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Evaluation of swallowing function with clinical and dosimetric parameters in head and neck cancer patients receiving radio (chemo)therapy

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► ***Original article***

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ABSTRACT

Background*:** This study aimed to evaluate the relationship between late dysphagia and dosimetric–clinical parameters in patients receiving radiotherapy for head and neck cancer (HNC). ***Materials and Methods*:** Twenty-six HNC patients treated with three-dimensional conformal radiotherapy were evaluated. A total dose of 66–70 Gy in 33–35 fractions was administered for curative purposes. Six swallowing organs at risk were contoured for each patient: the superior, middle and inferior pharyngeal constrictor muscles (SPCM, MPCM and IPCM); the cervical oesophagus (CE); the base of tongue (BOT); and the larynx. The mean dose in Gray [Dmean (Gy)], maximum dose in Gray [Dmax(Gy)] and percentages of organ volumes receiving ≥ 50 Gy, ≥ 60 Gy and ≥ 70 Gy [V50 (%), V60 (%) and V70 (%), respectively] were calculated from the dose–volume histograms for each structure. Dysphagia was evaluated using video laryngoscopy, the European Organization for Research and Treatment of Cancer quality of life module for HNC and the Leipzig scale. ***Results: Dmean, V60 and V70 for the BOT; Dmean and V60 for the SPCM; Dmean, Dmax, V60 and V70 for the IPCM; Dmean, Dmax, V60 and V70 for the larynx; and Dmean, Dmax, V50 and V70 for the CE were correlated with the presence of pharyngeal secretion. Only V50 for the CE was correlated with abnormal glottic closure. Dmean, Dmax, V60 and V70 for the BOT and the SPCM were correlated with liquid swallowing problems. Dmax for the MPCM; Dmean, Dmax, V60 and V70 for the IPCM; and Dmax, V60 and V70 for the CE were correlated with the Leipzig score. ***Conclusion:*** The dose–volume parameters of swallowing organs were found to be associated with different rates of late dysphagia in HNC patients receiving radiotherapy. The identification of dosimetric parameters that predict late dysphagia is not adequate yet. Well-designed multi-institutional studies are necessary to clarify the dose–volume constraints.

Keywords: *dysphagia, head and neck cancer, radiotherapy.*

INTRODUCTION

A multidisciplinary approach is necessary for the optimal management of head and neck cancer (HNC). The treatment options are surgery, radiotherapy, chemotherapy and the combination of these treatment modalities. Radiochemotherapy (RCHT) is the main treatment option for locally advanced HNC patients who are not suitable for surgical treatment or when the tumour is inoperable. With the use of intensified radiotherapy regimens in combination with concurrent chemotherapy, improved local control and survival rates have been observed in HNC patients [1, 2]. Most HNC patients can be cured,

especially in the early stages. Therefore, reducing RCHT-related toxicities has become even more important while preserving the high rate of cure.

Dysphagia is one of the most remarkable issues in HNC patients receiving RCHT. It can occur because of the disease itself or as an acute or late complication of RCHT. Patients with dysphagia may have difficulty in speech and may withdraw from daily activities. Impaired swallowing may lead to aspiration pneumonia and nutritional deficiency with severe weight loss, which could be life threatening. Consequently, dysphagia may worsen quality of life (QoL) in HNC patients.

Several dose–volume constraints associated with dysphagia have been suggested. Dirix et al. reported in their retrospective study that V50 and Dmean for the middle pharyngeal constrictor muscle (MPCM) and Dmean for the supraglottic larynx were associated with late dysphagia [3]. Caudell *et al.* reported that Dmean (greater than 41 Gy) and V60 (greater than 24%) for the larynx and V60 (greater than 12%) for the inferior pharyngeal constrictor muscle (IPCM) were associated with percutaneous endoscopic gastrostomy (PEG) tube dependence and aspiration [4]. Feng *et al.* showed a relationship between postradiation dysphagia and the dose received by the constrictor muscles and found that the strongest correlation was for the SPCM [5].

