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FULL PAPER

Dose–volume-related dysphagia after constrictor muscles definition in head and neck cancer intensity-modulated radiation treatment

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Objective: Dysphagia remains a side effect influencing the quality of life of patients with head and neck cancer (HNC) after radiotherapy. We evaluated the relationship between planned dose involvement and acute and late dysphagia in patients with HNC treated with intensity-modulated radiation therapy (IMRT), after a recontouring of constrictor muscles (PCs) and the cricopharyngeal muscle (CM).

Methods: Between December 2011 and December 2013, 56 patients with histologically proven HNC were treated with IMRT or volumetric-modulated arc therapy. The PCs and CM were recontoured. Correlations between acute and late toxicity and dosimetric parameters were evaluated. End points were analysed using univariate logistic regression.

Results: An increasing risk to develop acute dysphagia was observed when constraints to the middle PCs were not respected [mean dose (D_{mean}) ≥50 Gy, maximum dose (D_{max}) >60 Gy, V50 >70% with a $p = 0.05$]. The superior PC was not correlated with acute toxicity but only with late dysphagia. The inferior PC was not correlated with dysphagia; for the CM only, D_{max} >60 Gy was correlated with acute dysphagia ≥ grade 2.

Conclusion: According to our analysis, the superior PC has a major role, being correlated with dysphagia at 3 and 6 months after treatments; the middle PC maintains this correlation only at 3 months from the beginning of radiotherapy, but it does not have influence on late dysphagia. The inferior PC and CM have a minimum impact on swallowing symptoms.

Advances in knowledge: We used recent guidelines to define dose constraints of the PCs and CM. Two results emerge in the present analysis: the superior PC influences late dysphagia, while the middle PC influences acute dysphagia.

In the past decade, substantial progress has been made in the treatment of head and neck cancer (HNC). Several reports show that radiotherapy (RT) with concomitant chemotherapy or altered fractionation schedules improve tumour control and survival rate.[1,2]

However, xerostomia and dysphagia often remain relevant side effects for patients with HNC, compromising their quality of life (QoL), as a consequence of radiation damage to the parotid glands and to the organ at risk (OAR) involved in the swallowing process (SWOARs).[3]

Intensity-modulated radiation therapy (IMRT) and rotational intensity-modulated techniques, including volumetric-modulated arc therapy (VMAT), allow for a better dose conformation to target structures while reducing the dose.[4–8] In comparison with three-dimensional-conformal radiation therapy, several studies have shown that IMRT in HNC treatment reduces overall adverse effects such as xerostomia and dysphagia and thus improves QoL, even when chemotherapy is added.[9–13]

Regarding tolerance of the parotid glands, several studies have suggested significant recovery when the mean dose is inferior to 26 Gy. Open questions remain for SWOARs, especially with reference to the delineation modalities of the involved structures to the volumes or the dose constraints to be applied.[14–18] More authors hypothesized that sparing a portion of the constrictor muscles (PCs), not involved by tumour and not at risk of subclinical disease, might reduce

dysphagia.[19–21] These studies obtained different results, maybe, owing to a number of methodological issues and to the ambiguous contouring of the PCs. For this purpose, Christianen et al[22] recently defined guidelines for SWOARs contouring.

Based on these findings, the aim of this retrospective analysis is to evaluate potential relationships between planned dose–volume parameters and observed incidence of acute and late dysphagia in patients with HNC treated with IMRT or VMAT, after a recontouring of the PCs according to these recently published guidelines.

METHOD AND MATERIALS

Patients

Between December 2011 and December 2013, 56 patients (43 males and 13 females), with a median age of 64 years (range, 24–86 years) and with histologically proven HNC, received radiation treatment with IMRT or VMAT in Sacro Cuore-Don Calabria Hospital, Negrar-Verona, Italy. >10% of the patients had non-squamous histology (carcinoma undifferentiated, lymphoepithelial, sarcomatoid, mucoepidermoid). Patients' characteristics are shown in Table 1.

Each patient underwent a pre-treatment evaluation that included a complete history and physical examination, CT and/or MRI scans and/or fluorine-18 fludeoxyglucose–positron emission tomography (^{18}F-FDG-PET) of the head and neck region, and direct flexible fiberoptic endoscopic examination.

Planning

Immobilization of each patient for simulation and during treatment was achieved with a thermoplastic head and shoulder mask (Civco, Orange City, IA). A treatment-planning CT with 3-mm slice thickness and intravenous contrast was acquired in the treatment position and matched with ^{18}F-FDG-PET or MRI in the treatment position to better define the biological target volume and/or clinical target volume (CTV) and OARs.

