Computed Tomographic Evaluation of Posttreatment Soft-Tissue Changes by Using a Lymphedema Scoring System in Patients with Oral Cancer

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Computed tomographic evaluation of posttreatment soft-tissue changes by using a lymphedema scoring system in patients with oral cancer

Running Title: Lymphedema scoring of posttreatment change of neck

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Abstract

Background: This study aimed to evaluate posttreatment soft-tissue changes in patients with oral cancer with computed tomography (CT). To accomplish that purpose, a scoring system was established, referring to the criteria of lower leg lymphedema (LE).

Methods and Results: 106 necks in 95 patients who underwent oral oncologic surgery with neck dissection were analyzed retrospectively using routine follow-up CT images. A two-point scoring system to evaluate soft-tissue changes (so-called "LE score") was established as follows: Necks with a "honeycombing" appearance were assigned 1 point. Necks with "taller than wide" fat lobules were assigned 1 point. Necks with neither appearance were assigned 0 points. Comparisons between patients with LE score≥ 1 and LE score= 0 at 6 months postoperatively were performed using the Fisher exact test for discrete variables and the Mann-Whitney U test for continuous variables. Univariate predictors associated with posttreatment changes (i.e., LE score≥ 1 at 6 months postoperatively) were entered into a multivariate logistic regression analysis. Values of $p < 0.05$ were considered to indicate statistical significance. The occurrence of the posttreatment soft-tissue changes was 32%. Multivariate logistic regression analysis showed that postoperative radiation therapy and bilateral neck dissection were potential risk factors of posttreatment soft-tissue changes on CT images.

Conclusions: Sequential evaluation of “honeycombing” and the “taller than wide” appearances on routine follow-up CT revealed the persistence of posttreatment soft-tissue changes in patients who underwent oral cancer treatment, and those potential risk factors were postoperative RT and bilateral ND. [242/250 words]

Key words: soft-tissue changes, lymphedema, oral cancer, radiation therapy, neck dissection, computed tomography.

Introduction

Posttreatment soft-tissue changes of the head and neck, including skin thickening, epiglottic thickening, and stranding of subcutaneous fat, are commonly associated with previous radiation therapy (RT).[1] Recently, it is well-known that secondary lymphedema (LE) in patients with head and neck cancer is a common problematic condition, with its high incidence at 75% among these patients.[2,3] Head and neck LE is categorized as external, internal, or a combination of the two. External LE involves face and neck structures (e.g., facial and submental tissues), whereas internal LE involves the upper aerodigestive tract (e.g., tongue and epiglottis).[4,5] External LE may lead to skin tightness, pain, and body image issues. Internal LE results in difficulty chewing, swallowing, and speaking.[5] A recent study reported on the effectiveness of complete decongestive therapy for external head and neck LE after cancer treatment.[6] Early identification and timely LE physiotherapy have the potential to cause regression of the edema. Without timely therapy, however, LE causes head and neck soft tissues to become fibrotic, resulting in contraction.[5] It is noteworthy that those previous studies about LE included head and neck cancer patients (the majority of whom were patients with pharyngeal cancers), and few studies targeted only patients with oral cavity cancer.

Identifying LE is problematic in itself because there is no objective assessment modality.[7] Although physical examination is considered sufficient for diagnosing head and neck

LE, imaging examinations provide important supplemental guidance.[5] In a recent review, Deng et al. classified imaging modalities into two categories: (1) methods for evaluating the functional lymphatic structure and (2) those that identify tissue changes.[5] Computed tomography (CT) has been used to evaluate soft-tissue changes and is effective for identifying head and neck LE.[5] Another study provided evidence that facial edema assessed with CT scan could be an indicator of the prognosis for patients with head and neck cancer.[8]

This study established the scoring system to evaluate the posttreatment soft-tissue changes by referring to the previous study about lower leg swelling.[9] By using this scoring system, the incidence of the posttreatment soft-tissue changes in oral cancer patients was determined, and those risk factors were identified. We also discuss the meaning of physiotherapy in patients who underwent oral cancer treatment.

