin was implemented later. All other patient characteristics were fairly evenly distributed between both groups, with the exception of elective irradiation. Unilateral elective radiation was more

Table 1
Patient's demographics (n = 414).

	Total (n = 414)	3 mm (n = 208)	5 mm (n = 206)	p value
Age (mean, sd) (years)	63.1 (10.6)	63.3 (10.9)	62.7 (10.3)	0.6
Follow-up				
Median in months	23.2	17.2	34.9	<0.001*
Range in months	1.5–57.1	2.2–32.8	1.5–57.1	
Gender				0.5
Male	290 (70%)	149 (71.6%)	141 (68.4%)	
Female	124 (30%)	59 (28.4%)	65 (31.6%)	
Tumor site				0.6
Oropharynx	198 (47.8%)	103 (49.5%)	95 (46.1%)	
Oral cavity	34 (8.2%)	14 (6.7%)	20 (9.7%)	
Larynx	88 (21.3%)	40 (19.2%)	48 (23.3%)	
Hypopharynx	36 (8.7%)	20 (9.6%)	16 (7.8%)	
Nasopharynx	26 (6.3%)	12 (5.8%)	14 (6.8%)	
Salivary gland	32 (7.7%)	19 (9.1%)	13 (6.3%)	
T-stage				0.9
T1 + T2	225 (54.3%)	112 (53.8%)	113 (54.4%)	
T3 + T4	189 (45.7%)	96 (46.2%)	93 (45.1%)	
N-stage				0.2
N0	158 (38.2%)	72 (34.6%)	86 (41.7%)	
N1+	265 (61.8%)	136 (65.4%)	120 (58.3%)	
PORT				0.2
No	298 (72.2%)	155 (74.5%)	143 (69.4%)	
Yes	116 (28%)	53 (25.5%)	63 (30.6%)	
Tumor site PORT (n = 116)				0.2
Oral cavity	23 (19.8%)	9 (17%)	14 (22.2%)	
Pharynx	48 (41.4%)	20 (37.7%)	24 (38.1%)	
Larynx	17 (14.7%)	7 (13.2%)	10 (15.9%)	
Salivary gland	28 (24.1%)	17 (32.1%)	15 (23.8%)	
Systemic therapy				0.3
Yes	175 (42.3%)	83 (39.9%)	92 (44.7%)	
No	239 (57.5%)	125 (60.1%)	114 (55.3%)	
Type of systemic therapy (n = 175)				<0.001
Cisplatin-based CT	134 (32.4%)	51 (24.5%)	83 (40.3%)	
Cetuximab	41 (9.9%)	32 (15.4%)	6 (4.4%)	
Dose of cisplatin received (n = 134)				0.9
200–300 mg/m^2	102 (76.1%)	39 (76.5%)	63 (75.9%)	
<200 mg/m^2	32 (23.8%)	12 (23.5%)	20 (24.1%)	
Elective neck irradiation				0.003
No	37 (8.9%)	18 (8.7%)	19 (9.2%)	
One side	68 (16.4%)	47 (22.6%)	21 (10.2%)	
Both sides	309 (74.6%)	143 (68.8%)	166 (80.6%)	
Accelerated scheme				0.09
Yes	184 (43.3%)	101 (48.6%)	83 (40.3%)	
No	230 (56.7%)	107 (51.4%)	123 (59.7%)	
Baseline tube feeding				0.2
Yes	37 (8.9%)	15 (7.2%)	22 (10.7%)	
No	377 (91.1%)	193 (92.8%)	184 (89.3%)	
Dose of RT				0.9
70 Gy	349 (84.2%)	176 (84.6%)	173 (84%)	
66 Gy	60 (14.4%)	30 (14.4%)	30 (14.5%)	
<66 Gy	5 (1.2%)	2 (1%)	3 (1.5%)	

Abbreviations: sd: standard deviation; PORT: postoperative radiotherapy; CT: chemotherapy; RT: radiotherapy. * Mann–Whitney test was used to calculate p-value.

frequently applied in patients treated with 3 mm margin because of the slowly growing evidence in the last years that the incidence of contralateral regional failure in patients with well-lateralized HNC treated to one side of the neck is very low [13]. Although no significant differences were found between both groups with regard to the use of systemic therapy, more patients in the 3 mm groups were treated with cetuximab because cetuximab was increasingly used in the last years at our institution.