According to the Radiation Therapy Oncology Group (RTOG) guidelines,[23] the following OARs were contoured for the pre-treatment planning: the spinal cord, brain stem, ipsilateral and contralateral parotid glands, oral cavity and larynx (for non-laryngeal cancers). Whenever close to the planning target volume (PTV), the eyes, optic nerves, and optic chiasm were delineated.

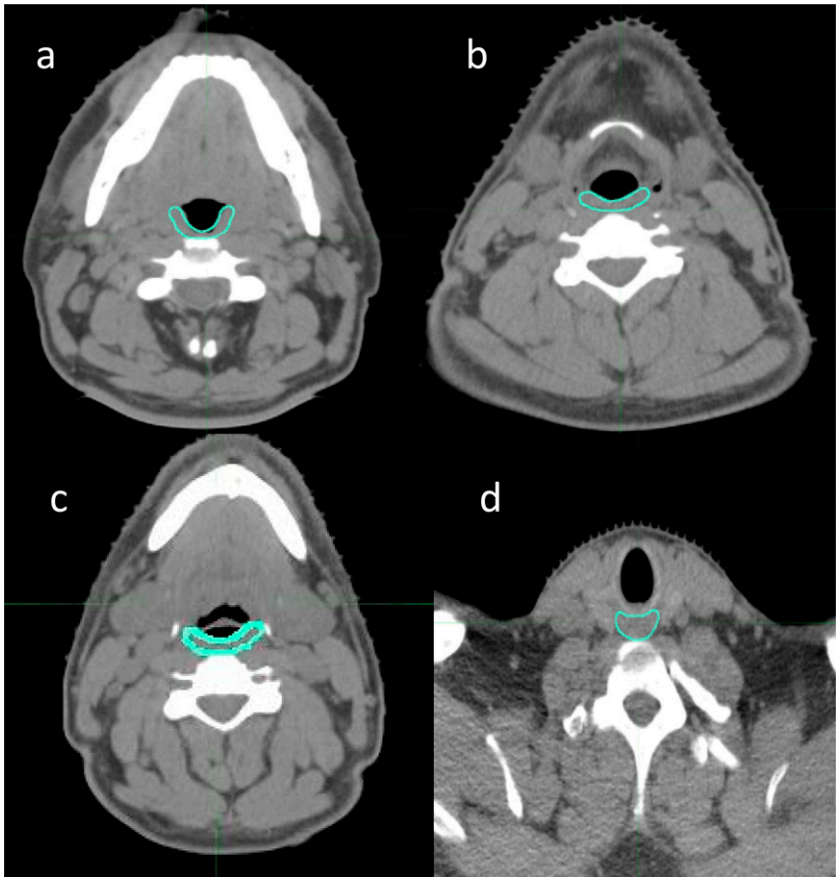
In radical setting, gross tumour volume (GTV), high-risk subclinical disease (CTV1) and low-risk subclinical disease (CTV2) were defined on CT scan after simulation procedure. PTV1, PTV2 and PTV3 were generated with an isotropic expansion of 5 mm from CTV1, CTV2 and CTV3, respectively. These volumes were irradiated to a total dose of 70 Gy (33–35 fractions), 59.94–63.00 Gy (33–35 fractions) and 54.45–58.1 Gy (33–35 fractions), respectively, with daily fractions of 2.12/2.00 Gy, 1.80/1.81 Gy and 1.65/1.66 Gy with simultaneous-integrated boost.

In the post-operative setting, two volumes of interest were identified: CTV1 including the tumour bed (primary and involved nodes) and CTV2 including elective lymphatic areas. PTV1 and PTV2 were generated with an isotropic expansion of

Table 1. Patient baseline characteristics and demographics (n = 56)

Factors	Description
Gender	
Male	77% (n = 43)
Female	23% (n = 13)
Age	
Age (years)	Median, 64; range 24–86
Smoker	
Yes	77% (n = 43)
No	23% (n = 13)
Diabetic	
Yes	5% (n = 3)
No	95% (n = 53)
Primary site	
Rinopharynx	9% (n = 5)
Oropharynx	30% (n = 17)
Oral cavity	18% (n = 10)
Larinx sovraglottic	9% (n = 5)
Larinx glottic	30% (n = 17)
Salivary glands	4% (n = 2)
Histology	
Epidemoidal	88% (n = 49)
Others	13% (n = 7)
Grading	
Grade 1	27% (n = 15)
Grade 2	46% (n = 26)
Grade 3	27% (n = 15)
Stage	
I	20% (n = 11)
II	13% (n = 7)
III	18% (n = 10)
IVA	46% (n = 26)
IVB	4% (n = 2)
Chemotherapy	
Cisplatino weekly	20% (n = 11)
Cisplatino 3-weekly	32% (n = 18)
Induction	2% (n = 1)
None	46% (n = 26)
Radiotherapy	
Radical	71% (n = 40)
Adjuvant	29% (n = 16)

Figure 1. (a–d) Definition of the constrictor and cricopharyngeal muscles in axial CT slice.