Materials and methods

This retrospective study included patients who underwent oral oncologic surgery with neck dissection (ND) at our department between 2006 and 2014. Histological diagnosis was squamous cell carcinoma in all cases. Patients who had recurrence at the primary site or the neck and secondary cervical lymph node metastases were excluded because the follow-up was not long enough to evaluate posttreatment soft-tissue changes. For evaluating posttreatment soft-tissue changes of necks, routine follow-up enhanced CT (6, 12, 18, and 24 months postoperatively) to monitor for tumor recurrence or metastasis was used. This retrospective study was performed under the Declaration of Helsinki. All patients had provided informed consent for the use of CT for the clinical study. Ethical approval was exempted by the institutional medical ethics committee because of the retrospective nature of the study.

Medical records were reviewed to collect data about the patients' age and gender, smoking and alcohol drinking status, the primary site of the cancer, prognosis stage, the surgical procedure including extent of ND and type of simultaneous reconstruction, postoperative RT, chemotherapy, ligation of internal jugular vein (IJV), and postoperative local infection with abscess formation. For all of the patients who underwent postoperative RT, the RT was initiated immediately after surgery. Hence, the postoperative RT was completed at the time of the CT scan 6 months after the surgery.

CT assessment of lymphedema

Two independent clinicians assessed the CT images in consensus. Discrepant results were solved by consecutive consensus readings. In a previous study, Shin et al. evaluated the same CT features (e.g., "honeycombing appearance" and "taller than wide" appearances of the fat lobules) that we use to compare LE, cellulitis, and generalized edema in regard to lower leg swelling.[9] Hadjis et al. reported the characteristic “honeycombing” pattern of the subcutaneous component on CT images of patients with primary LE of the lower leg.[10] “Honeycombing” appears as thickened interstitial tissues in the subcutaneous layer that cross each other and polygonally shaped fat attenuation with peripheral septa-like structures composed of fluid or fibrous tissue, or both.[9,10] In addition, Shin et al. described the polygonally shaped fat lobules as having a “taller than wide” appearance if the diameter was greater in the perpendicular direction than in the horizontal direction.[7] Referring to these criteria of lower leg LE, a two-point scoring system was established as follows (so-called “LE score”): Necks in which the “honeycombing” appearance was observed on CT images were assigned 1 point (Fig. 1). Necks in which the “taller than wide” fat lobules were observed on CT images were assigned 1 point (Fig 1). Necks in which neither “honeycombing” nor “taller than wide” appearances were observed on CT images were assigned 0 points (Fig 1). Using this scale, the maximum LE score was 2.

The representative images in two patients were shown in Figure 2. The persistence of “honeycombing” nor “taller than wide” appearances on CT images was found at 6 (Fig 2A) and 12 months (Fig 2B) postoperatively in a 64-year-old male patient who underwent bilateral ND, segmental mandibulectomy, reconstruction with double free flaps (radial forearm and fibula), and postoperative concomitant chemoradiotherapy. On the other hand, “honeycombing” nor “taller than wide” appearances were not observed at 6 months operatively in a 71-year-old female patient who underwent supraomohyoid ND, partial maxillectomy, and reconstruction with free radial forearm flap (Fig 2C).

Statistical analysis

The primary endpoints of this retrospective study were determination of the occurrence of the the abnormal CT findings (LE score≥ 1) at 6 months postoperatively in patients who underwent oral oncologic surgery, and identification of those risk factors. The data were analyzed with R software (R Development Core Team, 2011). Comparisons between patients with LE score≥ 1 and LE score= 0 at 6 months postoperatively were performed using the Fisher exact test for discrete variables and the Mann-Whitney U test for continuous variables. Logistic analyses were conducted to evaluate the relative influences of potential risk factors (bilateral ND, postoperative RT, chemotherapy, and IJV ligation). Subsequently, factors found by univariate analysis to be predictors whose odds ratios suggested an association with the abnormal CT findings (LE score≥ 1) at 6 months postoperatively were entered into the final multivariate logistic regression analysis model. A p value less than .05 was regarded as indicating statistical significance.