Clearly, the risk of radiotherapy-related dysphagia increases with a higher radiation dose. Therefore, the identification of dosimetric parameters that predict late dysphagia is crucial in a group of long-time survivors of HNC. The dose–effect relationship in dose and swallowing disorders should be clarified. Radiation oncologists should be aware of the correlations between planning dosimetry and radiotherapy-related dysphagia.

In this study, we aimed to evaluate late dysphagia in HNC patients receiving curative radiotherapy and to investigate its relationship with dosimetric parameters using both objective and subjective tools. Late dysphagia was objectively evaluated using video laryngoscopy and subjectively evaluated using the European Organization for Research and Treatment of Cancer quality of life module for HNC (EORTC QLQ-H&N35). Unlike other similar studies, we also used the Leipzig scale for subjective evaluation.

MATERIALS AND METHODS

Twenty-six HNC patients whom were referred for radiotherapy at Trakya University between March 2013 and October 2014, were included in this cross-sectional study. All patients had pathologically confirmed primary HNC and received curative three-dimensional conformal radiotherapy (3D-CRT). None of the patients had undergone surgery for HNC. Patients with distant metastases (M1) and patients who received unilateral neck radiotherapy were not included in the study. The ethical committee approval was received from the Ethics Committee of Trakya University Medical Faculty with the decision number of 2015/114. Written informed consent was obtained from all patients prior to enrolment.

Radiotherapy and dose–volume data

Each patient was immobilised using a thermoplastic head and shoulder mask in the supine position. Shoulder retractors were used to remove shoulders from the radiotherapy field. Patients were scanned with computed tomography (CT) from the vertex to the inferior border of the manubrium sterni with a scan thickness of 3 mm. No contrast agent was used. Organs at risk (OARs) and the target volumes were contoured and defined according to the Radiation Therapy Oncology Group (RTOG) consensus guidelines [6, 7].

Radiotherapy was administered by a linear accelerator using a five-field 3D-CRT technique (Elekta Synergy Platform; Elekta AB, Stockholm, Sweden). A total of 66–70 Gy (mean: 69.46 Gy) in 33–35 fractions was prescribed to the primary tumour and the involved lymph nodes (LN), 60 Gy in 30 fractions to the high-risk nodal areas and 50 Gy in 25 fractions to the low-risk nodal areas (once a day, for 5 days a week, 2 Gy per fraction). The treatment plans were conduct-

ed using the CMS XIO (4.70.02 version, Elekta) treatment planning system.

Swallowing organs at risk (SWOARs) were identified and contoured as suggested by Christianen *et al.* [8], and six swallowing-related organs were delineated on axial CT-slices for each patient: superior pharyngeal constrictor muscle (SPCM), MPCM, IPCM, cervical oesophagus (CE), base of tongue (BOT) and larynx. The SPCM was contoured from the caudal tip of the pterygoid plates through the upper edge of the hyoid bone, the MPCM from the upper edge of the hyoid bone through the lower edge of the hyoid bone and the IPCM from the lower edge of the hyoid bone through the inferior edge of the cricoid cartilage. The CE was contoured from the inferior edge of the cricoid cartilage through the caudal-most extent of the low-neck target. The BOT was contoured from below the soft palate through the upper edge of the hyoid bone (8). The mean dose in Gray [Dmean(Gy)], the maximum dose in Gray [Dmax (Gy)] and the percentages of organ volumes receiving ≥ 50 Gy, ≥ 60 Gy and ≥ 70 Gy [V50 (%), V60 (%) and V70(%), respectively) were calculated from the dose–volume histograms for each structure.

Chemotherapy

Among the 26 HNC patients, 25 received chemotherapy, 1 refused chemotherapy and was treated with radiotherapy alone, 3 received induction chemotherapy followed by concurrent RCHT and 22 received concurrent RCHT without induction therapy. The combination of docetaxel, cisplatin and 5-flourouracil was used as induction chemotherapy, and weekly cisplatin (40 mg/m^2) was used as the concurrent chemotherapeutic agent in the induction group. Half of the patients received weekly cisplatin (40 mg/m^2), and the other half received triweekly cisplatin (100 mg/m^2) in the non-induction group.

