

## Laryngeal sensation and pharyngeal delay time after (chemo)radiotherapy

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**Abstract** The objective of the study was to evaluate the association between changes in laryngeal sensation and initiation of swallowing reflex or swallowing function before and after (chemo)radiotherapy. A prospective study was conducted in a tertiary referral university hospital. Thirteen patients who received (chemo)radiotherapy for treatment of laryngeal or hypopharyngeal cancer were included. Laryngeal sensation was evaluated at the tip of the epiglottis before and 1, 3 months, and 1 year after (chemo)radiotherapy. Videofluoroscopy was performed at the same time. Quantitative determinations included changes in laryngeal sensation, computed analysis of pharyngeal delay time, the distance and velocity of hyoid

bone movement during the phase of hyoid excursion, and pharyngeal residue rate (the proportion of the bolus that was left as residue in the pharynx at the first swallow). Laryngeal sensation significantly deteriorated 1 month after (chemo)radiotherapy, but there was a tendency to return to pretreatment levels 1 year after treatment. Neither pharyngeal delay time nor displacement of the hyoid bone changed significantly before and after (chemo)radiotherapy. In addition, there was no significant difference in the mean velocity of hyoid bone movement and the amount of stasis in the pharynx at the first swallow before and after (chemo)radiotherapy. After (chemo)radiotherapy, laryngeal sensation deteriorated. But, in this study, videofluoroscopy showed that swallowing reflex and function were maintained.

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### Introduction

Cancer of the head and neck often has a profound impact on important quality-of-life functions, including swallowing. Treatment of these tumors may further impair these functions, and it is not unusual for patients to develop swallowing abnormalities and dysphagia after head and neck cancer resection, surgery with (chemo)radiotherapy, or radiotherapy alone. Some patients may require prolonged enteral alimentation with a gastrostomy tube. Radiation therapy can produce secondary fibrosis of the pharyngeal muscles and soft tissues, with resultant impairment of pharyngeal contraction and laryngeal elevation [1]. Moreover, inclusion of salivary glands into the

radiation field induces xerostomia and hyposalivation, which further impair mastication and initiation of the swallowing reflex [2].

Ozawa et al. [3] evaluated changes in laryngeal sensation before and after (chemo)radiotherapy for laryngeal and hypopharyngeal cancer. The laryngeal sensation of patients deteriorated significantly 1 and 3 months after (chemo)radiotherapy compared with before (chemo)radiotherapy. Sensitivity of the larynx is the trigger that sets off the swallowing reflex mechanism, thereby resulting in swallowing and protection of the airway [4]. Considering this, we expect that deterioration of laryngeal sensation causes a delay in initiation of the swallowing reflex and aspiration. The purpose of this study was to evaluate the association between changes in laryngeal sensation and initiation of the swallowing reflex by using videofluoroscopy before and after (chemo)radiotherapy for laryngeal and hypopharyngeal cancer.

## Methods

This study was approved by the ethics committee and institutional review board of our hospital (No. 534, 534-2). This work was supported by MEXT KAKENHI Grant-in-Aid for Scientific Research (C) Grant Number 23592525.

This study was conducted in 13 patients, 11 with laryngeal cancer and 2 with hypopharyngeal cancer, who received radiotherapy alone or chemoradiotherapy at our university hospital (Table 1). No patients received surgical treatment in the primary or neck.

After taking CT simulation at the treatment posture, the radiation dose plan was made for each individual patient. A conventional fractionation schedule of 2 Gy/day was used. In laryngeal cancer patients, the radiation target volume routinely included the upper border of the thyroid cartilage

at the top and the lower border of the cricoid cartilage at the bottom, and a minimum of 1–1.5 cm margins were put around all the clinically known disease extent of the individual patient. Two patients (No. 4 and 8 in Table 1) with laryngeal carcinoma had neck metastasis. So, the radiation target volume of these two patients was extended to include the upper border of the first cervical vertebra at the top and the lower border of the clavicle at the bottom for neck metastasis and prophylactic lymph node irradiation. The primary lesion and neck metastasis lesions were boosted with reduced fields after prophylactic nodal irradiation. The median total irradiated dose was 66 Gy (range 60–70 Gy).