Toxicity

Table 2 shows the differences between both groups with regard to acute toxicity. No grade 4 or 5 toxicity was reported. Overall acute grade 3 toxicity was significantly lower in 3 mm, compared to 5 mm group (53.8% vs. 65%, p = 0.032). The same was true for acute grade 3 mucositis (30.8% vs. 42.2%, p = 0.008) and acute grade 3 dysphagia (feeding tube-dependence) (22.1% vs. 33.5%, p = 0.026). Also the incidence of acute grade ≥2 dysphagia was lower in the 3 mm group; 62% vs. 71.4%, p = 0.036. The incidence of acute dermatitis of any grade was not significantly different between both groups. However, when we analyzed the incidence of dermatitis in patients irradiated with or without Cetuximab, significantly higher incidence of grade 3 dermatitis was seen when the radiotherapy was combined with Cetuximab (p < 0.001) (Fig. 1). With regard to the time to onset of any type of acute toxicity, no statistically significant differences were found between both groups (Table 2). Supplementary Fig. S1 demonstrates the incidence of any acute grade 3 toxicity and acute grade 3 dysphagia, dermatitis and mucositis by tumor subsites. In all subsites the incidence of grade 3 toxicity was lower in the 3 mm, compared to the 5 mm group.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.06.032.

The incidence of ongoing feeding tube-dependence after 3 months of treatment (late grade 3 dysphagia) was also significantly lower in the 3 mm, compared to 5 mm group (11.1% vs. 20.4%, respectively, p = 0.012). The incidence of late grade ≥2 xerostomia

Table 2
Comparison of acute toxicity between both groups.

	3 mm (n = 208) %	5 mm (n = 217) %	Chi-square p-value	Adjusted p-value*
Acute toxicity				
Acute any grade ≥2 toxicity	98.6	98.1	0.7	0.6
Acute grade 3 toxicity	53.8	65.0	0.02	0.032
Acute grade ≥2 dermatitis	77.4	71.8	0.19	0.17
Acute grade 3 dermatitis	27.4	25.2	0.6	0.6
Acute grade ≥2 mucositis	74.5	78.2	0.4	0.6
Acute grade 3 mucositis	30.8	42.2	0.015	0.008
Acute grade ≥2 dysphagia	62.0	71.4	0.009	0.036
Acute grade 3 dysphagia (tube feeding)	22.1	33.5	0.010	0.026
Acute grade ≥2 xerostomia	33.7	37.9	0.4	0.7
			Mann-Whitney p-value	
Time to onset grade 3 dermatitis; median (range) in days	39 (22–57)	39 (28–64)	0.6	
Time to onset grade 3 mucositis; median (range) in days	31 (14–53)	33 (11–63)	0.6	
Time to onset grade 3 dysphagia; median (range) in days	28 (11–63)	30 (10–64)	0.2	

* Adjusted for other variables in Logistic Regression with $p < 0.2$ (input variables: accelerated radiotherapy yes/no, chemo yes/no, T stage T3-4 vs. 1–2, postoperative yes/no, radiotherapy dose 70 Gy vs. 66 Gy, bilateral elective irradiation yes/no).