Results

Patients' characteristics are shown in Table 1. In all, 11 of 95 patients (12%) underwent bilateral ND. Thus, 106 necks were evaluated. Figure 3 shows the sequential change in the LE scores. The number of necks with an LE score of 2 decreased sequentially over time: 10 (9%) at 6 months, 3 (3%) at 12 months, 0 at 18 and 24 months. The most common pattern of change in the CT appearance for these necks was the "taller than wide" appearance diminishing first, followed by disappearance of the "honeycombing." The number of necks with an LE score of 0 sequentially increased: 71 (67%) at 6 months, 95 (90%) at 12 months, 101 (95%) at 18 months, 103 (97%) at 24 months. At 24 months postoperatively, "honeycombing" (i.e., LE score of 1) persisted only in 3 of 106 necks (3%).

At 6 months postoperatively, the number of patients with LE score≥ 1 was 30 (32%). The results of the Fisher exact test for discrete valuables and the Mann-Whitney U test showed that bilateral ND, postoperative RT, and chemotherapy associated LE score≥ 1 at 6 months postoperatively (Table 2). Results of the univariate logistic regression analysis showed that significant causative factors of the persistence of abnormal CT findings (LE score≥ 1) at 6 months postoperatively were also bilateral ND, postoperative RT, and chemotherapy (Table 3). Subsequently, the results of the multivariate logistic regression analysis showed that only bilateral ND and postoperative RT were statistically relevant to LE score≥ 1 at 6 months postoperatively (Table 3).

Overall, 66 of 95 patients (69%) had no potential risk factors (i.e., neither postoperative RT nor bilateral ND). A total of 11 of those 66 patients (17%) had an LE score≥ 1 at 6 months postoperatively. At 18 and 24 months postoperatively, all patients without potential risk factors had LE score of 0. In contrast, the long-term persistence of abnormal CT Findings (LE score≥ 1 at 12, 18, 24 months postoperatively) was significantly associated with postoperative RT but not bilateral ND (Table 4).

Discussion

This study showed that the scoring system using CT could reflect the state of posttreatment soft-tissue changes on the basis of the potential risk factors (postoperative RT and bilateral ND). In oral cancer patients, the percentage of posttreatment changes (i.e., LE score ≥ 1) at 6 months postoperatively was only 32%, and none of patients without the potential risk factors had posttreatment changes on CT images at 18 months postoperatively.

The characteristic CT findings were reported by Shin et al., who concluded that most patients with lower leg LE display skin thickening as well as “honeycombing” and “taller than wide” fat lobules.[9] Although another previous study reported that the “honeycombing” pattern is exclusive to LE and considered to be LE-specific,[10] Shin et al. noted that this pattern is also seen in patients’ lower legs that suffer from cellulitis and generalized edema. Hence, this radiologic feature is not LE-specific.[9] It remains unclear, however, whether "honeycombing" and "taller than wide" appearances on CT images are LE-specific for head and neck cancer. It is also unclear whether these conditions eventually result in irreversible fibrosis and reduced quality of life. In a literature review, Deng et al. mentioned a fibrosclerotic process of LE in regard to an experimental study in mice.[5] The authors hypothesized that lymphatic stasis initiates a cycle of inflammation → progressive tissue fibrosis → worsening lymphatic function. They went on to show that inflammation is a critical regulator of tissue fibrosis and lymphatic dysfunction in murine LE.[11] In the current study, "honeycombing" and the "taller than wide" patterns on CT images are due to inflammation, fibrosis, and probably LE. In almost cases following oral cancer treatment, the lymphatic system is repaired or compensates for lymphatic damage, resulting in disappearance of the "honeycombing."

Some previous methods for evaluating post-therapeutic head and neck LE were ultrasonography,[12] a moisture meter,[7] tape measurements,[6,7] flexible fiberoptic endoscopic examination,[2,13] and physical examination.[2] Although these methods play indispensable roles, medical and support staff should be trained to arrive at more accurate diagnoses. The scoring system used in this study is simple, necessitating only routine follow-up CT images. The strengths of this scoring system using routine follow-up CT are that the additional examinations are not required and that the evaluation is relatively easy even by less experienced medical staff.

The results of this study indicate that the assessment of both “taller than wide” and “honeycombing” appearances contribute to the evaluation of post-therapeutic soft-tissue changes in the head and neck by medical and support staff.