Hypopharyngeal cancer patients received prophylactic lymph node irradiation. The prophylactic nodal area (including the retropharyngeal region and supraclavicular nodes) was irradiated up to 40 Gy with parallel-opposed lateral fields with a matched anterior lower neck field. The primary lesion and neck metastasis lesion were boosted with reduced fields after prophylactic nodal irradiation. The total irradiated doses were 60 and 66 Gy. The content of chemotherapy is shown in Table 2.

All patients provided written informed consent. The procedure for measurement of the laryngeal sensation was as follows. A novel flexible laryngoscope (ENF-Y0005) with a maximum diameter of 3.3 and a 1.2 mm probe port was co-developed with Olympus (Tokyo, Japan) in previous research [5, 6]. The probes, also co-developed with Olympus, have a nylon filament attached to a wire tip and are protected by a sheath to prevent entanglement with the flexible laryngoscope. In the present study, four types of probes with nylon filament diameters of 0.06, 0.13, 0.20, and 0.30 mm were used as described previously [3]. At the time of the study, the flexible laryngoscope and probes were not commercially available, but provided by Olympus [3].

Laryngeal sensation was evaluated at the tip of the epiglottis. The flexible laryngoscope and probes were

**Table 1** Patient characteristics

No.	Age	Sex	Tumor site	TNM	Radiotherapy dose (Gy)	Chemotherapy
1	63	M	Larynx	T1bN0M0	60	Concomitant
2	58	M	Hypopharynx	T1N0M0	66	Concomitant
3	69	M	Hypopharynx	T4bN2cM0	60	Concomitant
4	53	M	Larynx	T1N2bM0	66	Concomitant
5	65	F	Larynx	T1aN0M0	70	None
6	72	M	Larynx	T1aN0M0	70	None
7	82	M	Larynx	T1aN0M0	70	None
8	56	M	Larynx	T3N1M0	70	Concomitant
9	70	M	Larynx	T2N0M0	60	None
10	75	M	Larynx	T2N0M0	63	None
11	83	M	Larynx	T1aN0M0	70	None
12	67	M	Larynx	T1N0M0	66	None
13	68	M	Larynx	T2N0M0	66	Concomitant

*M* male, *F* female, *TNM* tumor node metastasis score

**Table 2** Chemotherapy

No.	Treatment	Chemotherapy	Dose
1	CRT	TS-1	55.3 mg/m <sup>2</sup> /day
2	IC + RT	5-Fu/CDDP 2 cycle	5-Fu: 700 mg/m <sup>2</sup> CDDP: 80 mg/m <sup>2</sup>
3	IC + CRT	5-Fu/CDDP 4 cycle	5-Fu: 700 mg/m <sup>2</sup> CDDP: 80 mg/m <sup>2</sup>
4	Alternative CRT	5-Fu/CDDP 2 cycle	5-Fu: 700 mg/m <sup>2</sup> CDDP: 80 mg/m <sup>2</sup>
8	CRT	CDDP 2 cycle	(1) 80 mg/m <sup>2</sup> (2) 80 mg/m <sup>2</sup>
13	CRT	CDDP 3 cycle	(1) 80 mg/m <sup>2</sup> (2) 60 mg/m <sup>2</sup> (3) 60 mg/m <sup>2</sup>