Evaluation of dysphagia

All patients were examined for late dysphagia at least six months after the completion of radiotherapy. The presence of pharyngeal secretion and abnormal glottic closure was assessed using video laryngoscopy for the objective evaluation of dysphagia. For the subjective evaluation, the EORTC QLQ-H&N35 and Leipzig scale were used.

Each of the patients answered 35 questions of the EORTC QLQ-H&N35 [9], which were translated to Turkish. Pain within radiotherapy areas, swallowing problems with liquids/solid food, tasting and smelling problems, tooth and saliva problems, psychological state, eating and speaking problems, social relationship quality, sexual enjoyment, pain killer use, feeding tube use, nutritional support and weight change were all questioned using the EORTC QLQ-H&N35 [scoring for the first 30 questions: 'Not at all (1)', 'A little (2)', 'Quite a bit (3)' and 'Very much (4)'; scoring for the last 5 questions: 'No(1)' and 'Yes (2)']. Additionally, the patients were evaluated for swallowing disorder using the Leipzig scale (0, no aspiration; 1, occasional cough, no clinical problem; 2, constant cough worsening with meals or swallowing; 3, pulmonary complications due to aspiration).

The Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Spearman's correlation analysis was performed to analyse the relationship between the quality of life scores and the dose–volume data. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among the 26 patients, 21 (80.8%) were male and 5 (19.2%) were female, and the mean age on diagnosis was 56.46 years (range: 36–73). Tumour localisation was the nasopharynx in 9 patients (34.6%), larynx in 8 patients (30.8%), oropharynx in 4 patients (15.4%), hypopharynx in 3 patients (11.5%) and oral cavity in 2 patients (7.7%). The pathological diagnosis was squamous cell carcinoma in all patients. Four patients (15.4%) had stage II disease, 6 patients (23.1%) had stage III disease and 16 patients (61.5%) had stage IV disease. All patients with T1 disease also had lymph node involvement. The median follow-up was

22 months (range: 13–32). On follow-up, 3 patients (11.5%) had both local and systemic recurrence and 3 patients (11.5%) had a metachronous tumour. The patient and treatment characteristics are shown in table 1.

Objective evaluation with video laryngoscopy

Upon video laryngoscopic examination, the presence of pharyngeal secretion and abnormal glottic closure was assessed for the objective evaluation of dysphagia. Pharyngeal secretion was observed in 13 patients (50%) and abnormal glottic closure in 7 patients (26.9%). Figure 1 shows example images for the normal view, the presence of pharyngeal secretion and the presence of abnormal glottic closure.

Subjective evaluation with the EORTC QLQ-H&N35 and Leipzig scale

The patients answered 35 questions of the EORTC QLQ-H&N35. A total score was calculated for each patient, and the mean value was 53.42 (range: 42–96). Twenty-three patients (88.4%) had 'quite a bit' or 'very much' dry mouth, 15 patients (57.7%) had 'quite a bit' or 'very much' sticky saliva and 12 patients (46.2%) had 'quite a bit' or 'very much' problems with teeth. Moreover, none of the patients had pain in the mouth, became bored with their appearance and had trouble eating in front of family or having social contact with family.

Another subjective evaluation, performed at least six months after the completion of radiotherapy, was conducted using the Leipzig scale. Sixteen patients (61.5%) had no aspiration sign. None of the patients had pulmonary complications due to aspiration.

Dose–volume data correlated with the objective and subjective measures

The aforementioned dose-volume parameters of the swallowing organs were analyzed. Liquid swallowing problems was correlated with increased radiation dose to the BOT and the SPCM. Table 2 shows the associated dose-volume parameters.

Total score (TS) obtained from EORTC-QLQ-H&N35 was correlated with the increased radiation dose to almost all swallowing organs. Table 3 shows the significant correlations between dose-volume parameters and the TS.

Age, gender, smoking history, alcohol history, T stage and N stage were not correlated with TS. TS was statistically higher in patients with nasopharyngeal carcinoma than in those with other head and neck tumours.