Smith et al. reported the effectiveness of a head and neck cancer-specific regimen for treating external LE.[6] It included manual lymph drainage, tissue compression with bandaging and/or garments, remedial exercises, and skin care.[6] They started manual lymph drainage a minimum of 4–6 weeks postoperatively or waited until the RT regimen was completed. Patients’ response to that treatment was significantly better in those who underwent surgery alone than in patients who underwent postoperative RT.[6] In this study, the “honeycombing” appearance did not persist in patients, who did not undergo bilateral ND and RT 18 months postoperatively. Other factors, such as ligation of IJV, local infection with abscess formation, and type of reconstruction—which were previously analyzed[8]—did not relate to the posttreatment change (LE score≥ 1 at 6 months postoperatively). To determine whether the persistence of abnormal CT findings (i.e., “honeycombing”, “taller than wide” fat lobules) truly relate to reduced quality of life, a further study using an evaluation tool (e.g., Lymphedema Symptom Intensity and Distress Survey–Head and Neck used by Deng et al.[13]) is required. Based on the results of the present study and previously conducted studies, immediate initiation of physiotherapy in patients who undergo bilateral ND or RT for oral cancer may be meaningful.

In conclusion, the two-point scoring system used in this study is useful for identifying post-therapeutic tissue changes that are probably due to inflammation, fibrosis, and external LE. Sequential evaluation of “honeycombing” and the “taller than wide” appearances on routine follow-up CT showed that the incidence of posttreatment soft-tissue changes was 32 % in patients who underwent oral cancer treatment, and those potential risk factors were postoperative RT and bilateral ND. The most important limitation of this study is the lack of investigation of correlation between LE score and clinical symptoms such as skin tightness, pain, body image, trismus, and dysphagia. Further study is needed to analyze the relation between patients’ symptoms and the abnormal CT findings (“honeycombing” and “taller than wide” appearances).

Author Disclosure Statement

The authors have no conflicts of interest or financial ties to disclose.

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Figure Legends

Fig. 1. Representative computed tomography images of “honeycombing” and “taller than wide” appearance (A). Arrows indicate the “honeycombing” appearance. The box contains both the “honeycombing” and “taller than wide” appearances. Neck without either “honeycombing” or the “taller than wide” appearance (B). An enlarged image of the area enclosed by the box in Fig. 1A. The height of the fat lobule is measured as “a” and its width as “b”. Necks in which the a/b ratio is > 1 are defined as having a “taller than wide” appearance (positive). In contrast, necks in which the ratio is lower < 1 (e.g., c/d) are defined as having a “wider than tall” appearance (negative). This characterization was originally described in the study about lower leg swelling (Shin et al., 2013).

Fig. 2. Representative computed tomography images of the long-term persistence of “honeycombing” nor “taller than wide” appearances at 6 (A) and 12 months (B) postoperatively in a 64-year-old male patient. Representative computed tomography images of immediate regression of “honeycombing” nor “taller than wide” appearance at 6 months operatively in a 71-year-old female patient (C).

Fig. 3. Sequential decreases in the lymphedema (LE) scores (2, 1, 0 points) over time. The presence of either a “honeycombing” appearance or “taller than wide” fat lobules is assigned a score of 1 point (dark gray columns). The presence of both conditions is assigned a total score

of 2 (black columns). If neither condition is present, the score is 0 (light gray columns).