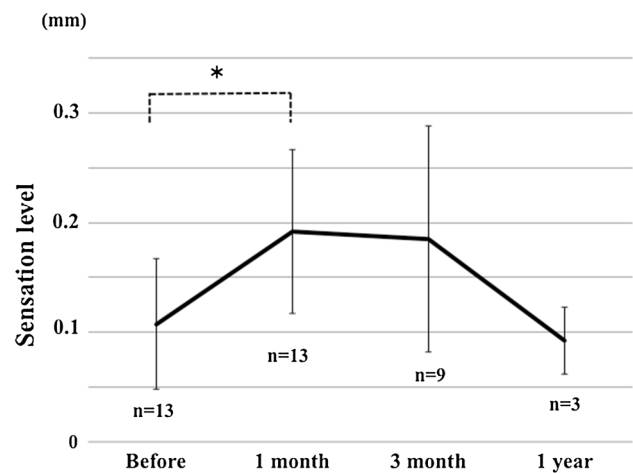
CRT chemoradiotherapy, IC induction chemotherapy

manipulated, whenever possible, by the same person. Patients were asked to ring a buzzer or tap their hand when they felt the probe. For objective evaluation, the laryngeal adductor reflex was observed. Agreement between the subjective and objective findings was considered “positive”. Testing started with the thinnest probe, and the sensation level was based on the probe giving two of three positive responses [3]. Measurements of laryngeal sensation were taken before (chemo)radiotherapy, 1, 3 months, and 1 year after completion of (chemo)radiotherapy. Videofluoroscopy was performed at the same time. The contrast medium was 40 % barium sulfate, and a digital videocassette recorder was used to record the images observed from the lateral and frontal perspectives (NTSC format, 30 frames/sec). The digital images were downloaded to a personal computer, and then Image software was used to measure the coordinates. Image analysis was performed using Ditect Image Processing Products (DIPP-Motion Pro2D) software (DITECT Corporation, Tokyo, Japan). Quantitative determinations included pharyngeal delay time (PDT); changes in laryngeal sensation, hyoid bone movement, and mean velocity of hyoid bone movement in the phase of hyoid excursion; and pharyngeal residue rate (the proportion of the bolus that was left as residue in the pharynx) before and after (chemo)radiotherapy. The maximum hyoid bone movement was defined as the greatest distance of hyoid bone movement during a swallow, and the forward and vertical dimensions were calculated on the same video frame. PDT was measured from when the leading edge of a food bolus reached the lower border of the mandible until the greatest elevation of hyoid bone movement. Qualitative determinations included the penetration–aspiration scale [7] (Table 3).

Dates were analyzed to evaluate differences between before (chemo)radiotherapy, and 1, 3 months, and 1 year after completion of (chemo)radiotherapy. Analysis included the Wilcoxon-signed rank test with Bonferroni correction. In all cases, statistical significance was set at  $P < 0.05$ .

**Table 3** Penetration–Aspiration scale [7]

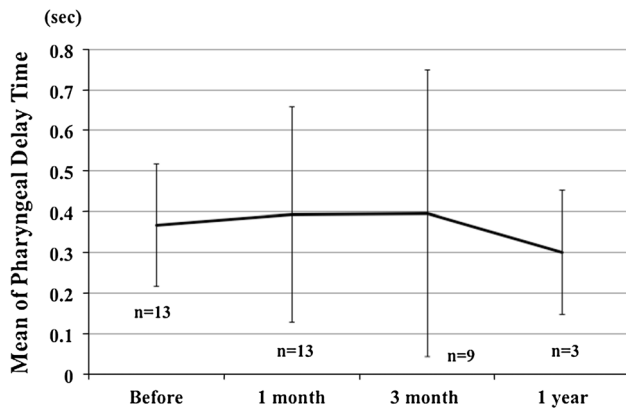
1. Material does not enter the airway
2. Material enters the airway, remains above the vocal folds, and is ejected from the airway
3. Material enters the airway, remains above the vocal folds, and is not ejected from the airway
4. Material enters the airway, contacts the vocal folds, and is ejected from the airway
5. Material enters the airway, contacts the vocal folds, and is not ejected from the airway
6. Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway
7. Material enters the airway, passes below the vocal folds, and is ejected from the trachea despite effort
8. Material enters the airway, passes below the vocal folds, and no effort is made to eject



**Fig. 1** Sensation levels of the larynx. Mean value of sensation levels of the larynx in patients who underwent this examination before, 1, 3 months, and 1 year after radiotherapy. \* $P < 0.05$