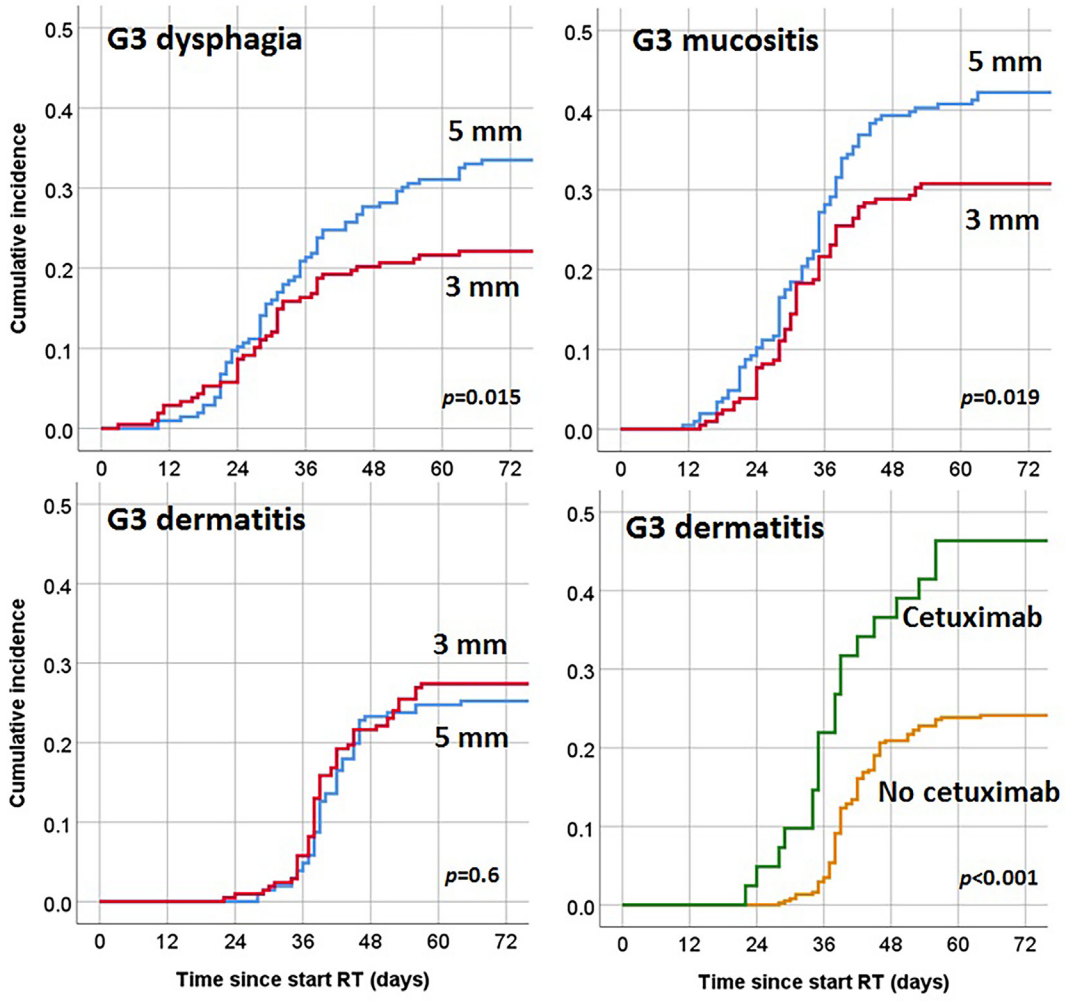

Fig. 1. The cumulative incidence of grade 3 dysphagia, dermatitis, and mucositis of patients treated with 3 and 5 mm CTV-PTV margin.

at 2 years were 15.8% and 19.4%, in the 3 mm and 5 mm groups, respectively (p = 0.8).

Outcome

The 2-year LRC-rates of patients treated in 3 mm and 5 mm-groups were 79.9% and 79.2%, respectively (log-rank p = 1.0), with a HR of 1.0 (90% CI 0.69–1.47). The figures for disease-free survival were 71.5% and 72.7 (log-rank p = 0.6) with a HR of 1.11 (90% CI 0.81–1.53), and for overall survival 75.2% versus 75.1% (log-rank p = 0.9), with a HR of 0.98 (90% CI 0.69–1.37). Fig. 2 shows the Kaplan–Meier curves for outcomes of both groups.

Multivariable analysis

Margin reduction was independently predictive for the reduction of any acute grade 3 toxicity, acute grade 3 mucositis, acute and late grade 3 dysphagia in the multivariable analysis.

The predictive variables for different types of acute and late toxicities are illustrated in Table 3 and Supplementary Table 1.

Doses of organs at risk

Table 4 shows the differences in the mean dose at different organs-at-risk between both groups. Significant reduction of the mean dose was achieved for both parotid glands and constrictor muscles and trend toward significant dose reduction to the larynx and oral cavity. Reducing the CTV-PTV from 5 to 3 mm lowered the mean radiation dose to these structures by 2.7–4.3 Gy. By analyzing the difference between both groups by tumor subsites, significant reduction of the dose to the parotid glands, oral cavity and the larynx was seen in case of oropharyngeal cancer. For laryngeal

