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Original Article

Morphological Changes and Durability of Skin and Mucosal Flaps in Intraoral and Pharyngeal Reconstructions: Long-term Follow-up and Literature Review for Potential Second Carcinomas

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The long-term changes in tissues implanted in the oral cavity and pharynx after head and neck reconstruction have not been fully evaluated. This study aimed to clarify the morphological changes, long-term durability, and potential for secondary carcinogenesis in such tissues. In our single-center study, the rough morphological changes in 54 cases of intraoral and pharyngeal skin and mucosal flaps were evaluated more than 10 years after flap transfer. In addition, the literature on the development of second carcinomas from skin flaps was reviewed. The mean follow-up period for transferred flaps was 148 months. The reconstruction areas and the probability of morphological changes were significantly correlated ($p = 0.006$), especially in cases with tongue, lower gingiva, and buccal mucosal reconstruction. Free jejunal flap surfaces were well maintained, whereas tubed skin flaps showed severe morphological changes in cases with pharyngeal reconstruction. None of the flaps in our series developed second primary carcinomas. Skin flaps generally had good durability for > 10 years in intraoral environments, while mucosal flaps had better durability for pharyngeal reconstruction. Second squamous carcinomas arising from skin flaps are extremely rare; however, surgeons should take this possibility into consideration and conduct meticulous and long-term follow-up.

Key words: skin flap, mucosal flap, oral reconstruction, morphological change, second primary carcinoma

When surgical treatment of head and neck cancers requiring reconstructive surgery is undertaken, patients generally have a poor prognosis; however, advances in treatment modalities for the primary tumor have increased the number of patients who survive for more than 10 years. In contrast, there is little information on the long-term durability of skin or mucosal flaps transferred to intraoral and pharyngeal spaces or on the potential for second primary carcinomas to develop in the transferred flaps.

This study aimed to retrospectively investigate the morphological changes in skin or mucosal flaps more than 10 years after surgery in patients who underwent oral and pharyngeal reconstruction at our institution. The long-term durability of the transplanted tissue and the development of second primary cancers in our cases and as reported in the literature were also investigated.

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Materials and Methods

We retrospectively reviewed 178 patients who underwent oral and pharyngeal reconstruction between August 2000 and December 2009 at Okayama University Hospital, and we included the patients who had lived more than a decade after the reconstructive surgery. The durability of skin or mucosal flaps was assessed based on the rough morphological changes that appeared in the flaps > 10 years after the reconstructive surgery. The analysis was performed by one plastic surgeon engaged in head and neck reconstructive surgery based on gross findings for skin flaps implanted in the oral cavity and endoscopic findings for skin and jejunal flaps implanted in the pharyngeal cavity. Changes in the transferred flaps were classified into three types based on the report by Choi *et al.* : type 1, normal skin or normal mucosa; type 2, the color tone was a mixture of silver-white and reddish; type 3, reddish mucosal-like surface [1]. Statistical analysis of several factors associated with the types of morphological change observed in the flaps was performed. Statistical evaluation was performed using the χ^2 test and Kruskal-Wallis analysis. The level of significance was set at 5% ($p < 0.05$).

This study was approved by the Ethics Committee of Okayama University, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences on March 27, 2020 (reference No. 2004-14).

Results

Patient demographics and representative cases. By December 31, 2019, 59 patients had died from their primary disease, whereas 17 had died from other diseases. Because some patients returned to their hometowns after completing the primary tumor treatment, we could not determine the clinical outcome in 49 patients. Finally, we extracted the medical records of 53 patients who were alive as of December 31, 2019.

These patients included 36 men and 17 women, and their ages ranged from 17 to 75 years at the time of the reconstructive surgery. Their age at final examination ranged from 36 to 89 years, and the follow-up period was > 10 years (range: 120-229 months) after the reconstructive surgery. One patient underwent free flap transfer twice for reconstruction of the same areas. Therefore, a total of 54 free flaps were transferred for 53 patients, and among them, 11 received postoperative radiotherapy.

The intraoral reconstructions performed included resection of the lower gingiva in 17 patients, the tongue in 15, the upper gingiva in 5, the floor of the mouth in 4, the buccal mucosa in 4, and the oropharyngeal wall in 2. Several kinds of flaps including rectus abdominis musculocutaneous flaps (RAMCs), anterolateral thigh flaps (ALTs), peroneal flaps with fibula bone, and radial forearm flaps (RFs) were transferred.

Of the cases that underwent pharyngeal space reconstruction, 3 patients underwent total pharyngo-laryngo esophagectomy (TPLE) and reconstruction with a free jejunal flap (FJ), 1 underwent TPLE and reconstruction with an FJ and tubed deltopectoral flap (DP), and 3 underwent laryngectomy and reconstruction of the anterior pharyngeal wall with a pedicled pectoralis major myocutaneous flap (PMMC) (Table 1).

The classification of the rough morphological

Table 1 Characteristics of patients who lived for more than a decade after reconstructive surgery

No. of patients (M: F):	53 (36: 17)
No. of operations:	54
Mean age of reconstruction (range):	58.4 years (17–75)
Mean age of final examination (range):	71.1 years (36–89)
Mean follow-up period (range):	148.7 months (120–229)
Total No. of intraoral reconstruction:	47
Lower gingiva ca.	17
Tongue ca.	15
Upper gingiva ca.	5
Floor of mouth ca.	4
Buccal mucosa ca.	4
Oropharynx ca.	2
Used flap for intraoral reconstruction	
Rectus abdominis MC flap	13
Anterolateral thigh flap	13
Peroneal flap with vascularized fibular	10
Radial forearm flap	7
Deep inferior epigastric perforator flap	2
Tensor fasciae latae flap	1
Groin flap with vascularized iliac	1
Total No. of pharyngeal reconstruction:	7
Laryngeal ca.	4
Pharyngeal ca.	2
Thyroid ca.	1
Used flap for pharyngeal reconstruction	
Free jejunal flap	3
Free jejunal flap + tubed Deltopectoral flap	1
Pedicled pectoralis major MC flap	3

ca., carcinoma; MC, musculocutaneous

changes of the flaps at >10 years after reconstruction is shown in Table 2. In the 15 patients who underwent tongue reconstruction, all 3 types of morphological changes were observed in the transferred flaps (Fig. 1). In the 5 patients with upper gingiva reconstruction, 4 had type 1 and 1 had type 2 changes. Of the 17 patients who underwent lower gingiva reconstruction, 8 had type 3, 2 had type 2, and 7 had type 1 changes (Fig. 2). In 4 patients with oral floor reconstruction, all flaps showed type 1 changes except one flap which showed a type 2 change.