5 mm from CTV1 and CTV2, respectively. These volumes were irradiated to a total dose of 60 Gy in 30 fractions and 54 Gy in 30 fractions, respectively, with daily fractions of 2 Gy and 1.8 Gy, respectively.

The dose was prescribed to cover 95% of the PTV. Target dose homogeneity was obtained by maintaining $V_{107\%}$ dose prescription (D_p) <3% and a maximum dose (D_{max}) <110% D_p.

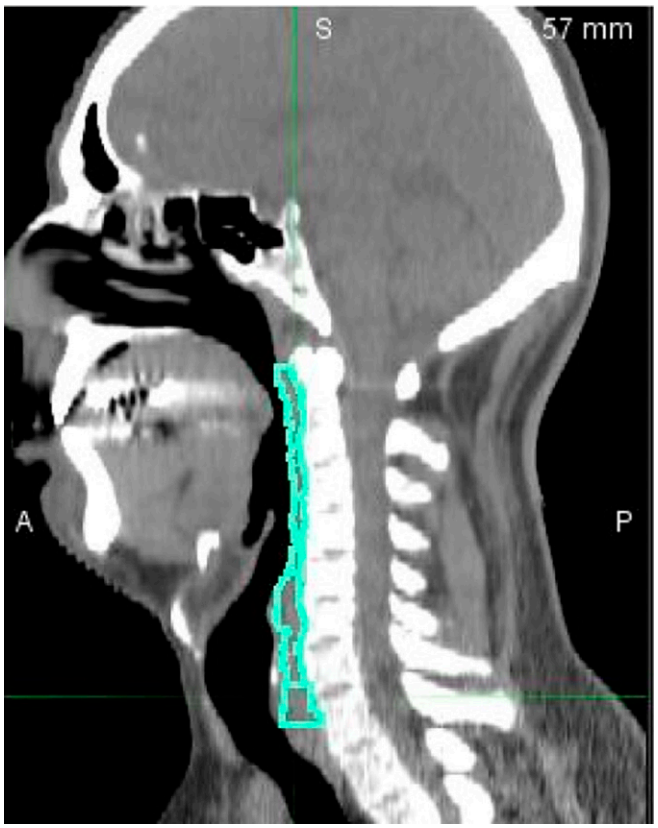
Planning objectives required PTV coverage of 95–107%. Concerning OARs, they were set as follows: the spinal cord: D_{max} 0.1 cc <46 Gy; brain stem: D_{max} 0.1 cc <54 Gy; parotid glands: V30 <45%; mean dose (D_{mean}) <26 Gy; larynx, V40 <50%; and oral cavity (not involved), V40 <50%. All dose distributions were computed with the anisotropic analytical algorithm v. 10.0.28 implemented in the Eclipse™ (Varian, Palo Alto, CA) treatment planning system with a calculation grid resolution of 2.5 mm.

Table 2. Anatomic borders of constrictors and cricopharyngeal muscles

Muscle	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Superior PCM	Caudal tip of the pterygoid plates (hamulus)	Lower edge of C2	Hamulus of pterygoid plate; mandibula; base of tongue; pharyngeal lumen	Prevertebral muscle	Medial pterygoid muscle	Pharyngeal lumen
Middle PCM	Upper edge of C3	Lower edge of hyoid bone	Base of tongue; hyoid bone	Prevertebral muscle	Greater horn of hyoid bone	Pharyngeal lumen
Inferior PCM	First slice caudal to the lower edge of hyoid bone	Lower edge of the arythenoid cartilages	Soft tissue of supraglottic/glottic larynx	Prevertebral muscle	Superior horn of thyroid cartilage	Pharyngeal lumen
Cricopharyngeal muscle	First slice caudal to the arytenoid cartilages	Lower edge of the cricoid cartilages	Posterior edge of cricoid cartilage	Prevertebral muscle	Thyroid cartilage, fatty tissue, thyroid gland	

C2, second cervical vertebra; C3, third cervical vertebra; PCM, pharyngeal constrictor muscle.

Figure 2. Definition of the constrictor and cricopharyngeal muscles in sagittal projection. A, anterior; P, posterior; S, superior.



All plans were performed with 9-field sliding window IMRT or 4-arc VMAT (Rapid Arc; Varian Medical System, Palo Alto, CA) and nominal energy of 6 MV.

Treatment procedure

Before each daily fraction, the patients were submitted to image-guided radiotherapy (IGRT) procedure by means of a daily tube potential–cone beam CT (CBCT) to check and correct in real-time set-up errors and to follow anatomical changes of the treated region.