Leipzig score, which represents aspiration, was correlated with increased radiation dose to the MPCM, the IPCM and the CE. Table 4 shows the significant correlations between dose-volume parameters and Leipzig score. Figure 2 and figure 3 show the scatterplot graphs of the dose-volume parameters of the MPCM, the IPCM and the CE, for each Leipzig score.

Only V50 for the CE was correlated with abnormal glottic closure (p=0.023). Pharyngeal secretion was correlated with the increased radiation dose to almost all swallowing organs. *Table 5* shows the the associated dose-volume parameters.

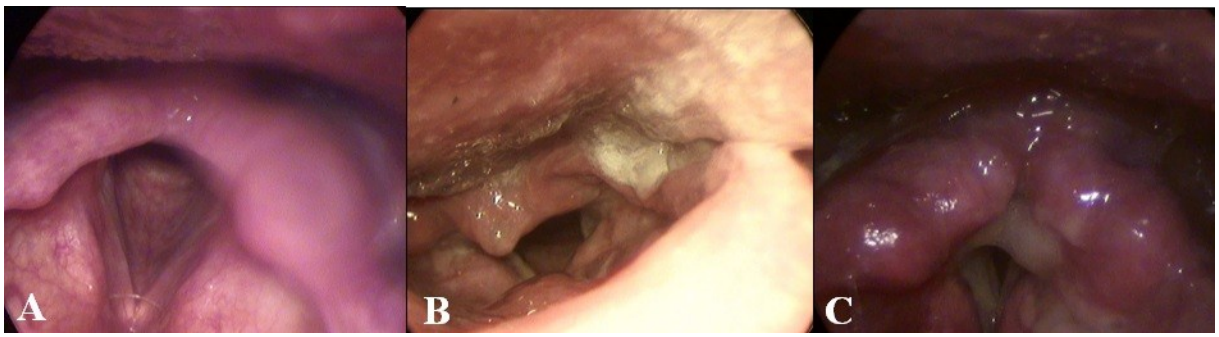

Figure 1. Example video laryngoscopy images for the normal view, the presence of pharyngeal secretion and the presence of abnormal glottic closure. (1-A) Normal view, (1-B) The presence of pharyngeal secretion, (1-C) The presence of abnormal glottic closure.

Table 1. Patient and treatment characteristics

Characteristic	Value (%)
Gender	
Female	5 (19,2)
Male	21 (80,8)
Age on diagnosis (year)	
Mean	56
Range	36-73
Karnofsky Performance Status Scale (points)	
80-100	23 (88,5)
60-80	3 (11,5)
Smoking history	
Yes	20 (76,9)
No	6 (23,1)
Alcohol history	
Yes	12 (46,1)
No	14 (53,9)
Primary site	
Nasopharynx	9 (34,6)
Larynx	8 (30,8)
Oropharynx	4 (15,4)
Hypopharynx	3 (11,5)
Oral cavity	2 (7,7)
T Stage	
T1	4 (15,4)
T2	7 (26,9)
T3	5 (19,2)
T4	10 (38,5)
N Stage	
N0	5 (19,2)
N1	6 (23,1)
N2	13 (50)
N3	2 (7,7)
M Stage	
M0	26 (100)
Stage	
I	0
II	4 (15,4)
III	6 (23,1)
IV	16 (61,5)
Treatment type	
Surgery	0
Induction chemotherapy plus concurrent radiochemotherapy	3 (11,5)
Concurrent radiochemotherapy	22 (84,6)
Radiotherapy alone	1 (3,8)
Radiotherapy dose (Gy)	
Median	69,46
Range	66-70
Chemotherapy	
Docetaxel/cisplatin/5-flourouracil plus weekly cisplatin (40 mg/m²)	3 (11,5)
Weekly cisplatin (40 mg/m²)	11 (42,3)
Three-weekly cisplatin (100 mg/m²)	11 (42,3)
No chemotherapy	1 (3,8)

Table 2. Relationship between dose-volume parameters and liquid swallowing problems.