Three ALTs and one RF were used for buccal mucosal reconstruction in 4 patients. One patient had undergone ALT reconstruction of a buccal mucosa defect approximately 20 years earlier. Thirteen years after the surgery, the flap became hypertrophic and edematous, and lost its skin wrinkles. Because this type 3 change caused trismus, we replaced the ALT in this patient. However, the replanted ALT became an edematous, reddish mucosal surface 6 years after the secondary reconstruction. The remaining 2 flaps also had a type 3 appearance (Fig. 3).

Regarding the patients with pharyngeal space reconstruction, all three FJs used for reconstruction after TPLE showed normal mucosa on endoscopy. The three PMMCs used for reconstruction of the anterior pharyngeal wall showed that the neo-pharynx was coated with saliva, but the surface of the PMMC looked like

Table 2 Factors associated with the types of morphological changes in flaps

	No. of operations	Type1 (n=25)		Type2 (n=15)		Type 3 (n=14)		*P*-value (χ^2 test)	
		n	%	n	%	n	%		
Reconstructive area								0.006	
Tongue	15	4	26.7	9	60.0	2	13.3		
Oropharynx	2	1	50.0	1	50.0	0	0.0		
Lower gingiva	17	7	41.2	2	11.8	8	47.1		
Upper gingiva	5	4	80.0	1	20.0	0	0.0		
Floor of mouth	4	3	75.0	1	25.0	0	0.0		
Buccal mucosa	4	0	0.0	1	25.0	3	75.0		
Pharyngeal space	7	6	85.7	0	0.0	1	14.3		
Irradiation								0.284	
No	43	19	44.2	14	32.6	10	23.3		
Yes	11	6	54.5	1	9.1	4	36.4		
Mean age at last examination	71.1	68.8		71.1		74.4		0.056	※
Mean term after reconstruction (Months)	148.7	137.9		159.9		153.4		0.211	※
Sex								0.869	
Male	37	17	45.9	11	29.7	9	24.3		
Female	17	8	47.1	4	23.5	5	29.4		
Transferred flap								0.106	
RF	7	4	57.1	2	28.6	1	14.3		
ALT	13	3	23.1	7	53.8	3	23.1		
RAMC	13	5	38.5	4	30.8	4	30.8		
DIEP	2	1	50.0	1	50.0	0	0.0		
Peroneal	10	6	60.0	0	0.0	4	40.0		
FJ	3	3	100.0	0	0.0	0	0.0		
FJ+DP	1	0	0.0	0	0.0	1	100.0		
PMMC	3	3	100.0	0	0.0	0	0.0		
Groin	1	0	0.0	0	0.0	1	100.0		
TFL	1	0	0.0	1	100.0	0	0.0		

※Kruskal-Wallis analysis; RF, radial forearm flap; ALT, anterolateral thigh flap; RAMC, rectus abdominis musculocutaneous flap; DIEP, deep inferior epigastric artery flap; FJ, free jejunal flap; DP, deltopectoral flap; PMMC, pectoralis major musculocutaneous flap; TFL, tensor-fasciae-latae flap.

Fig. 1 Intraoral images of morphological changes after tongue reconstruction. (A) A 64-year-old woman who had undergone oral subtotal glossectomy and reconstruction with an RF 10 years earlier. The flap surface exhibited a nearly normal skin color and wrinkles (type 1). (B) A 72-year-old man who had undergone subtotal glossectomy and reconstruction with an RAMC 15 years earlier. The flap showed mixed colors of silver-white and reddish with a loss of skin creases (type 2). (C) A 44-year-old woman who had undergone subtotal glossectomy and reconstruction with an RAMC. The image was taken 10 years after surgery. The surface of the flap appeared completely smooth, and all wrinkles were lost. The skin color had changed to red and resembled a mucosal surface (type 3). RF, radial forearm flap; RAMC, rectus abdominis musculocutaneous flap; TFL, tensor fasciae latae flap.

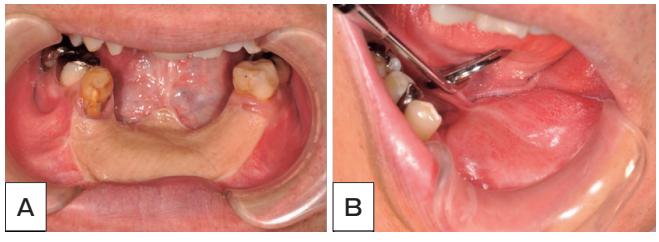

Fig. 2 Morphological changes in the lower gingiva. (A) A 55-year-old man who had undergone lower gingiva mandibulotomy and reconstruction with a fibular osteocutaneous flap 11 years earlier. The flap exhibited normal skin (type 1). (B) A 79-year-old man who had undergone lower gingiva mandibulotomy and reconstruction with an RAMC and reconstructive mandibular plate 11 years earlier. The flap looks edematous and red in color (type 3). RF, radial forearm flap; RAMC, rectus abdominis musculocutaneous flap.