CBCT low-dose head model (80 kVp, 0.4 mAs) was used to generate images; clockwise and anticlockwise 180° gantry rotations were used alternatively to reduce dose to patients.[24]

All corrections carried out after matching between CBCT and planning CT were recorded and collected.

Chemotherapy

Cisplatinum 100 mg mq^{-1} was added every 21 days during RT for patients with performance status (PS) Eastern Co-operative Oncology Group (ECOG) = 0–1, age less than 70 years, disease T/N+ or T3–T4/N0; cisplatinum 30 mg mq^{-1} was added weekly if PS = 2, age less than 70 years, disease T/N+ or T3–T4/N0; induction TCF (docetaxel, cisplatin, 5-floruracile) if PS = 0, age less than 65 years, disease T/N3; and no chemotherapy if PS ECOG >2, disease T1–T2/N0, age over 70 years.[25]

Toxicity evaluation and follow-up

At baseline, no cases of dysphagia and xerostomia were recorded. Toxicity was evaluated weekly during radiation treatment, and periodically after the end of the treatment: 1 month after RT clinical evaluation, then regular visits every 3 months for the first 2 years.

Toxicities occurring within 3 months from the beginning of radiotherapy were defined as acute, and those occurring after 3 months as late toxicity. Patients were assessed for toxicities by the European Organization for Research and Treatment for Cancer/RTOG radiation morbidity scoring criteria. Clinical data were collected and evaluated for statistical evaluation.

Re-contouring

The compliance to radiation treatment was 100%; no patient interrupted or discontinued the planned IMRT or VMAT schedule; and, for the end point of the study, all clinical and dosimetrical data were retrospectively evaluated.

On planning CT scan, the PCs were retrospectively contoured according to Christianen et al[22] guidelines by a single observer and subsequently reviewed by another radiation oncologist as shown in Figure 1. The PCs and the cricopharyngeal muscle (CM) were indicated as shown in Table 2.

Statistical analysis

Descriptive statistics were used to analyse the data. End points were analysed using univariate logistic regression and contingence tables with Fisher's exact test for the association between acute/late dysphagia, dose–volume and clinical parameters.

Dosimetric parameters for each PC and CM were related to acute and late toxicities (during RT, at 3, 6 and 12 months from RT). We evaluated a sort of "constraints-escalation" from V30 increasing every 5 Gy until maximum dose was reported in the dose–volume histogram (DVH) of each structure (Figure 2).

The dosimetric parameters for ipsilateral and contralateral parotid glands were D_{mean} >26 Gy and V30 >50%.

$p \leq 0.05$ was considered significant. Data were analysed using R-software (Varian, Palo Alto, CA).

Locoregional control and overall survival were estimated using the Kaplan–Meier method. Time to recurrence and overall survival were calculated from the date of diagnosis to the date of relapse and the date of death or last follow-up, respectively.

RESULTS

Acute and late toxicity

During RT, acute dysphagia and xerostomia were registered as follows: Grade (G) 0–1 in 10 patients (18%), G2 in 36 patients (64%), G3 in 10 patients (18%); and G0–1 in 25 patients (45%), G2 in 30 patients (54%), G3 in 1 patient (1%), respectively. No case of G4 toxicity was registered.

At 3 months from the end of RT, toxicity was reported as follows: G0–1 dysphagia in 33 patients (59%), G2 in 18 patients (32%), G3 in 5 patients (9%); G0–1 xerostomia in 30 patients (54%) and G2 in 26 patients (46%).

Table 3. Dosimetric factors for constrictors: univariate logistic regression analysis