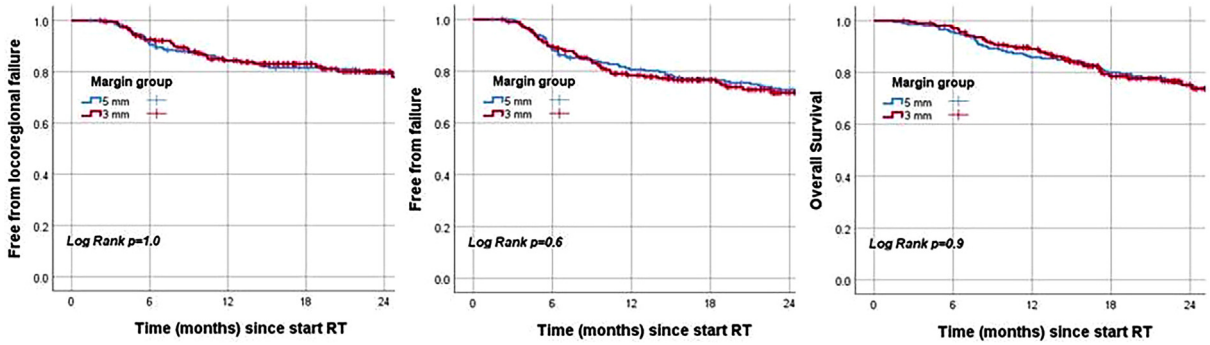

Fig. 2. The cumulative incidence of freedom from locoregional failure, freedom from any failure and overall survival of both groups.

Table 3
Multivariable logistic regression analyses; acute toxicity.

	Any acute Grade 3 toxicity		Grade 3 mucositis		Grade 3 dysphagia		Grade 3 dermatitis	
	OR	*p*-value	OR	*p*-value	OR	*p*-value	OR	*p*-value
Margins (3mm vs. 5 mm)	0.63	0.032	0.54	0.008	0.58	0.026	1.1	0.6
T-stage (T3-4 vs. T1-2)	x		x		x		x	
Systemic therapy (yes vs. no)	1.8	0.013	1.5	0.13	2.7	<0.001	1.8	0.027
Dose RT (70 Gy vs. 66 Gy)	2.6	0.007	x		3.1	0.054	x	
Elective RT neck (bilateral vs. unilateral and no)	x		1.4	0.3	5.6	0.001	x	
RT scheme (accelerated vs. conventional)	x		1.9	0.016	x		2.3	0.001
Timing RT (postoperative vs. primary)	x		x		x		1.8	0.043
Tumor subsites (oropharynx as reference)	categorical	0.005	categorical	<0.001	categorical	0.058		
Hypopharynx	0.3	0.005	0.1	<0.001	0.3	0.006		
Larynx	0.5	0.028	0.2	<0.001	0.7	0.2		
Nasopharynx	1.2	0.7	0.5	0.2	1.5	0.4		
Oral cavity	0.9	0.8	0.8	0.6	1.0	1.0		
Salivary glands	0.3	0.011	0.1	0.008	0.6	0.7		

Abbreviations: CT: chemotherapy; RT radiotherapy; OR: odds ratio. x means that variable was not selected in the stepwise forward method ($p > 0.2$) and therefore not included in the final model.

Table 4
Comparison of the mean doses at different organs at risk between both groups.

OAR:	Ipsilateral PG		Contralateral PG		Oral cavity		Constrictor muscle		Larynx	
	Mean dose in Gy	p^*	Mean dose in Gy	p^*	Mean dose in Gy	p^*	Mean dose in Gy	p^*	Mean dose in Gy	p^*
All subsites										
3 mm	32.7	0.005	16.6	<0.001	30.2	0.089	47.3	0.015	46.0	0.071
5 mm	36.9		20.9		32.9		51.3		49.1	
Oropharynx										
3 mm	36.6	0.004	17.9	0.01	37.8	0.05	48.3	0.2	44.8	0.017
5 mm	41.7		21.9		41.4		50.5		48.7	
Larynx										
3 mm	20.0	0.014	12.9	<0.001	11.5	0.028	58.0	0.11		
5 mm	25.1		18.4		15.6		60.9			
Hypopharynx										
3 mm	28.5	0.07	19.0	0.09	21.1	0.067	59.5	0.3	61.2	1
5 mm	38.4		24.6		28.9		63.4		61.3	
Oral Cavity										
3 mm	34.5	0.6	17.7	0.9	48.4	0.3	33.7	0.3	33.3	0.11
5 mm	37.4		18.0		44.2		38.7		42.9	
Nasopharynx										
3 mm	43.3	0.6	31.4	0.1	35.3	0.4	51.5	0.7	46.0	0.13
5 mm	46.1		39.8		37.9		53.0		49.5	
Salivary Gland										
3 mm			4.1	0.4	21.5	0.9	23.3	0.4	23.0	0.13
5 mm			3.6		21.3		19.9		15.7	

Abbreviations: OAR: organ at risk; PG: parotid gland. * *p*-values were calculated using the *t*-test.

cancer patients, significant reduction of the dose to both parotid glands and oral cavity was seen.