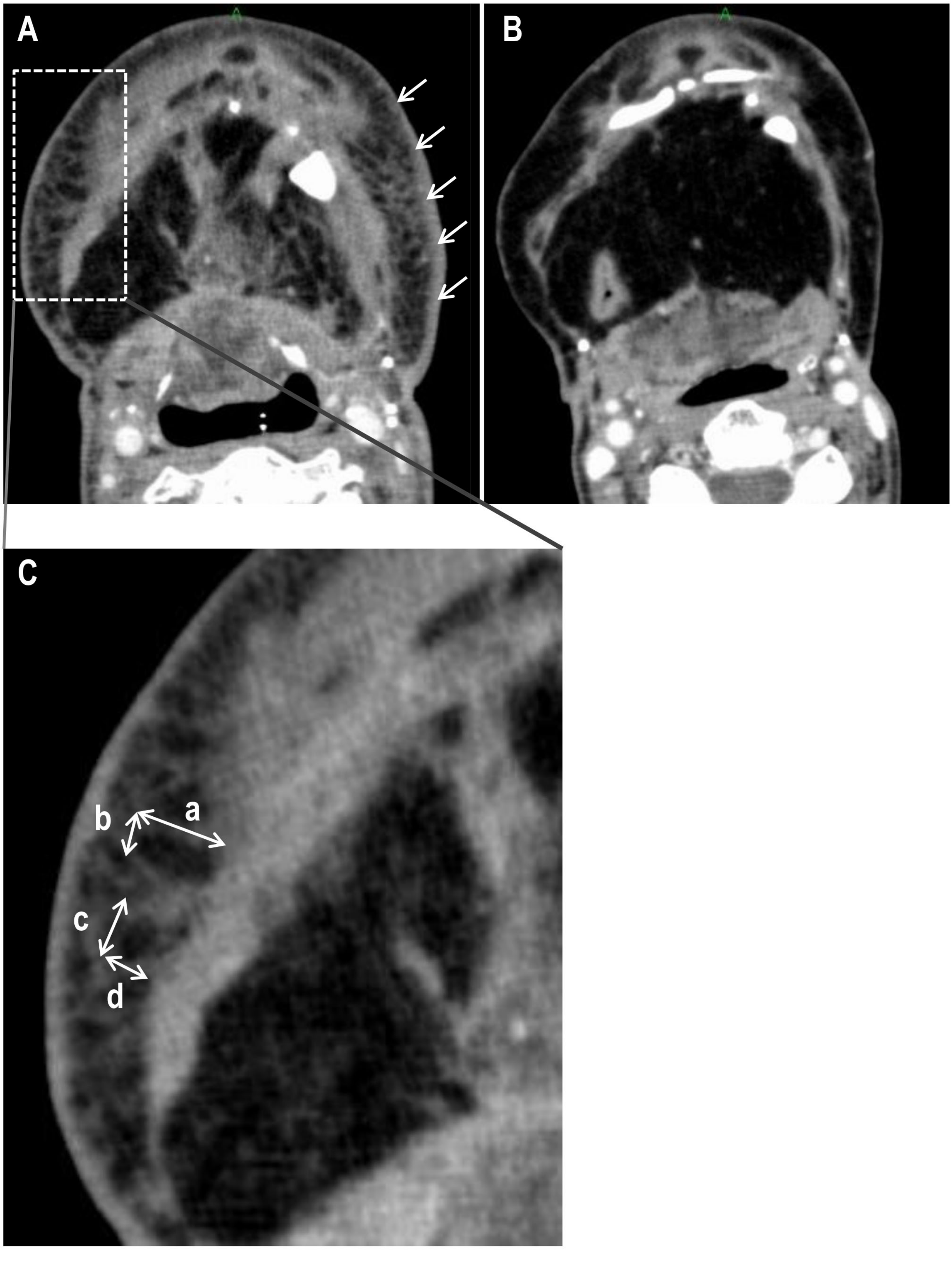

Figure 1

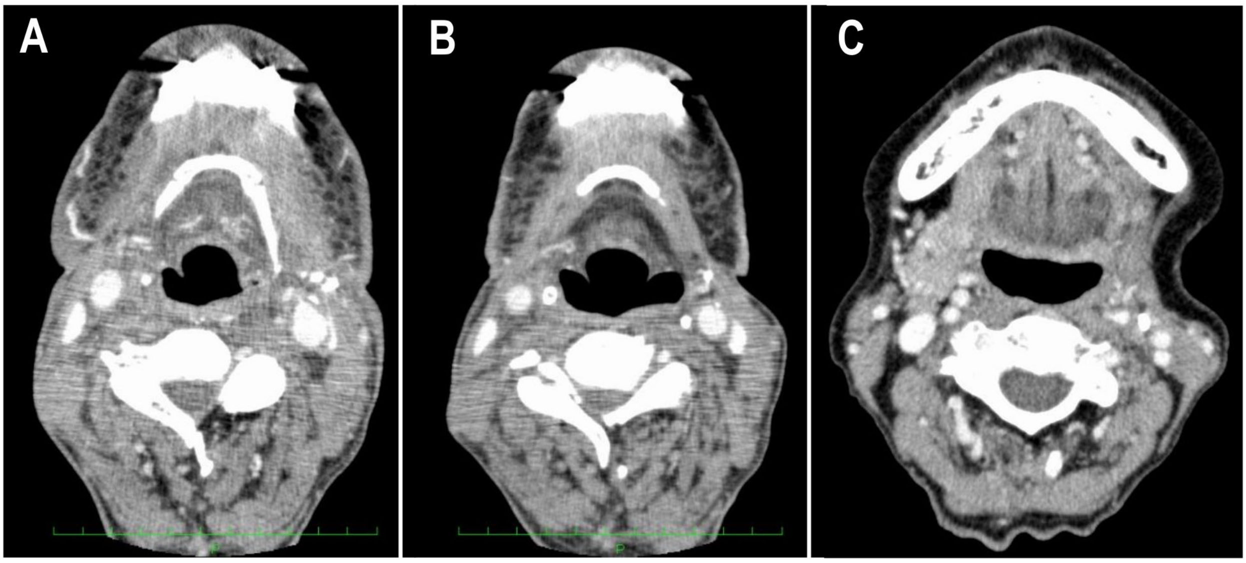

Figure 2

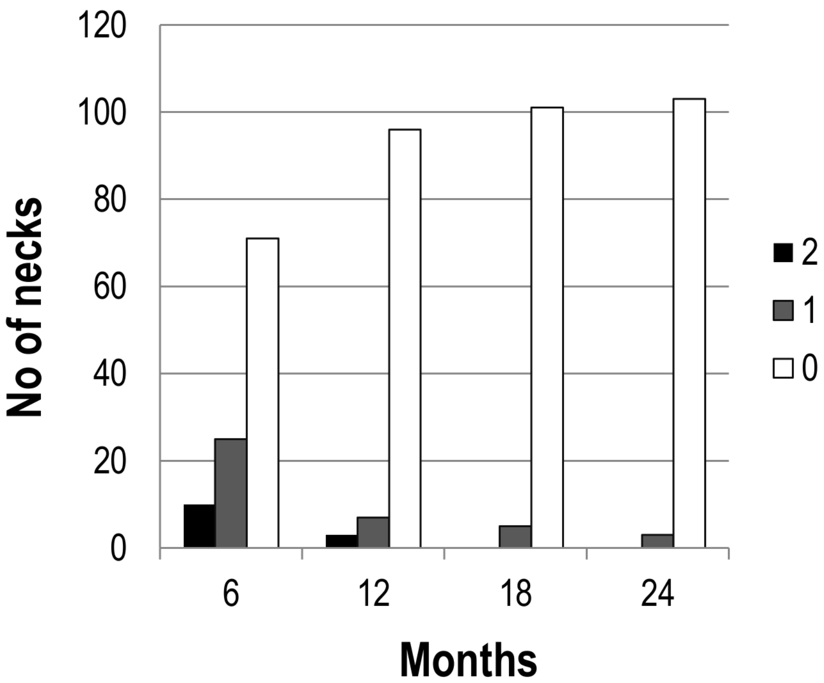

Figure 3

Table 1. Characteristics of study population

variables	No. of patients[a] (n = 95)
Age at surgery (yr), median (range)	69 (31–87)
Gender	
Male	56 (59)
Female	39 (41)
Smoking status	
Never	57 (60)
Active or quit	38 (40)
Drinking alcohol status	
Never	40 (42)
Active or quit	55 (58)
Diabetes mellitus	22 (23)
Primary site	
Tongue	39 (41)
Mandibular gingiva	23 (24)
Buccal mucosa	13 (14)
Floor of mouth	11 (12)
Maxillary gingiva	9 (9)
T stage	
1	2 (2)
2	57 (60)
3	18 (19)
4	18 (19)
N stage	
0	41 (44)
1	27 (28)
2	27 (28)
Prognosis stage	
Stage I	1 (1)
Stage II	25 (26)
Stage III	27 (28)
Stage IV	42 (45)
Neck dissection (level)	
I – III	69 (73)
I – IV	24 (25)

I – V	2 (2)
Ipsilateral neck dissection (level)	11 (12)
I	1 (1)
I – III	2 (2)
I – V	8 (8)
Reconstruction[b]	89 (94)
Radial forearm	51 (54)
Pedicled flaps	14 (15)
Rectus abdominis	10 (10.5)
Fibula	10 (10.5)
Other free flaps	4 (4)
IJV[c] ligation	3 (3)
Radiation (dose), Gy	22 (23)
50	3 (3)
60	3 (3)
66	15 (16)
70	1 (1)
Chemotherapy	8 (8)
Postoperative local infection	6 (6)

[a]Unless otherwise noted, data are reported as number (percentage) of study patients.