Structures	Dysphagia	Constraints	Volume (cm^3) and median (range)	Univariate analysis		
				OR	*p*-value	95% CI
SPC	Acute	D_{max} 60	11.3 (10.8–12.4)	3.18	0.197	0.38–11.6
		D_{mean} 50		1.875	0.450	0.41–8.51
		V50		1.55	0.702	0.34–7.02
		V55		2.16	0.449	0.46–10.16
		V65		1.05	1.00	0.18–5.97
	3 months	D_{max} 60		12.52	0.01	1.48–105.58
		D_{mean} 50		9.6	0.006	1.89–48.6
		V50		6.78	0.007	1.64–28.04
		V55		10	0.001	2.38–12.01
		V65		2.25	0.304	0.60–8.42
	6 months	D_{max} 60		1.86	0.65	0.33–10.41
		D_{mean} 50		9.33	0.03	0.99–87.38
		V50		NA	0.027	NA
		V55		NA	0.01	NA
		V65		4.37	0.117	0.74–25.8
MPC	Acute	D_{max} 60	2.02 (1.70–2.64)	3.18	0.197	0.68–14.88
		D_{mean} 50		8.5	0.01	1.50–47.96
		V50		13.25	0.008	1.48–116.26
		V55		9.1	0.05	1.03–80.08
		V65		NA	0.08	NA
	3 months	D_{max} 60		12.52	0.009	1.48–105.58
		D_{mean} 50		7.52	0.013	1.48–38.07
		V50		4.2	0.039	1.13–15.49
		V55		2.71	0.144	0.81–90
		V65		2.36	0.204	0.66–8.35
	6 months	D_{max} 60		1.86	0.65	0.33–10.41
		D_{mean} 50		3.26	0.39	0.35–30.7
		V50		4.77	0.204	0.51–44.32
		V55		5.75	0.189	0.61–53.42
		V65		0.51	1	0.054–4.89
IPC	Acute	D_{max} 60	5.4 (4.2–5.8)	2.06	0.43	0.45–9.41
		D_{mean} 50		1.42	0.711	0.31–6.40
		V40		2.53	0.24	0.55–11.69
		V50		1.09	1.00	0.24–4.89
		V55		1.09	1.00	0.24–4.89
		V65		2.30	0.44	0.42–12.67
	3 months	D_{max} 60		1.14	1	0.34–3.83
		D_{mean} 50		0.81	0.772	0.25–2.59
		V40		0.86	1	0.25–2.97
		V50		0.58	0.39	0.18–1.87
		V55		0.58	0.39	0.18–1.87
		V65		0.4	0.23	0.11–1.40
	6 months	D_{max} 60		1.07	1	0.17–6.54
		D_{mean} 50		1.44	1	0.23–8.73
		V40		2.41	0.65	0.25–22.66
		V50		0.86	1	0.15–4.80
		V55		0.86	1	0.15–4.80
		V65		NA	NA	NA
Crico	Acute	D_{max} 60	1.4 (1.2–1.8)	NA	0.04	NA
		D_{mean} 50		1.66	0.7	0.35–7.8
		V40		3.18	0.197	0.68–14.88
		V50		2.75	0.277	0.50–15.07
		V55		3.73	0.411	0.42–33.07
		V65		NA	0.176	NA
	3 months	D_{max} 60		0.43	0.35	0.11–1.63
		D_{mean} 50		0.66	0.56	0.21–2.11
		V40		1.13	1	0.31–4.02
		V50		0.59	0.55	0.18–1.92

(Continued)

Table 3. (Continued)

Structures	Dysphagia	Constraints	Volume (cm^3) and median (range)	Univariate analysis		
				OR	*p*-value	95% CI
	6 months	V55		0.43	0.35	0.11–1.63
		V65		0.46	0.33	0.1–1.95
		D_{max} 60		NA	0.159	NA
		D_{mean} 50		0.95	1	0.17–5.26
		V40		0.86	1	0.14–5.33
		V50		1.15	1	0.2–6.35
		V55		0.37	0.64	0.039–3.49
		V65		NA	0.314	NA

CI, confidence interval; Crico, cricopharyngeal muscle; D_{max}, maximum dose; D_{mean}, mean dose; IPC, interior constrictor muscle; MPC, middle constrictor muscle; NA, OR not estimable; OR, odds ratio; SPC, superior constrictor muscle; V40, volume structure receiving ≥40 Gy; V50, volume structure receiving ≥50 Gy; V55, volume structure receiving ≥55 Gy; V60, volume structure receiving ≥60 Gy.
p-value estimated with Fisher's exact test.

At 6 months from RT, G0–1 dysphagia was recorded in 43 patients (77%) and G2 in 13 patients (23%), while G0–1 xerostomia was registered in 39 patients (70%) and G2 in 17 patients (30%), respectively. No G3 toxicity occurred.

At 12 months from RT, toxicity was: G0-1 dysphagia in 44 patients (91%), G2 in 4 patients (9%); G0–1 xerostomia in 41 patients (85%), G2 in 7 patients (15%). No G3 toxicity occurred.

In five patients with oropharynx disease and in two patients with supraglottic disease feeding tubes [percutaneous endoscopy gastrostomy (PEG)] were placed. In detail, in two patients they were placed prophylactically by surgeon, and in the other case for G3 acute dysphagia, only in two patients was the treatment stopped for 7 days. Five patients maintained PEG for 6 months after the end of treatment, and in two patients, PEG was removed after 3 months for symptom resolution.

Clinical outcomes

At a median follow-up of 24 months (range, 10–36 months), 2 years actuarial overall survival (OS) was 100% and 2 years actuarial local control was 96.3%. 3 years OS was 88.9% (we registered one death), while 3 years local control was 57%; in detail, we registered four local failures (all patients with locally advanced disease treated without concomitant chemotherapy). All patients received their chemotherapy as planned.