## Results

Four of 13 patients (No. 1, 2, 4, and 13) did not undergo videofluoroscopy examination 3 months after radiotherapy because they withdrew from the study for personal reasons. Three of the remaining nine patients underwent videofluoroscopy examination 1 year after radiotherapy. Laryngeal paralysis did not occur before or after treatment in any patient. Figure 1 shows laryngeal sensation level before, 1, 3 months, and 1 year after radiation therapy. Laryngeal sensation significantly deteriorated 1 month after (chemo)radiotherapy in all patients and, in some cases, remained at almost the same level 3 months after therapy. Eleven of 13 patients experienced sensory deterioration 3 months after (chemo)radiotherapy compared with before therapy, but laryngeal sensation returned to the pretreatment level 1 year after (chemo)radiotherapy in two (No. 5

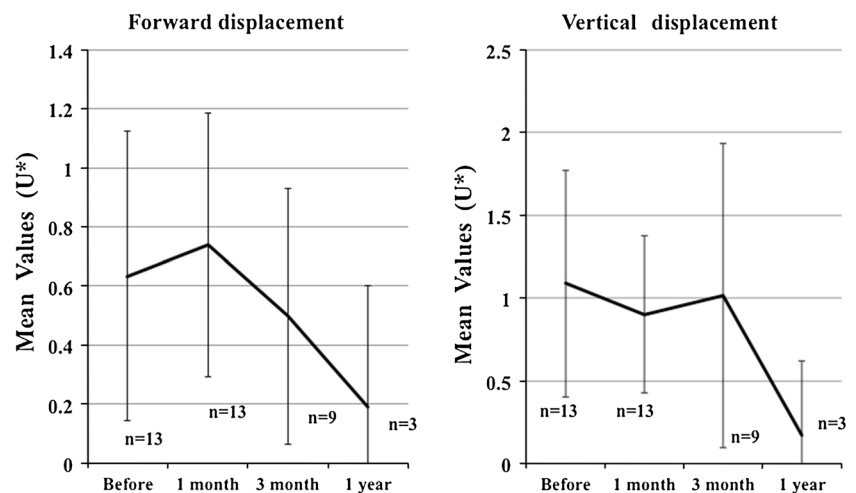


**Fig. 2** Mean pharyngeal delay time (PDT). Mean PDT in patients who underwent this examination before, 1, 3 months, and 1 year after radiotherapy. Vertical bars represent standard deviations

and 8) of three patients (No. 5, 8, and 10) who underwent the sensory examination 1 year after (chemo)radiotherapy.

Figure 2 shows the results of PDT. Six patients showed prolonged PDT 3 months after radiotherapy. However, PDT measured before, 1, 3 months, and 1 year after (chemo)radiotherapy did not differ significantly. Hyoid bone movement by both the forward direction (anterior or  $x$  axis, horizontal) and the vertical direction (upward or  $y$  axis) is shown in Fig. 3. The mean velocity of the hyoid bone 1 year after (chemo)radiotherapy did not differ compared with values before, 1, and 3 months after (chemo)radiotherapy. There was a tendency for vertical and horizontal movements to be less at 1 year after (chemo)radiotherapy, although there were no significant differences compared with before and after (chemo)radiotherapy in either direction. On the other hand, the pharyngeal residue rate was 3.3, 2.1, 5.5, and 3.0 % before, 1, 3 months, and 1 year after (chemo)radiotherapy, respectively. There were no significant differences between before and after (chemo)radiotherapy (Fig. 4).