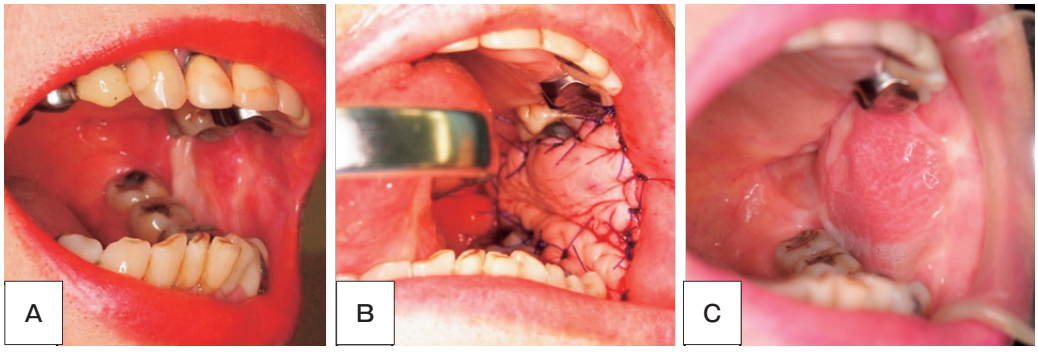

Fig. 3 A representative case with buccal mucosal reconstruction. (A) A 70-year-old woman who had undergone buccal mucosal reconstruction with ALT 13 years earlier. The hardness of the flap increased (type 3), and the patient complained of trismus. (B) Removal of the scar and ALT; re-transfer of ALT. (C) Although trismus was not recognized, the replanted ALT appeared edematous with a reddish mucosal-like surface (type 3) 6 years after secondary reconstruction. ALT, anterolateral thigh flap.

normal skin, and its skin wrinkles were maintained (Fig. 4). One patient with TPLE underwent a complicated reconstruction with both FJ and tubed DP. Eleven years after surgery, the patient complained of occasional swallowing difficulty and vomiting while eating because of a mild stricture at the anastomosis site between the tubed DP and FJ. Although the tubed DP color changed from yellow to silver-white, with some parts showing desquamation (type 2), the grafted jejunum surface was well maintained (Fig. 5).

There were no second primary carcinomas among the cases included in this study.

Statistical analysis of factors associated with the type of morphological flap change. The correlations

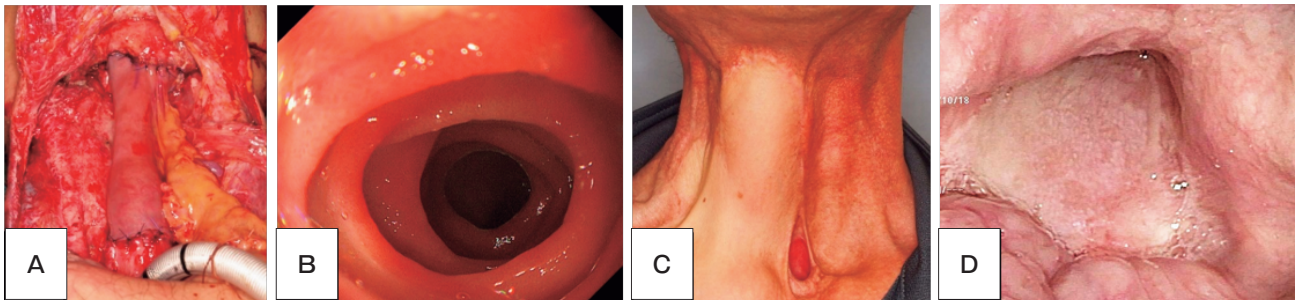

Fig. 4 A representative case of pharyngeal reconstruction with an FJ and PMMC after TPLE. (**A**) A 60-year-old man who had undergone TPLE and FJ reconstruction. (**B**) An endoscopic image taken 11 years postoperatively. The FJ surface was completely maintained (type 1). (**C**) A 54-year-old man who had undergone laryngectomy after radiation therapy. Unfortunately, a postoperative fistula developed. The anterior pharyngeal wall was reconstructed with a PMMC and the neck skin was covered with a DP 10 years earlier. (**D**) The patient did not complain of swallowing difficulty. An endoscopic image revealed the well-maintained skin surface of the PMMC (type 2) with slight saliva pooling. TPLE, total pharyngo-laryngo esophagectomy; FJ, free jejunal flap; PMMC, pectoralis major musculocutaneous flap; DP, deltopectoral flap.

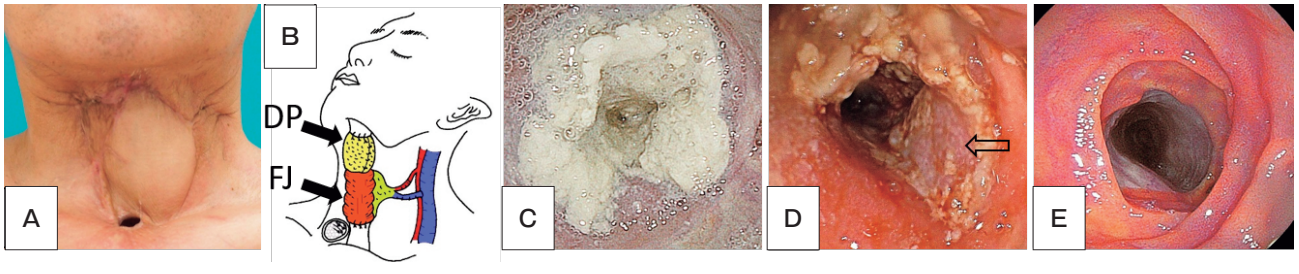

Fig. 5 A representative case of pharyngeal reconstruction with a tubed DP. (**A**) A 60-year-old man who had undergone TPLE and reconstruction with an FJ. Because of a postoperative major fistula, the patient had undergone several additional reconstructive procedures, including transfer of the tubed DP. The image shows the neck appearance 1 year after the last reconstructive surgery. (**B**) Schema showing the neo-pharynx reconstructed with both a tubed DP and an FJ. (**C**) Eleven years after surgery, the patient complained of swallowing difficulty and vomiting occasionally while eating because of mild stenosis between the tubed DP and FJ. The endoscopic image shows the entrance of the reconstructed neo-pharynx. The surface of the DP was totally covered with a large amount of food debris. (**D**) After the food debris was cleared, the color of the tubed DP (arrow) changed from yellow to silver-white, indicating desquamation (type 2). A small erosive lesion was also recognized. (**E**) The surface of the grafted jejunum was well maintained. TPLE, total pharyngo-laryngo esophagectomy; DP, deltopectoral flap; FJ, free jejunal flap.