	Dose-Volume Parameters	Mean ± Standard Deviation values	p-value
Liquid Swallowing Problems	BOT-Dmean(Gy)	59.05 ± 12.87	p=0.015
	BOT -Dmax(Gy)	67.53 ± 6.64	p=0.003
	BOT -V60(%)	52.23 ± 33.13	p=0.007
	BOT -V70(%)	12.87 ± 28.07	p=0.002
	SPCM-Dmean(Gy)	58.03 ± 10.73	p=0.001
	SPCM -Dmax(Gy)	69.27 ± 5.29	p=0.010
	SPCM -V60(%)	48.49 ± 31.62	p=0.007
	SPCM -V70(%)	13.57 ± 23.07	p=0.011

Table 3. Relationship between dose-volume parameters and total score obtained from EORTC QLQ-H&N35

	Dose-Volume Parameters	Mean ± Standard Deviation values	p-value
Total score obtained from EORTC QLQ-H&N35	BOT-Dmean(Gy)	59.05 ± 12.87	p=0.042
	BOT-Dmax(Gy)	67.53 ± 6.64	p=0.016
	BOT-V60(%)	52.23 ± 33.13	p=0.018
	BOT-V70(%)	12.87 ± 28.07	p=0.005
	SPCM-Dmean(Gy)	58.03 ± 10.73	p<0.0001
	SPCM-Dmax(Gy)	69.27 ± 5.29	p=0.009
	SPCM-V50(%)	90.30 ± 17.50	p=0.041
	SPCM-V60(%)	48.49 ± 31.62	p<0.0001
	SPCM-V70(%)	13.57 ± 23.07	p<0.0001
	MPCM-Dmean(Gy)	64.16 ± 3.89	p=0.025
	MPCM-Dmax(Gy)	69.46 ± 4.97	p=0.016
	MPCM-V70(%)	17.97 ± 24.59	p=0.011
	IPCM-Dmean(Gy)	64.13 ± 5.13	p=0.036
	IPCM-Dmax(Gy)	68.51 ± 4.99	p=0.001
	IPCM-V70(%)	23.76 ± 35.97	p=0.006
	Larynx-Dmean(Gy)	66.37 ± 4.84	p=0.011
	Larynx-Dmax(Gy)	70.73 ± 5.43	p=0.014
	Larynx-V60(%)	93.22 ± 9.33	p=0.030
	Larynx-V70(%)	37.14 ± 40.75	p=0.005

Table 4. Relationship between dose-volume parameters and Leipzig score.

	Dose-Volume Parameters	Mean ± Standard Deviation values	p-value
Leipzig Score	MPCM-Dmax(Gy)	69.46 ± 4.97	p=0.019
	IPCM-Dmean(Gy)	64.13 ± 5.13	p=0.004
	IPCM-Dmax(Gy)	68.51 ± 4.99	p=0.032
	IPCM-V60(%)	76.02 ± 25.39	p=0.005
	IPCM-V70(%)	23.76 ± 35.97	p=0.018
	CE-Dmax(Gy)	61.36 ± 7.19	p=0.007
	CE-V60(%)	12.37 ± 17.82	p=0.036
	CE-V70(%)	1.40 ± 3.98	p=0.018

Table 5. Relationship between dose-volume parameters and pharyngeal secretion

	Dose-Volume Parameters	Mean ± Standard Deviation values	p-value
Pharyngeal Secretion	BOT-Dmean(Gy)	59.05 ± 12.87	p=0.019
	BOT-V60(%)	52.23 ± 33.13	p=0.005
	BOT-V70(%)	12.87 ± 28.07	p=0.042
	SPCM-Dmean(Gy)	58.03 ± 10.73	p=0.022
	SPCM-V60(%)	48.49 ± 31.62	p=0.026
	IPCM-Dmean(Gy)	64.13 ± 5.13	p=0.009
	IPCM-Dmax(Gy)	68.51 ± 4.99	p=0.012
	IPCM-V60(%)	76.02 ± 25.39	p=0.032
	IPCM-V70(%)	23.76 ± 35.97	p=0.001
	Larynx-Dmean(Gy)	66.37 ± 4.84	p=0.006
	Larynx-Dmax(Gy)	70.73 ± 5.43	p=0.014
	Larynx-V60(%)	93.22 ± 9.33	p=0.032
	Larynx-V70(%)	37.14 ± 40.75	p=0.024
	CE-Dmean(Gy)	47.92 ± 12.24	p=0.030
	CE-Dmax(Gy)	61.36 ± 7.19	p=0.046
	CE-V50(%)	58.27 ± 27.47	p=0.014
	CE-V70(%)	1.40 ± 3.98	p=0.031