**Fig. 3** The greatest displacement of the hyoid bone from resting position during a swallow. Each data point is the mean of the distance from resting position in patients who underwent this examination. Vertical bars represent standard deviations. \* $U$  = thickness of C4 vertebrae

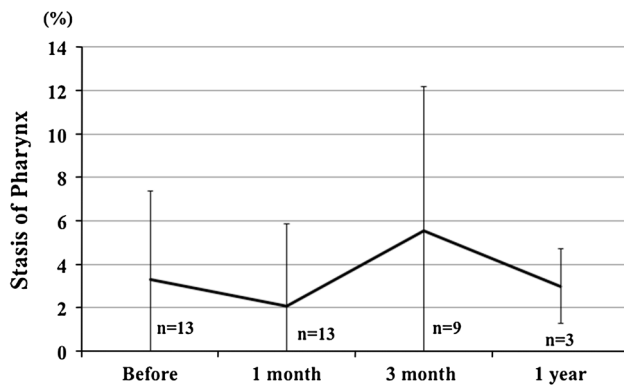


In the penetration–aspiration scale, three patients showed an increase in the score of the penetration–aspiration scale at 1 month after (chemo)radiotherapy, and the median score increased 1 month after (chemo)radiotherapy compared with before (chemo)radiotherapy. However, there was no significant difference before, 1, 3 months, and 1 year after (chemo)radiotherapy (Fig. 5).

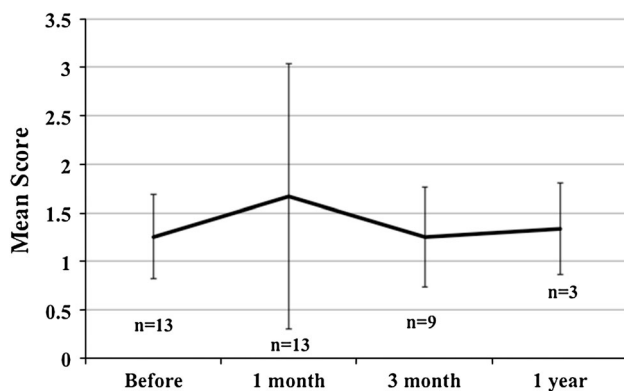
## Discussion

(Chemo)radiotherapy of the laryngopharynx sometimes leads to functional disabilities including swallowing dysfunction [8–11]. The reasons for these disabilities include mucosal and muscular inflammation, fibrosis, reduced saliva secretion, and deterioration of laryngeal sensation [10]. This study showed that laryngeal sensation was significantly reduced 1 month after (chemo)radiotherapy. There was a tendency for the sensation level to return to the preradiation level after that. Because only three patients were examined for laryngeal sensation at 1 year after radiotherapy, we were unable to show a statistical difference between 1 year after (chemo)radiotherapy and preceding points of time. However, recovery to the laryngeal sensation level at 1 year after (chemo)therapy was typical as described by Ozawa et al. [3]. In our study, laryngeal sensation was clearly reduced by radiotherapy, and one patient who had severe sensory deterioration had aspiration pneumonia during and after (chemo)radiotherapy. It was felt that the sensory deterioration was closely associated with decrease of airway protective reflex.

Van der Molen et al. [11] showed that the most common abnormalities occurring after (chemo)radiotherapy in patients with laryngeal cancer are delayed pharyngeal swallowing, reduced laryngeal elevation, and reduced cricopharyngeal opening. In contrast, our study showed no significant differences before and after



**Fig. 4** Pharyngeal residue rate (the proportion of the bolus that was left as residue in the pharynx). Each data point is the mean of the pharyngeal residue rate in patients who underwent this examination. Vertical bars represent standard deviations



**Fig. 5** Score of Penetration-Aspiration Scale. Each data point is the mean of the Score of Penetration-Aspiration Scale in patients who underwent this examination. Vertical bars represent standard deviations

(chemo)radiotherapy in PDT or in the penetration–aspiration scale. Smith et al. [12] showed that all patients receiving radiation–hydroxyurea therapy showed aberrantly increased durations of laryngeal motion during swallowing, and that this prolonged laryngeal motion correlated with a delay in peak laryngeal elevation; however, their findings were not statistically significant. Swallowing abnormalities after (chemo)radiotherapy include trismus and reduced oral tongue control in patients with nasopharynx tumors, and reduced tongue base retraction and reduced tongue strength in patients with oropharynx tumor.