between the type of change of the morphological flap and several factors were analyzed. The selected factors that were assessed included the reconstructive area, postoperative irradiation, mean age at last examination, mean term after reconstruction, sex, and type of transferred flap. The results showed that the reconstructed area correlated significantly with the type of change observed in the morphological flap ($p = 0.006$) (Table 2). The severe morphological type changes were strongly related to the reconstruction sites of the tongue, lower gingiva, and buccal mucosa. The other factors did not correlate significantly with morphological changes in the intraoral or pharyngeal space flaps.

Discussion

It is generally difficult to conduct long-term follow-up of patients who undergo head and neck reconstruction with flap transfers. There are several reasons for the difficulty: the challenge of continuing the care and surveillance of patients at the specific hospital where the reconstruction operation was performed, the older age of the patients at reconstruction, and the poor prognosis of patients with head and neck cancers. In fact, we were only able to perform follow-up investigations of 2 patients (8.7%) among 23 with inferior pharyngeal cancer. In contrast, the number of patients who survive for 10 years or more has increased with improved treatments for primary tumors. Therefore, information

regarding the durability of the transferred flaps and the possibility of a second primary cancer in the transferred flaps must be shared between doctors at the hospital where the reconstruction was performed and doctors in the town where the patient is currently living.

In the following, we discuss several issues regarding the durability of flaps transferred into intraoral or pharyngeal spaces with reference to selected key papers.

What types of changes occur in intraoral skin flaps over time? In our series, the transferred skin flap appeared to have lost thickness since the time of the reconstruction, and the number of hairs on the flap had markedly decreased (Fig. 2A). Shibahara *et al.* [2] reported histological changes in intraoral RFs. At 10 months after surgery, the stratum spinosum and basal cell layers had become thin. Decreased melanin pigmentation as well as shrinkage of skin appendages were also observed. These phenomena may be explained by atrophic changes in the skin tissue post-transplantation into the oral space due to constant exposure to moisture and the absence of ultraviolet light (from sunlight). Denervation of the flap may also cause a decrease in the secretory activity of the sweat glands [3]. Short-term follow-up has been reported after surgery in such cases and has shown that the basic structure of the epidermis and dermis was histologically observable irrespective of the cutaneous phenotypes being maintained in various kinds of transferred intraoral skin flaps, including skin grafts [1, 2, 4-13].

In contrast, the surface area of the normal skin gradually decreased and resembled a mucosal-like surface within a few years after surgery in our series (Fig. 1C). Regarding the mucosal-like surface of intraoral skin flaps, key papers have pointed out that the main factor that causes such changes is inflammation. Maria *et al.* [13] reported that the flaps with intense inflammatory changes tended to resemble oral mucosa, and histologically, epidermal hyperplasia with increasing thickness of the epidermis, parakeratosis, the disappearance of the stratum corneum, decreased thickness of the stratum granulosum, elongation of the epidermal ridges, and inflammatory infiltration of both the epidermis and dermis were present in most cases. Similar histological findings have been described by several authors [2, 5, 7-9].

The main contributory factor in cases with inflammation is fungal infection of the intraoral skin flap. Beahm *et al.* [7] first reported fungal infections involving *Candida* species in 4 of 8 intraoral skin flaps. Katou *et al.* [9] reported a high fungal infection rate in 15 of 20 RFs ≥ 2 years after surgery. Other reports have also described chronic hyperplastic candidiasis in transferred intraoral skin flaps [6, 10, 13-15].

Other exogenous factors that have been reported to initiate inflammatory changes include several tiny scratches on the epidermis induced by mechanical stimuli during eating [9, 16] and unstable dentures that came in contact with the intraoral skin flap [10, 17]; poor intraoral hygiene may accelerate these processes [10, 13]. Chemical stimuli introduced through smoking and alcohol may also promote inflammatory changes [9, 10, 13, 15]. Conversely, two other studies reported that there was no clear correlation between postoperative irradiation and inflammatory changes in the flap [7, 10]. In our present study, we also found no association between irradiation and morphological changes of the skin flap, and consequently our findings suggested no correlation between irradiation and inflammatory changes.

Various types of skin flaps transferred into an intraoral environment are thought to undergo changes across time [11, 12]. However, our > 10-year follow-up showed no relationship between changes in the skin flaps and their duration in the intraoral environment. Thus, in our cases the morphological changes in transferred flaps were determined by the type of environment. Generally, skin flaps transferred into oral spaces initially show atrophic changes. Subsequently, inflammatory changes caused by several exogenous factors occur, and the flap will then begin to show various features, including the development of a mucosal appearance (Fig. 6). However, transformation of intraoral skin flaps into mucosa does not generally occur, with various reasons for this having been proposed, including differentiation of the epidermis, intrinsic divergence [18], and external modulation [19].