[b]Pedicled flaps: pectoralis major, deltopectoral, cervical island.

Other free flaps: double free flap (forearm and fibula), latissimus dorsi, scapula.

[c]IJV: internal jugular vein.

Table 2. Risk factors of persistence of abnormal CT findings (LE score≥ 1) at 6 months postoperatively in 95 patients

	LE score≥ 1 at 6 months postoperatively (n = 30)[a]	LE score=0 at 6 months postoperatively (n = 65)[a]	p value
Age (yr), median (range)	64 (35–87)	70 (31–87)	.25[c]
Gender			.37[d]
Male	20 (67)	36 (55)	
Female	10 (33)	29 (45)	
Smoking status			.38[d]
Never	16 (53)	41 (63)	
Active or quit	14 (47)	24 (37)	
Drinking alcohol status			.83[d]
Never	12 (40	28 (43)	
Active or quit	18 (60)	37 (57)	
Diabetes mellitus	5 (17)	17 (26)	.43[d]
Primary site			.46[d]
Tongue	9 (30)	30 (46)	
Mandibular gingiva	8 (27)	15 (23)	
Buccal mucosa	6 (20)	7 (11)	
Floor of mouth	3 (10)	8 (12)	
Maxillary gingiva	4 (13)	5 (8)	
T stage			1[d]
T1	0 (0)	2 (3)	
T2	18 (60)	39 (60)	
T3	6 (20)	12 (18)	
T4	6 (20)	12 (18)	
Prognosis stage			.1[d]
Stage I	0 (0)	1 (2)	
Stage II	4 (13)	21 (32)	
Stage III	8 (27)	19 (29)	
Stage IV	18 (60)	24 (37)	
Bilateral neck dissection	7 (23)	4 (6)	**.03**[d]
IJV[b] ligation	2 (7)	1 (2)	.23[d]
Radiation therapy	16 (53)	6 (9)	**<.001**[d]
Chemotherapy	7 (23)	1 (2)	**.001**[d]
Flap reconstruction	28 (93)	61 (94)	1[d]
Osseous reconstruction with composite flap	5 (17)	7 (11)	.51[d]
Postoperative local infection	3 (10)	3 (5)	.38[d]

[a]Unless otherwise noted, data are reported as number (percentage) of study patients.
[b]IJV: internal jugular vein.
[c]By Mann-Whitney U test.
[d]By Fisher exact test.

Table 3. Univariate and multivariate logistic analysis of potential risk factors of the persistence of abnormal CT findings (LE score≥ 1) at 6 months postoperatively in 95 patients

Variables	Univariate p value	Multivariate odds ration (95% CI[b])	Multivariate p value
Bilateral neck dissection	.033	4.70 (1.05-21.0)	.043
IJV[a] ligation	.234	0.85 (0.05-14.4)	.909
Radiation therapy	< .001	8.11 (1.97-33.3)	.004
Chemotherapy	.001	3.51 (0.30-41.5)	.320

[a]IJV: internal jugular vein.

[b]CI: confidence interval.

Table 4. Association of long-term persistence of abnormal CT findings (LE score≥ 1) with potential risk factors

	Potential risk factors[a]					
	Postoperative radiation			Bilateral neck dissection		
	Yes (n = 22)	No (n = 73)	p value[b]	Yes (n = 11)	No (n = 84)	p value[b]
LE score≥ 1						
Postoperative (months)						
12	5 (23)	3 (4)	**.015**	4 (36)	4 (5)	**.006**
18	4 (18)	1 (.2)	**.001**	2 (18)	2 (2)	.06
24	3 (14)	0 (0)	**.01**	1 (9)	2 (2)	.3

[a]Data are reported as the number (percentage) of patients.

[b]By Fisher exact test.