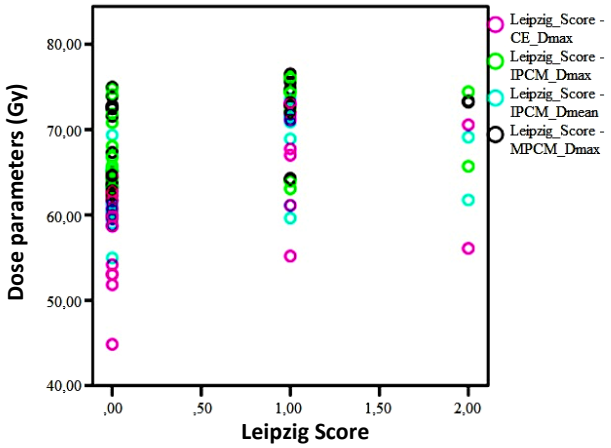

Figure 2. Scatterplot depicting Leipzig score and significant dose parameters (Gy).

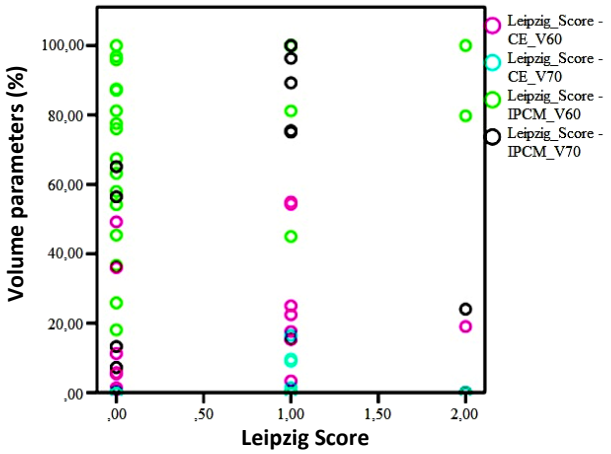

Figure 3. Scatterplot depicting Leipzig score and significant volume parameters (%).

DISCUSSION

The combination of radiotherapy and chemotherapy resulted in improved local control and survival for patients with HNC. These intensified treatment protocols generated high rates of acute and late toxicity. Xerostomia and dysphagia are the most prominent late complications of radiotherapy for HNC.

Intensity modulated radiotherapy (IMRT) has become the standard of care in patients with HNC treated by radiation therapy. However, in developing countries, 3D-CRT is still widely used for the radiation treatment of HNC. The use of IMRT has allowed radiation oncologists to preserve the parotid glands from high dose radiation and avoid permanent xerostomia. Clear dose constraints have been defined to decrease the incidence and severity of xerostomia. Unfortunately, the same improvements could not have been achieved for dysphagia. Dysphagia is one of the determinants of QoL for patients with HNC. Dysphagia was associated with worse quality of life, increased treatment expenses and duration of stay in the hospital and, more importantly, life-threatening conditions such as aspiration pneumonia [5, 10]. Nevertheless, dysphagia associated dose–volume constraints still remain inadequate, and dysphagia is considered a dose-limiting toxicity of radical radiotherapy for HNC.

In recent years, the incidence of radiotherapy -related dysphagia has increased because of intensified treatment protocols. Deantonio et al. and Feng et al. reported late dysphagia (all grades) rates of 60% and 56%, respectively [5, 11]. In our study, late dysphagia (all grades) was observed in 14 (53.8%) of the 26 patients, and our observed late dysphagia rate was similar to these studies.