Are the changes in intraoral skin flaps affected by the reconstructed area? Our results showed that the reconstructed areas within the mouth affected the type of morphological changes observed in the flaps. Reconstructions of the tongue, lower gingiva, and buccal mucosal were more likely to evince marked morphological changes. A reconstructed tongue will always have contact with foods, surrounding tissues, teeth, and dental prostheses, if worn. The lower gingiva also undergoes direct mechanical pressure and irritation

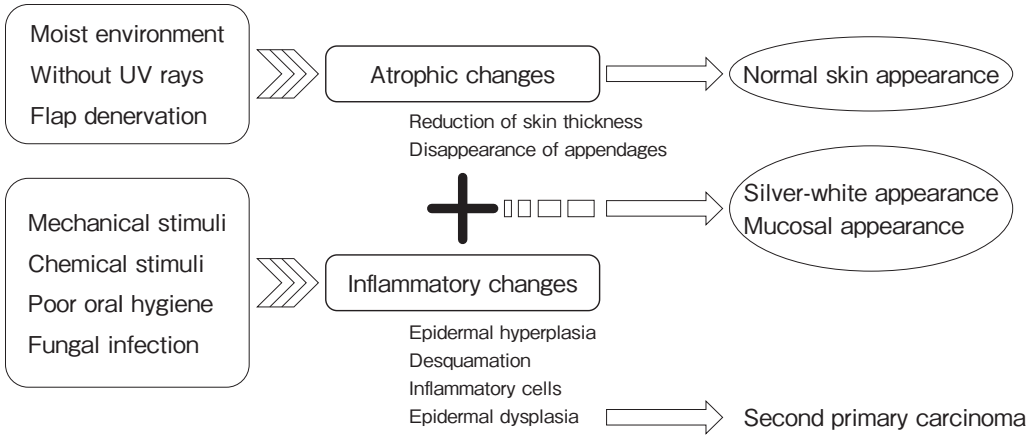

Fig. 6 Relationships between several factors and morphological changes in skin flaps. UV, ultraviolet.

caused by chewing and unstable dentures [10]. The buccal mucosa has a thin mucosal epithelium and lamina propria on the muscles that confers better flexibility and extensibility than can be attained by skin flaps. In contrast, the buccal mucosa reconstructed with a less flexible skin flap easily comes into contact with the teeth and food. This can lead to many scratches and potentially chronic inflammatory changes, ultimately resulting in trismus (Fig. 3). Therefore, in buccal mucosa reconstruction, it is better to implant a thinner flap with a larger area in order to avoid postoperative trismus. Additional revision surgery may also be required if trismus occurs, and careful long-term follow-up of these patients is warranted.

What are the optimal materials for pharyngeal reconstruction? In Japan, FJ is widely used for circumferential pharyngeal reconstruction because of its high vascularity and low postoperative complication rate [20]. However, fascio-cutaneous flaps using ALT [21] have recently become more widely used in place of FJs. There is no clear consensus regarding the optimal materials to use for pharyngeal reconstruction. Therefore, in this study we investigated and analyzed the more than 10-year courses of patients who underwent pharyngeal reconstruction with either jejunal or skin flaps, and investigated which type of flap was superior in terms of long-term durability. It was found that the surfaces of FJs were completely maintained more than a decade after the transplant. However, the surfaces of tubed skin flaps showed type 2 changes with erosive lesions, and the patients complained of difficulty with swallowing.

The pharyngeal space is always exposed to saliva, boluses of food, irritation, and occasional regurgitation of gastric juice. Therefore, the internal surface of the neo-pharynx should have a long-term defense mechanism against this stimulating environment similar to that of the esophagus, which has extensibility and a secretory function. Although the FJ surface is composed of a monolayer of squamous epithelium, our results showed that it has a defense mechanism and good durability for use in pharyngeal reconstruction. As for the neo-pharynx reconstructed with a tubed skin flap, circumferential suturing of the skin tends to lead to contracture-related mild stenosis of the neo-pharynx at distal anastomotic sites. This situation can lead to the involvement of many exogenous factors in the neo-pharynx that cause inflammatory changes in the skin flap. The inflammatory changes of the skin surface of the neo-pharynx can cause second neoplasms, to be discussed below. Recently, a meta-analysis by Koh *et al.* [22] showed that FJs were still a better choice than fascio-cutaneous flaps for circumferential pharyngeal reconstruction. Our experience supports their findings; however, considering that it involves minimally invasive surgery, reconstruction with skin flaps should still be considered. If circumferential skin flap reconstruction is selected, care is needed to ensure a good postoperative swallowing function and to monitor for the subsequent development of skin cancers caused by morphological changes in the skin flaps. This can be achieved by endoscopic monitoring of the patient for the remainder of his or her life.

Do morphological changes in skin flaps contribute to the development of second primary squamous cell carcinoma? To diagnose a second primary squa-

mous cell carcinoma (SCC) arising in the flap, the following conditions are required: 1) the tumor must be limited to the skin flap and far from the oral mucosa; 2) there should be no tumor remnant after the initial treatment; 3) some years should have elapsed since the end of the initial treatment; 4) skin SCC should be confirmed by histopathologic examination; and 5) there should be no skin malignancies elsewhere on the body [23-25].

In this study, 53 patients who were followed up for more than 10 years did not develop second primary carcinomas. Apart from the cases in this study, we experienced one patient with a second primary SCC arising in a transferred skin flap four years after reconstruction. In a 73-year-old woman who underwent upper gingiva and hard palate reconstruction with a vascularized fibula osteocutaneous flap, a lower tooth was postoperatively found to be coming into frequent contact with the transferred skin flap during chewing. Approximately four years later, a 1×2-cm leucoplakia was recognized inside the skin flap. A biopsy of the center of this lesion revealed an SCC in the base layer of the epidermis with hyperkeratosis (Fig. 7).