Discussion

Within the radiation oncology society, there is still a lack of consensus regarding the optimal margins around the radiation target volumes. The relative uncertainty surrounding this issue reflects the lack of clinical data reporting on LRC, in relation to the used CTV and PTV margins. The main concern when the margins around the target volume are reduced is the potential increased risk of geographical miss and subsequent increase in marginal locoregional failures. The current study compared the toxicity and oncologic outcomes of 2 fairly comparable groups of consecutively treated HNC patients with 5 mm and 3 mm margins and showed a significant reduction of radiation-related toxicity without jeopardizing LRC. In the current study, margin reduction was independently predictive for the reduction of any acute grade 3 toxicity, acute grade 3 mucositis, acute and late grade 3 dysphagia in the multivariable analysis but not for acute grade 3 dermatitis. However, as already reported in the literature [14], the incidence of acute dermatitis was significantly higher in patients irradiated in combination with Cetuximab.

To the best of our knowledge, only two studies reporting on outcomes of patients with HNC treated by IMRT, with different CTV-PTV margins were published. In the study of Chen et al. [15], 367 patients were treated with IMRT for HNSCC, in conjunction with daily image-guidance using either kilovoltage or megavoltage volumetric imaging. The 3-year LRC for patients treated using 5 mm and 3 mm CTV-PTV margin were 78% and 80%, respectively ($p = 0.75$). The incidence of gastrostomy-tube dependence at 1 year was 10% and 3%, respectively ($p = 0.001$) and the incidence of post-treatment esophageal stricture was 14% and 7%, respectively ($p = 0.01$). Furthermore, Caudell et al. [16] concluded in their study that using smaller margins or expanding the GTVs volumetrically did not increase the risk of local failure. In contrast to the study of Chen et al. [10], the current study also presents the achieved reduction of doses at different organs-at-risk such as parotid glands, oral cavity, larynx, and constrictor muscles (Table 4). Different studies have shown that reducing the radiation dose to these structures resulted in significant reduction of radiation-related toxicity, especially dry mouth and dysphagia [2,17–20]. The reduction of the dose at these specific organs (range 2.7–4.3 Gy) resulted in reduction of the severity and frequency of toxicity observed in patients treated with 3 mm, compared to 5 mm margin. The results of the current study increases, therefore, the bulk of evidence that reducing the radiation treatment volume by reducing the CTV-PTV margin will results in reduction of the toxicity while maintaining LRC.

Large irradiated volumes, the use of chemotherapy, bilateral radiation, and radiation technique are most important predictors of radiation-related toxicity and deterioration of quality of life in patients with HNC treated by radiotherapy, with or without concomitant chemotherapy [3,21,22]. In the current study, the reduced treatment volumes resulted in favorable toxicity profile and are expected to result in decreased incidence and severity of late toxicity, since patients with severe acute toxicity are at considerable risk of severe late side effect, the so-called consequential late effect [23,24]. Furthermore, reducing the CTV-PTV margin results in reduced integral radiation dose and might subsequently lead to reduced second cancer induction [25,26]. This advantage is becoming more and more important as more patients with HNC live longer as a result of improved oncologic outcome and also because of the increasing incidence of HPV-related oropharyngeal cancer among young people [27,28].

The current study has several recognized drawbacks. Patients treated with 5 mm margin have longer follow-up, compared to those treated at the second phase of the study with 3 mm margin. However, follow-up was maximized at 26 months, and events after that time were not taken into account in the statistical analyses. Although the present study concerns a retrospective analysis, the impact of potential selection bias is quite small because we included all consecutive patients treated at our institution between 2013 and 2017. Furthermore, it is uncertain whether the achieved reduction of acute and late toxicity is partly the result of slight differences in patient and tumor characteristics. However, the differences were small and statistically not significant, with exception of elective irradiation. Moreover, an adjusted p-value for these differences was calculated in the logistic regression model used to identify predictive factors for different types of toxicity (Table 2–4).

In conclusion, reducing the CTV-PTV margin from 5 to 3 mm resulted in reduction of the frequency, severity and duration of radiation-related toxicity without jeopardizing oncologic outcome. The results of the current study increased the evidence that a CTV-PTV margin of 3 mm combined with advanced image-guided volumetric modulated arc therapy is safe since the favorable toxicity profile was achieved with maintaining LRC.

Conflict of interest

None.

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