Dosimetric parameters for superior constrictor muscle

For acute dysphagia ≥G2, no dosimetric parameters showed a statistical correlation.

At 3 months from RT, $D_{mean} \geq 50$ Gy, $D_{max} \geq 60$ Gy, V50 and V55 ≥70% increased the risk of toxicity ($p < 0.01$, $p < 0.05$, $p < 0.01$ and $p < 0.01$, respectively). No statistical correlation was found with the other constraints.

For late dysphagia ≥G2 (at 6 months from RT), the dosimetric parameters that showed major correlations were V50, V55 and V60 ≥70% with an increasing risk of toxicity from three to nine times ($p < 0.05$). For late dysphagia ≥G2 (at 12 months from RT), no dosimetric parameters showed a statistical correlation.

Dosimetric parameters for middle constrictor muscle

For acute dysphagia ≥G2, $D_{mean} \geq 50$ Gy and 55 Gy, and V50 ≥70% increased the risk of toxicity ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively). No statistical correlation was found with other constraints.

At 3 months from RT, $D_{mean} \geq 50$ Gy, $D_{max} \geq 60$ Gy and V50 ≥70% increased the risk of toxicity ($p < 0.01$, $p < 0.05$ and $p < 0.01$, respectively). No statistical correlation was found with other constraints.

For late dysphagia ≥G2 (at 6 and 12 months from RT), no dosimetric parameters showed a statistical correlation.

Dosimetric parameters for inferior constrictor muscle

No dosimetric parameter showed a statistical correlation for acute/late dysphagia ≥G2 (during treatment and at 3, 6 and 12 months from RT).

Dosimetric parameters for cricopharyngeal muscle

During treatment, only $D_{max} > 60$ Gy showed a correlation with dysphagia ≥G2 ($p < 0.05$), while no dosimetric parameter was related to acute/late toxicity.

Dosimetric parameters for ipsilateral parotid gland

$D_{mean} > 26$ Gy and V30 >50% are statistically related with acute xerostomia ≥G2 ($p < 0.0001$; odds ratio: 1.06; 95% CI: 1.03–1.10) with an increasing risk of 1.06 times for every Gray over 26 Gy and xerostomia at 6 and 12 months from RT [$p < 0.05$; odds ratio: 1.04; 95% confidence interval (CI): 1.01–1.07], with an increasing risk of 1.04 times for every Gray over 26 Gy, at 6 and 12 months.

Dosimetric parameters for contralateral parotid gland

$D_{mean} > 26$ Gy and V30 >50% are statistically related with acute xerostomia ≥G2 ($p < 0.001$; odds ratio: 1.21; 95% CI:

1.10–1.33) with an increasing risk of 1.2 times for every Gray over 26 Gy and xerostomia at 6 and 12 months from RT ($p < 0.05$; odds ratio: 1.10; 95% CI: 1.03–1.17), with an increasing risk of 1.1 times for every Gray over 26 Gy, at 6 and 12 months.

All dosimetric data of PCs are shown in Table 3.

Correlations between clinical factors and dysphagia

Univariate logistic regression analysis for clinical parameters showed a significant correlation with oropharynx primary site ($p < 0.05$) and acute/late dysphagia. No correlations with sex, smoke of cigarette, diabetes, stage of disease and chemotherapy, when added, were shown. Moreover, late xerostomia ≥G2 is statistically related with dysphagia ≥G2 ($p < 0.05$).

DISCUSSION

IMRT and VMAT achieved an excellent dose distribution, especially in a concave-shaped target volume and for patients with HNC; they have shown a reduction in RT toxicity.[4–8] For this reason, in the past few years, the evaluation of OARs, in terms of variation in volume, geometry or contouring methods, was analysed by several authors to improve therapeutic ratio reducing the risk of toxic effects.[17–21,26–28]

Swallowing dysfunction after radiotherapy is correlated with compromised QoL and can lead to life-threatening complications. Limiting the radiation dose to the crucial SWOARs is expected to decrease the incidence and severity of radiation-induced dysphagia.

Based on the findings of video fluoroscopy, Eisbruch et al[20] were the first to identify the dysfunction of PCs and other structures crucial for long-term dysphagia and aspiration in HNC after concurrent chemoradiotherapy. No distinction was made in this study among the various levels of the PCs, so they were outlined as a single structure for dose assessment purpose. In their analysis, mean dose to the PCs and larynx >50 Gy both correlated significantly with the occurrence of late dysphagia and aspiration, respectively.