We also reviewed 27 cases, including 1 case that we treated, with second primary carcinomas arising in the skin flap (24 cases) and skin graft (3 cases) in the pharyngeal and esophageal areas (Table 3) [16, 24-43]. The mean duration from reconstruction to the second carcinoma was 18.2 (range: 4-37) years. Papillomatous or exophytic clinical findings were most commonly observed.

Our case was the ninth reported in Japan since 1989. According to a registry of Japanese clinical statistics of head and neck cancer, approximately 2,000 reconstructive surgeries in the oral cavity, oropharynx, and hypopharynx have been performed every year. Therefore, the rate of second SCCs arising from skin flaps is extremely low.

Several reports [13, 25, 36] suggested possible mechanisms for the development of a second SCC in a skin flap. Robinson *et al.* [44] investigated 10 specimens sampled from a white patch or erythematous lesion of an intraoral skin flap; 4 out of the 10 specimens showed severe dysplasia with significantly higher Ki-67 and increased expression of p53. The researchers reported that these changes have the potential for malignant transformation. Thus, the rate of dysplasia is high in intraoral skin flaps. The mechanism by which second SCCs develop is difficult to conceptualize and remains unknown; thus, further studies are essential. However, we think that the most probable mechanism by which second SCCs develop is a carcinogenic effect caused by the different environment and by several exogenous factors that lead to severe inflammatory changes. Therefore, surgeons should take this possibility into consideration and conduct meticulous and long-term follow-up of their patients.

Do skin flaps in intraoral and pharyngeal environments survive over the long-term? In the case of skin flaps used for intraoral reconstruction, the answer to the above question is "Yes." However, the characteristics of skin flaps can be changed by several factors, and this may cause a functional deficit, especially in the buccal area. Moreover, careful monitoring is needed to detect the possible development of a second primary carcinoma arising from the transferred skin flap.

Regarding skin flaps used for pharyngeal reconstruction, the answer to the above question is "No." For circumferential pharyngeal reconstruction, the optimal choice is an FJ because of its durability in a severe stim-

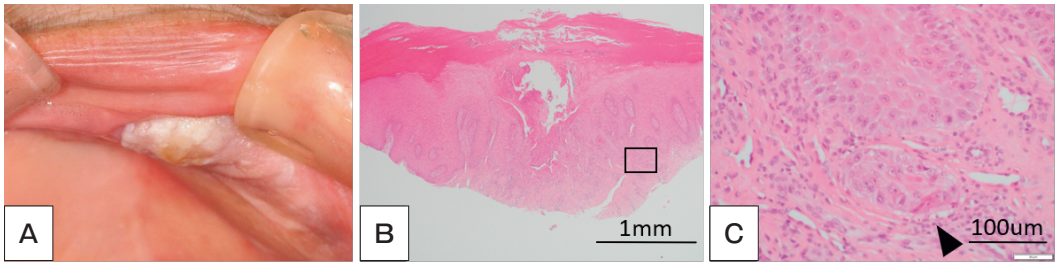

Fig. 7 A 73-year-old woman who had undergone upper gingiva reconstruction with a fibular osteocutaneous flap 4 years earlier. (A) At the margin of the flap, leucoplakia was recognized. (B) Biopsy of the leucoplakia. Massive hyperkeratosis and SCC (rectangular) at the basic layer are shown. HE staining. (C) Magnified image from the rectangular area of the center photo showing an SCC (arrowhead). SCC, squamous cell carcinoma.

Table 3 Review of cases with second primary carcinomas arising in transferred skin flaps

Case No.	Authors and reference No.	Year	Age/ Sex	Reconstructive site	Kind of flap	RT (Gy)	Duration (yr)	Histology	Clinical findings
1	Petrov, [26]	1954		Esophagus	Skin tube	−	30	cancer	Papillomatous
2	Jayes, [27]	1957	53/F	Esophagus	Skin tube	−	23	SCC	Papillomatous
3	Kanisawa, [28]	1959	46/M	Esophagus	Skin tube	−	30	SCC	Polypoid
4	Fogh-Andersen, [29]	1961	42/M	Esophagus	Skin tube	−	34	SCC	Papillomatous
5	Bromberg, [30]	1968	69/M	Esophagus	Skin tube	−	21	SCC	Papillomatous
6	Sapozhnikova, [31]	1985		Esophagus	SG	−		SCC	Papillomatous
7	Sapozhnikova, [31]	1985		Esophagus	SG	−		SCC	Papillomatous
8	Yoshino, [32]	1989	74/F	Neo-pharynx	Skin flap	−	8	SCC	
9	Yoshino, [32]	1989	78/F	Neo-pharynx	Skin flap	40	6	SCC	
10	Yoshino, [32]	1989	76/F	Neo-pharynx	DP	64	16	SCC	Exophytic
11	Deans, [16]	1990	61/M	Neo-pharynx	DP	−	24	SCC	Endophytic
12	Takeda, [33]	1990	59/M	Tongue	PMMC	−	7	SCC	Exophytic
13	Scott, [34]	1992	67/M	Floor of mouth	Skin flap	−	37	SCC	Ulcer
14	Sa'do, [35]	1994	70/F	Buccal mucosa	SG	−	19	SCC	
15	Sakamoto, [36]	1998	73/M	Neo-pharynx	RF	−	10	SCC	Exophytic
16	Ohtsuka, [37]	1998	72/F	Lower gingiva	PMMC	−	8	SCC	Exophytic
17	Iseli, [38]	2002	67/M	Neo-pharynx	DP	−	25	SCC	Exophytic
18	Monnier, [24]	2008	62/M	Oropharnx	RF	−	4	SCC	Leucoplakia
19	Monnier, [24]	2008	64/M	Oropharnx	DP	+	20	SCC	Endophytic
20	Ho, [23]	2011	65/M	Floor of mouth	PMMC	60	12	SCC	Exophytic
21	Yamasaki, [40]	2011	75/M	Hypopharynx	RF	−	5	SCC	Exophytic
22	Zemann, [41]	2011	62/F	Palate	Skin flap	−	30	SCC	Exophytic
23	Cymerman, [42]	2013	62/M	Floor of mouth	RF	−	23	SCC	Erythroplakia
24	Tokita, [25]	2013	80/M	Lower gingiva	Rf	−	6	SCC	
25	Taranto, [43]	2018		Esophagus	Skin flap		23	SCC	
26	Taranto, [43]	2018		Esophagus	Skin flap		30	SCC	Leucoplakia
27	Our case	2020	73/F	Upper gingiva	Peroneal	−	4	SCC	Leucoplakia