The pharyngeal swallow response is believed to be initiated by stimulation of pharyngeal receptors in the region of the anterior tonsillar pillars by the advancing bolus and the tongue via interneurons within the medullary swallow center [13]. The anterior tonsillar pillar region has been proposed to be one of the most sensitive areas for triggering initiation of the swallowing reflex, but stimulation

of a wide range of regional receptors is capable of initiating the swallowing reflex [14]. The superior laryngeal nerve, which innervates the laryngeal region, is known to be the most important afferent nerve for initiation of the swallowing reflex [15–19]. Animal studies have shown that electrical stimulation of the superior laryngeal nerve elicits reflex swallowing [20]. In our study, the pharyngeal delay was not associated with laryngeal sensory deterioration.

Four patients (No. 2, 3, 4 and 8) received 40 Gy prophylactic radiation to the wide area. After the prophylactic radiation, they received radiation up to 60–70 Gy to the primary and its adjacent area. In two patients (No. 3 and 8), the suprahyoid muscle was included in the adjacent area and irradiated up to 60 Gy. The laryngeal sensation, PDT, hyoid bone displacement and velocity, pharyngeal residue rate, and penetration–aspiration score were not different significantly between four patients who received the prophylactic radiation to the wide area and the remaining nine patients. In our study, such extended radiation did not exert significant influence on the hyoid bone movement.

Kim et al. [21] showed that PDT in normal populations was  $-0.10 \pm 0.05$  s in younger subjects (range 21–51 years) and  $0.17 \pm 0.05$  s in older subjects (range 70–87 years). In our study, PDT was longer than that of the normal population data. The age effect must be considered in addition to the tumor therapy effect. Future investigations that include patients with oral and oropharyngeal cancer and that evaluate variables such as motion of the tongue and cricopharyngeal opening are needed.

Hyoid displacement is a critical component of swallowing [22], and this study showed that hyoid bone displacement did not change compared with before and after (chemo)radiotherapy. In-time and adequate hyoid movement provides adequate airway protection, completes the opening of the cricopharyngeus muscle during the process of swallowing, and ensures safe passage of food into the esophagus [23–25]. The displacement of the hyoid bone depends on a sequenced and balanced contraction of the suprahyoid and infrahyoid muscles [26]. Reduced displacement of the hyoid bone may come from fibrosis of muscles resulting from radiotherapy [22]. Kapur [26] has described muscle tissue change in patients many years after they had completed (chemo)radiotherapy. These changes indicated a weakening of muscle power and caused a reduction of hyoid bone movement after (chemo)radiotherapy. The reduction of the displacement of hyoid bone may cause inadequate airway protection, and pyriform sinus stasis may arise. Both of these factors increase the risk of aspiration [22]. There was a tendency for vertical and horizontal hyoid movements to be less at 1 year after the (chemo)radiotherapy, although differences were not significant. In addition to the level of displacement of the hyoid bone, the velocity of hyoid bone movement is the

other key factor that determines the risk of aspiration [27]. Reduced velocity of hyoid bone movement may delay the sealing of the laryngeal vestibule and threaten aspiration. In this study, almost all patients showed reduced hyoid bone movement velocity, but there were no statistical differences. Furthermore, our study also found that pharyngeal residue rate did not statistically increase from before to after (chemo)radiotherapy. It was possible that our study included comparatively young cases. Future studies need to be done including patients with a wider age range, as well as with not only laryngeal or hypopharyngeal cancer but also oral or oropharyngeal cancer.

## Conclusions

Our findings showed that sensory deterioration of the larynx that deteriorates airway protective reflex can result from (chemo)radiotherapy. On the other hand, pharyngeal delay time, the distance and velocity of hyoid bone movement during the phase of hyoid excursion, and pharyngeal residue rate did not change compared with before and after (chemo)radiotherapy. It is possible that the sensory deterioration of the larynx does not affect initiation of the swallowing reflex and swallowing function.

**Conflict of interest** We do not have a financial relationship with the organization that sponsored the research.

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