Levendag et al[21] assessed the relationship between RT dose received by the muscular components of the PCs and dysphagia related to QoL in oropharyngeal cancer. For late dysphagia, ≥G3 significant relationships were found between a $D_{mean} > 50$ Gy for superior and middle PC. The probability of PC disorders increased significantly with dose (±19% per 10 Gy after 55 Gy) for the superior and middle PCs. In the multivariate analysis, concomitant chemotherapy was not an influencing factor.

Caglar et al[29] evaluated early dysfunction of SWOARs after IMRT with or without chemotherapy and attempted to determine the clinical and/or dosimetric factors correlating with swallowing toxicity. They did not find any correlation with the superior PC dose and early dysphagia, whereas the $D_{mean} \geq 50$ Gy to the larynx and inferior PC was a significant predictor for aspiration.

Similar to these studies, in our series a possible correlation of dose to middle PC was noted, with an increasing risk to develop acute toxicity when constraints are not respected. Superior PC was not correlated with acute toxicity, but statistical analysis showed a probable pathogenetic role in late dysphagia.

Dirix et al[30] wanted to establish a relationship between late dysphagia and RT doses to the SWOARs correlating clinical parameters such as the impact of tumour site, tumour stage and pre-treatment swallowing problem. The SWOARs identified were PCs, base of the tongue, supraglottic larynx, glottic larynx and CM. At univariate analysis, a mean dose ≥50 Gy to middle PC, inferior PC and to supraglottic larynx significantly correlated with late dysphagia.

Only one study[31] did not find any relationship between dose to the PCs and late dysphagia.

In the study of Mortensen et al,[32] 65 patients were examined for PC disorders with modified barium swallow (MBS). Similar to our analysis, PCs were delineated as described by Christianen et al[22], and the DVHs of OARs were analysed. Late dysphagia correlated with the dose to superior and middle PCs (all $p < 0.04$). D_{mean} to the superior PC <60 Gy correlated with low risk of aspiration (<30%) and D_{mean} to the middle PC <60 Gy correlated with low risk of high MBS score (<30%).

With regard to our results, several considerations could be performed. In our series, only ten patients developed G3 acute dysphagia; at 3 months, five patients developed G3 dysphagia; and no case of G3 developed dysphagia at 6 months and 12 months. We decided to homogenize the toxicity in two classes: G0–1 and ≥G2, because no significantly statistical result was found for G3 toxicity owing to limited cases.

The inferior PC seems not to be correlated with acute or late dysphagia, for CM only $D_{max} > 60$ Gy is correlated with dysphagia during RT ≥G2. Thus, these structures seem to have a minimum or not impact for swallowing symptoms. On the contrary, the superior PC seems to have a major role, being correlated with dysphagia at 3 and 6 months, while middle PC maintains this correlation only until 3 months from the beginning of RT, and it seems to not have an influence on late dysphagia.

The studies available in literature retrieved different results, this may be owing to a number of methodological issues and the unambiguous contouring of swallowing structures. With these uncertainties, it is necessary to standardize these aspects.

In our analysis, using Christianen guidelines to define PMs and CM, interesting results for the readers have been reported. The first finding was that when changing limits of the structures, in particular of the superior PC, using Christianen definition, results are similar to data reported in literature. It means that, maybe, the volume of the structures did not influence the constraints. Another interesting finding was that the middle pharyngeal constrictor was related to acute dysphagia, while the superior pharyngeal constrictor influenced late dysphagia. A clear definition of different structures (and an evaluation of