Blank area; no records in paper; DP, deltopectoral flap; PMMC, pectoralis major musculocutaneous flap; SG, skin graft; RF, radial forearm flap.

ulatory environment. As in the case of intraoral skin flaps, careful monitoring by endoscopy is needed to detect the possible development of a second primary carcinoma.

In conclusion, we reviewed 54 skin or mucosal flaps after a period of 10 years since their transplantation. Although histological investigation was necessary to confirm the findings reported in the literature, we obtained valuable and informative results, some of which were quoted from several key papers. Overall, the transferred flaps revealed various features, including a mucosal-like appearance. The skin flaps generally showed good durability for >10 years in an intraoral environment. However, in pharyngeal reconstruction, mucosal flaps using FJs were a better choice than fascio-cutaneous flaps with regard to long-term durability.

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References

1. Choi JW, Kim KN, Park EJ, Eom JS, Hong JP, Park HN, Park CS, Kim SY, Nam SY, Choi SH, Roh JL and Koh KS: Analysis of morphological and histologic changes in intraoral fasciocutaneous free flaps used for oropharyngeal reconstruction. Ann Plast Surg (2014) 72: 674–679.
2. Shibahara T, Noma H, Takeda E and Hashimoto S: Morphologic changes in forearm flaps of the oral cavity. J Oral Maxillofac Surg (2000) 58: 495–499.
3. Rubino C, Dessy LA, Farace F, Ena P and Mazzarello V: Microscopic and immunohistochemical analysis of the skin changes of free forearm flaps in intraoral reconstruction. Ann Plast Surg (2002) 49: 362–368.
4. Dellon AL, Tarpley TM and Chretien PB: Histologic evaluation of intraoral skin grafts and pedicle flaps in humans. J Oral Surg (1976) 34: 789–794.
5. Wei WI, Lam KH and Lau WF: Fate of skin element of pectoralis major flap in intraoral reconstruction. Arch Otolaryngol Head Neck Surg (1989) 115: 360–363.
6. Behera S, Mohsina S, Tripathy S, John JR, Sharma RK, Panda NK,