Radiation-induced late dysphagia is considered related to radiation-induced free radical damage to the pharyngeal constrictor muscles as published by Truong *et al.* [12]. Various dose constraints for SWOARs have been suggested for preventing radiotherapy-related dysphagia and were summarised in the QUANTEC reviews [13, 14]. In their IMRT study, Feng et al. analysed the relationship between postradiation dysphagia and the dose received by the constrictor muscles and found that the strongest correlation was for SPCM [5]. Christianen et al. found that the mean doses of SPCM and MPCM were significantly correlated with swallowing dysfunction [15]. The TS obtained from the EORTC QLQ-H&N35 was correlated with Dmean and Dmax for the SPCM, the MPCM and the IPCM in our study, and the results were compatible with the literature. Moreover, Dmean and Dmax for the BOT and the larynx were correlated with the TS. The dose–volume parameters of the BOT and the SPCM were correlated with liquid swallowing problems as expected. Briefly, the TS was found to be correlated with nearly all dose–volume parameters of swallowing-related organs except CE.

Feng *et al.* revealed a relationship between the mean doses of SWOARs and dysphagia in their prospective study that evaluated postradiation dysphagia in patients treated with chemoradiotherapy. The mean dose to the pharyngeal constrictor muscles exceeding 60 Gy was strongly correlated with aspiration [5]. Jensen et al. reported that aspiration risk was low when the supraglottic area, larynx and upper oesophageal sphincter received less than 60 Gy of radiation dose in their retrospective study [16]. In the present study, the dose–volume parameters of the CE, the MPCM and the SPCM were correlated with the Leipzig score, which represents aspiration.

Upon objective evaluation, almost all of the dose–volume parameters of swallowing-related organs were correlated with the presence of pharyngeal secretion, and only the V50 for the CE was correlated with abnormal glottic closure. The proximity of the anatomical structures and the CE that received high doses the same as the planning target volume may explain this result.

The differences in dosimetric parameters of swallowing organs may be associated with the varied contouring of the pharyngeal constrictor muscles. Therefore, a common guide is needed for contouring SWOARs and comparing the results of different studies as suggested by Christianen *et al.* [8]. We found a significant relationship between QoL scores and radiation dose/dose receiving volumes of SWOARs in our study. Erkal et al. reported that Dmax, Dmean, V60 and V70 for the SPCM; V60, V70 and Dmean for the pharyngeal constrictor muscle; and Dmean and Dmax for the BOT were correlated with the QoL scores [17]. These results are compatible with ours.

In HNC patients, the incidence of postradiation late dysphagia has been shown to be associated with primary tumour localisation. Deantonio et al. reported that grades 2–3 late dysphagia rates were significantly higher in patients with the primary tumour location in the oropharynx [11]. Caudell et al. and Dirix et al. found that late dysphagia was associated with primary tumour localisation in the larynx, hypopharynx and posterior pharyngeal wall [3, 18]. In the present study, the TS obtained from the EORTC QLQ-H&N35 was significantly higher in patients with primary nasopharyngeal carcinoma. This fact can be related to salivary gland toxicity due to the definitive radiotherapy of nasopharyngeal carcinoma using 3D-CRT. As parotid glands are in close proximity to the radiation field, providing a sharp dose gradient is difficult with 3D-CRT in comparison with modern radiotherapy techniques such as IMRT. Therefore, higher rates of xerostomia that lead to worse QoL total scores may explain this fact.

In the literature, QoL questionnaires have been widely used in the studies for the subjective evaluation of radiotherapy induced dysphagia. But Leipzig scale was not much used for subjective evaluation. The novelty of our study is that, we used also Leipzig scale in addition to EORTC QLQ-H&N35 for subjective evaluation to strengthen our study results.

The limitations of our study are as follows: 1) It is cross-sectional but not prospective. 2) The patient number is relatively small. 3) All of the patients underwent definitive radiotherapy

using 3D-CRT. Using modern radiotherapy techniques (e.g. IMRT and Volumetric Modulated Arc Therapy) may improve the QoL questionnaire scores.

In conclusion, the dose–volume parameters of swallowing organs were found to be associated with the different rates of late dysphagia in HNC patients receiving RCHT. Clearly, the risk of radiotherapy-related dysphagia increases with a higher radiation dose. The identification of dosimetric parameters that predict late dysphagia is not yet adequate. Well-designed multi-institutional studies are still necessary to clarify the dose–volume constraints.