Table 4. Studies assessing dose–volume analyses for late dysphagia

Study	Patients	Site	Dosimetric factors correlated with late dysphagia	Limits	Anatomical borders			
					SPC	MPC	IPC	Crico
Feng[34]	36	OP/ NP	PCs (mean dose, V50, V60, V65)	Cranial Caudal	Caudal tips of pterygoid plates Upper edge hyoid bone	Upper edge of the hyoid bone Lower edge of the hyoid bone	Below the hyoid bone Inferior edge of the cricoid	Not mentioned Not mentioned
Levendag[21]	56	OP	SPC, MPC (mean dose)	Cranial Caudal	Mild C2 Upper C3	Upper C3 Upper C4	Upper C5 Mid C6	Mild C6 First ring of trachea
Jensen[35]	25	PH	SL (mean dose, V60, V65)	Cranial Caudal	Lower part transverse process C2 Top of cricoid cartilage	Lower part transverse process C2 Top of cricoid cartilage	Lower part transverse process C2 Top of cricoid cartilage	Not mentioned Not mentioned
Caglar[29]	96	M	IPC (mean dose, V50, V60)	Cranial Caudal	Pterygoid plates Upper edge of the hyoid bone	Upper edge of the hyoid bone Lower edge of the hyoid bone	Inferior edge hyoid bone Lower edge cricoid	Not mentioned Not mentioned
Dirix[30]	53	M	MPC (mean dose,V50)	Cranial Caudal	Caudal tip of the pterygoid plates Upper edge hyoid bone	Upper edge of the hyoid bone Lower edge of the hyoid bone	Inferior edge hyoid bone Lower edge cricoid	Lower edge cricoid Upper edge of trachea
Bhide[31]	37	M	No correlations	Cranial Caudal	Base of the skull Superior end hyoid bone	Superior end of the hyoid bone Caudal end of the cartilage cricoid	Inferior edge hyoid bone Lower edge cricoid	Not mentioned Not mentioned
Caudell[36]	83	M	IPC (V60, V65)	Cranial Caudal	Pterygoid plates Upper edge of the hyoid bone	Upper edge of the hyoid bone Lower edge of the hyoid bone	Inferior edge hyoid bone Lower edge cricoid	Not mentioned Not mentioned
Mortensen[32]	65	M	SPC, MPC (mean dose)	Cranial Caudal	Caudal tip of the pterygoid plates Lower edge of C2	Upper edge of C3 Lower edge of hyoid bone	First slice caudal to the lower edge of hyoid bone Lower edge of the arytenoid cartilages	First slice caudal to the arytenoid cartilages Lower edge of the cricoid cartilages
Current study	56	M	SPC (D_{max} <60,V50	Cranial Caudal	Caudal tip of the pterygoid plates Lower edge of C2	Upper edge of C3 Lower edge of hyoid bone	First slice caudal to the lower edge of hyoid bone Lower edge of the arytenoid cartilages	First slice caudal to the arytenoid cartilages Lower edge of the cricoid cartilages

C2, second cervical vertebra; C3, third cervical vertebra; C4, fourth cervical vertebra; C5, fifth cervical vertebra; C6, sixth cervical vertebra; Crico, cricopharyngeal muscle; D60, minimum dose received by 60% of a structure; D_{max}, dose maximum; IPC, inferior constrictor muscle; M, miscellaneous; MPC, middle constrictor muscle; NP, nasopharynx; OP, oropharynx; PCs, all constrictors; PCS, pharyngeal constrictor muscle; PH, pharynx; SL, supraglottic larynx; SPC, superior constrictor muscle; V50, volume of a structure receiving 50 Gy; V60, volume of a structure receiving 60 Gy; V65, volume of a structure receiving 65 Gy; V70, volume of a structure receiving 70 Gy.

their involvement) could influence differently acute and late settings of toxicities.

Future evaluations on the impact of volumes of the critical structures on coverage and homogeneity of the target are needed.

Starting from this background, we decided to propose and apply in our department the following constraints for PCs, with a minor priority with respect to PTV coverage: $D_{mean} \leq 50$ Gy, $D_{max} \leq 60$, V50 <70% for middle PC; $D_{max} \leq 60$ Gy, V50 <70% for superior PC; $D_{max} \leq 60$ Gy for CM.

Regarding to the dose constraints for parotid glands, our analysis showed that for ipsi and contralateral parotid glands, $D_{mean} > 26$ Gy and V30 >50% are statistically related with acute and late xerostomia ≥G2, as reported in literature.[33] Moreover the presence of late xerostomia >G2 is statistically related with dysphagia ≥G2 ($p < 0.05$), showing a close relationship between salivation and swallowing.

We are conscious that the results of the present study are influenced by several limitations. The main limitation regards the lack of methodology due to the retrospective approach. For this reason we will use the previously described constraints in clinical practice in a prospective way, before validating their value definitively. The second limitation regards the population of study: first of all the sample size is small, and moreover, we analysed in the same group radical and adjuvant treated patients, with different primary disease sites in head and neck region and subsequently with different treated volume. However, these limitations are quite similar to the other reports previously published as shown in Table 4,[29–32] where several results seems to be close to ours and furthermore, despite the declared limitations, the results about parotid glands confirmed the literature data.

Another criticism of the present analysis is that it was focused only to PCs and CM, with a lack of evaluation of other SWOARs, including base of tongue, supraglottic larynx, upper oesophagus. The rationale of this choice depended on the mixed population of study composed by several cases of oropharynx and larynx diseases. In our opinion, in these cases, due to being involved with the diseases, it was not possible to consider them as SWOARs and for this reason we restricted the analysis only to role of PCs in swallowing disorders.

CONCLUSION

Based on Christianen guidelines, dose constraints to the superior and middle PCs seem to play a role as dosimetric predictors of early/late swallowing disturbances.

A common contouring is needed to define structures that are involved in the swallowing process to suggest dose–volume constraints. In this scenario, prospective trials could be activated to elucidate the importance of doses to the pharyngeal PCs. Functional and anatomic treatment-related disorders and QoL assessment, including dedicated questionnaires, will be further evaluated in a prospective way in future analysis.

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