Bakshi J, Radotra BD and Sahu RK: Assessment of Clinical and Histological Changes in the Skin Paddle of Pectoralis Major Myocutaneous Flap in Intraoral Reconstruction: A Prospective Cohort Study. Ann Plast Surg (2020) 84: 173–177.
7. Beahm EK, Evans GR and Colome-Grimmer MI: Histologic changes of intraoral free skin flaps. Am J Surg (1997) 174: 492–494.
8. Badran D, Soutar DS, Robertson AG, Reid O, Milne EW, McDonald SW and Scothorne RJ: Behavior of radial forearm skin flaps transplanted into the oral cavity. Clin Anat (1998) 11: 379–389.
9. Katou F, Motegi K, Tagami H, Shirai N, Echigo S and Nagura H: Unique inflammatory features noted in intraorally transferred skin flaps: correlation with Candida albicans infection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod (1999) 87: 676–684.
10. Sinclair A, Johnston E, Badran DH, Neilson M, Soutar DS, Robertson AG and McDonald SW: Histological changes in radial forearm skin flaps in the oral cavity. Clin Anat (2004) 17: 227–232.
11. Shibahara T, Mohammed AF, Katakura A and Nomura T: Long-term results of free radial forearm flap used for oral reconstruction: functional and histological evaluation. J Oral Maxillofac Surg (2006) 64: 1255–1260.
12. Pinto FR, Kanda JL, Diniz MT, Santos CP and Zveibil DK: Delayed histological changes in cutaneous portion of pectoralis major flaps employed in upper aero-digestive tract reconstruction. Eur Arch Otorhinolaryngol (2009) 266: 553–558.
13. Maria L, Ioannis D, Konstantinos V, Fotis I and Konstantinos A: Histological Changes in Nasolabial Cutaneous Flaps Employed in Intraoral Reconstruction. J Maxillofac Oral Surg (2017) 16: 292–299.
14. Khan AL, Cloke DJ, Hodgkinson PD, McLean NR and Soames JV: Do intraoral radial forearm free flaps re-mucosalise and is candida infection relevant? Br J Plast Surg (2001) 54: 299–302.
15. Woolgar JA and Triantafyllou A: Histological changes in intra-oral skin flaps. Head Neck Oncol (2009) 1: 2.
16. Deans JA, Hill J, Welch AR and Soames JV: Late development of a squamous carcinoma in a reconstructed pharynx. J Laryngol Otol (1990) 104: 827–828.
17. Takeda N, Ishida K and Kishimoto M: Intraoral carcinoma arising from the myocutaneous flap covered an original malignant lesion, in 14th Japanese Congress of Head and Neck Cancer Abstract Collection, 1990: 244.
18. Doran TI, Vidrich A and Sun TT: Intrinsic and extrinsic regulation of the differentiation of skin, corneal and esophageal epithelial cells. Cell (1980) 22: 17–25.
19. Wessells NK: Differentiation of epidermis and epidermal derivatives. N Engl J Med (1967) 277: 21–33.
20. Kimata Y, Uchiyama K, Sakuraba M, Ebihara S, Nakatsuka T and Harii K: Simple reconstruction of large pharyngeal defects with free jejunal transfer. Laryngoscope (2000) 110: 1230–1233.
21. Yu P, Hanasono MM, Skoracki RJ, Baumann DP, Lewin JS, Weber RS and Robb GL: Pharyngoesophageal reconstruction with the anterolateral thigh flap after total laryngopharyngectomy. Cancer (2010) 116: 1718–1724.
22. Koh HK, Tan NC, Tan BK and Ooi ASH: Comparison of Outcomes of Fasciocutaneous Free Flaps and Jejunal Free Flaps in Pharyngolaryngoesophageal Reconstruction: A Systematic Review and Meta-Analysis. Ann Plast Surg (2019) 82: 646–652.
23. Ho AC, Fan PY, Shek TW, Ho D and Wei WI: Second primary squamous cell carcinoma arising in the skin of a pectoralis major myocutaneous flap 12 years after floor of mouth reconstruction. Eur Arch Otorhinolaryngol (2011) 268: 147–150.
24. Monnier Y, Pasche P, Monnier P and Andrejevic-Blant S: Second primary squamous cell carcinoma arising in cutaneous flap reconstructions of two head and neck cancer patients. Eur Arch Otorhinolaryngol (2008) 265: 831–835.
25. Tokita R, Nagashio S, Shinohara A and Kurita H: Second primary squamous cell carcinoma arising in a skin flap: a case report and literature review on etiologic factors and treatment strategy. J Oral Maxillofac Surg (2013) 71: 1619–1625.
26. Petrov BA and Khundadze GR: [Retrosternal artificial esophagus]. Khirurgiia (Mosk) (1954) 1: 108–116.
27. Jayes PH: Carcinoma in a reconstructed œsophagus. British Journal of Plastic Surgery (1957) 10: 212–217.
28. Kanisawa M, Homma Y, Suzuki k and Kayama T: An autopsy case of squamous cell carcinoma derived from reconstructed esophagus. Acta Pathol Jpn (1959) 9 (Suppl): 843–849.
29. Fogh-Andersen P: Reconstruction after cancer in an antethoracic skin tube oesophagus. Acta Chir Scand Suppl (1961) Suppl 283: 298–302.
30. Bromberg BE, Song IC, Mishrick A and Collins R: Carcinoma in a reconstructed esophagus. Ann Surg (1968) 168: 269–273.
31. Sapozhnikova MA, Kanshin NN, Abakumov MM and Pogodina AN: [Pathology of the artificial esophagus made of skin]. Arkh Patol (1985) 47: 29–35.
32. Yoshino K, Sato T, Umaya K, Fuji T, Hatta C, Kakibuchi M and Sawada T: A case of squamous cell carcinoma originated in the transferred skin flap after resection of hypopharynx carcinoma. Otolaryngol Head Neck Surg (1989) 61: 1127–1130 (in Japanese).
33. Takeda N, Ishida K and Kishimoto M: Intraoral carcinoma arising from the myocutaneous flap covered an original malignant lesion. (Abstract). in: 14th Japanese Congress of Head and Neck Cancer Abstract Collection, 1990: 244.
34. Scott MJ and Klaassen MF: Squamous cell carcinoma in a tube pedicle forty years after jaw reconstruction. Br J Plast Surg (1992) 45: 70–71.
35. Sa'do B, Nakamura N, Higuchi Y, Ozeki S, Harada H and Tashiro H: Squamous cell carcinoma of the oral cavity derived from a skin graft: a case report. Head Neck (1994) 16: 79–82.
36. Sakamoto M, Nibu K, Sugasawa M, Nakatsuka T, Harii K and Ichimura K: A second primary squamous cell carcinoma arising in a radial forearm flap used for reconstruction of the hypopharynx. ORL J Otorhinolaryngol Relat Spec (1998) 60: 170–173.
37. Ohtsuka A, Minemura T, Imai K, Kobayashi K, Kurita H and Kurashina K: A case of squamous cell carcinoma arising in a PM-MC reconstruction flap 8 years after surgery. Jpn J Oral Maxillofac Surg (1987) 44: 987–989 (in Japanese).
38. Iseli TA, Hall FT, Buchanan MR and Kleid SM: Squamous cell carcinoma arising in the skin of a deltopectoral flap 27 years after pharyngeal reconstruction. Head Neck (2002) 24: 87–90.
39. Akin H, Coskun ME, Akin EG and Ozdemir AK: Multidisciplinary approach for esthetic, functional, and quality-of-life outcome in soft palate cleft patient. Cleft Palate Craniofac J (2012) 49: 622–625.
40. Yamasaki A, Monden N, Takishita T, Yamashita Y, Ishikawa T, Teramoto N and Kitano H: Squamous cell carcinoma derived from a skin flap used for reconstruction of the hypopharynx. Yonago Acta Med (2011) 54: 33–36.
41. Zemann W, Jacobsen C, Malek M, Metzler P and Obwegeser JA: Squamous cell carcinoma arising in a skin flap: case report and review on malignant transformations in skin grafts and microvascular cutaneous flaps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod (2011) 112: e54–58.
42. Cymerman JA, Kulkarni R, Gouldesbrough D and McCaul JA: First report of squamous cell carcinoma arising within an intraoral radial forearm free flap. Int J Surg Case Rep (2013) 4: 731–734.
43. Di Taranto G, Elia R, Pafitanis G, Amorosi V, Liao LY, Chen SH and Chen HC: Late occurrence of squamous cell carcinoma arising from skin-lining flap. Microsurgery (2019) 39: 96–97.
44. Max Robinson C, Prime SS, Paterson IC, Guest PG and Eveson JW: Expression of Ki-67 and p53 in cutaneous free flaps used to reconstruct soft tissue defects following resection of oral squamous cell carcinoma. Oral Oncol (2007) 43: 263–271.