Conflicts of interest*: *Declared none.

REFERENCES

1. Adelstein DJ, Li Y, Adams GL, Wagner H, Jr., Kish JA, Ensley JF, Schuller DE, Forastiere AA (2003) An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol, **21(1)**: 92-8*.
2. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G (2004) Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol, **22(1)**: 69-76*.
3. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S (2009) Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys, **75(2)**: 385-92*.
4. Caudell JJ, Schaner PE, Desmond RA, Meredith RF, Spencer SA, Bonner JA (2010) Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys, **76(2)**: 403-9*.
5. Feng FY, Kim HM, Lyden TH, Haxer MJ, Feng M, Worden FP, Chepeha DB, Eisbruch A (2007) Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys, **68(5)**: 1289-98.*
6. Gregoire V, Eisbruch A, Hamoir M, Levendag P (2006) Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. *Radiother Oncol, **79 (1)**: 15-20*.
7. Gregoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V, Chao C, Coche E, Cooper JS, Cosnard G, Eisbruch A, El-Sayed S, Emami B, Grau C, Hamoir M, Lee N, Maingon P, Muller K, Reychler H (2003) CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. *Radiother Oncol, **69(3)**: 227-36*.
8. Christianen ME, Langendijk JA, Westerlaan HE, van de Water TA, Bijl HP (2011)Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. *Radiother Oncol, **101(3)**: 394-402*.
9. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF, Biorklund A, de Leeuw JR, Fayers PM, Jannert M, Westin T, Kaasa S (1999) Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. *J Clin Oncol, **17(3)**: 1008-19*.
10. Mittal BB, Pauloski BR, Haraf DJ, Pelzer HJ, Argiris A, Vokes EE, Rademaker A, Logemann JA (2003) Swallowing dysfunction--preventative and rehabilitation strategies in patients with head-and-neck cancers treated with surgery, radiotherapy, and chemotherapy: a critical review. *Int J Radiat Oncol Biol Phys, **57(5)**: 1219-30*.
11. Deantonio L, Masini L, Brambilla M, Pia F, Krengli M (2013) Dysphagia after definitive radiotherapy for head and neck cancer. Correlation of dose-volume parameters of the pharyngeal constrictor muscles. *Strahlenther Onkol, **189 (3)**: 230-6*.
12. Truong MT, Lee R, Saito N, Qureshi MM, Ozonoff A, Romesser PB, Wang J, Sakai O (2012) Correlating computed tomography perfusion changes in the pharyngeal constrictor muscles during head-and-neck radiotherapy to dysphagia outcome. *Int J Radiat Oncol Biol Phys, **82(2)**: e119-27*.
13. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, Bentzen SM, Nam J, Deasy JO (2010) Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys, **76(3 Suppl)**: S10-9*.
14. Rancati T, Schwarz M, Allen AM, Feng F, Popovtzer A, Mittal B, Eisbruch A (2010) Radiation dose-volume effects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys, **76 (3 Suppl)**: S64-9*.
15. Christianen ME, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR, Doornaert P, Koken PW, Leemans CR, Rinkel RN, de Bruijn MJ, de Bock GH, Roodenburg JL, van der Laan BF, Slotman BJ, Verdonck-de Leeuw IM, Bijl HP, Langendijk JA (2012) Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. *Radiother Oncol, **105(1)**: 107-14*.
16. Jensen K, Lambertsen K, Grau C (2007) Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: frequency, intensity and correlation with dose and volume parameters. *Radiother Oncol, **85(1)**: 74-82*.
17. Erkal EY, Canoglu D, Kaya A, Aksu G, Sarper B, Akansel G, Meydanci T, Erkal HS (2014) Assessment of early and late dysphagia using videofluoroscopy and quality of life questionnaires in patients with head and neck cancer treated with radiation therapy. *Radiat Oncol, **9**: 137*.
18. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, Magnuson JS, Spencer SA, Bonner JA (2009) Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys, **73(2)**: 410-5*.