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A New Conception of Oral Potentially Malignant Disorders (PMDs) from Cytological and Clinical Viewpoints and Related Disorders of Upper Digestive Tract

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Most of the oral soft tissue diseases, however, derived from the oral squamous cells. More than 80 % of oral malignancies are squamous cell carcinoma. Oral squamous cell carcinoma (OSCC) sometimes shows the features of oral epithelial dysplasia (OED), carcinoma in situ (CIS) or oral intraepithelial neoplasia (OIN). Though cytology has been applied to the diagnosis of oral lesions, the number of false-positive and false-negative diagnosis affected cases may indicate the difficulty in the cytological diagnosis of borderline lesions. Recently, such a borderline lesions has been categorized to potentially malignant disorders (PMDs), and most of the squamous cell carcinoma are thought to develop from PMDs. This review paper describes this new conception of PMDs from the viewpoints of cytology, distinguishability of PMDs and our surgical approach of oral tumors. Furthermore, relationship between oral and upper digestive tract diseases are discussed.

Key words: oral squamous cell carcinoma, potentially malignant disorders, cytology, upper digestive tract diseases, treatment

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Overview of oral structure and function

The oral cavity is unique in structure. It contains the teeth, and the salivary glands discharge their secretions into it. It has the taste buds and can be used to perceive and sense in other ways. Its structure varies an apparent adaptation to function in different regions of the oral cavity. Areas involved in the mastication of food, such as the gingiva and the hard palate, have a much different structure than does the floor of the mouth or the mucosa of the cheek [1].

Basing classification on these functional criteria, the oral mucosa may be divided into three major types: 1. Masticatory mucosa (gingiva and hard palate), 2. Lining mucosa (lip, cheek, vestibular fornix, alveolar mucosa, floor of the mouth and soft palate), 3. Specialied mucosa (dorsum of the tongue and taste buds).

The structure of the oral mucous membrane is composed of two layers, epithelium and connective tissue, which form an interface that is folded into corrugations. The epithelium of the oral mucous membrane is of the stratified squamous variety, which may be keratinized, parakeratinized or nonkeratinized, depending on location. Keratinized oral epithelium has four cell layers: basal, spinous, granular and cornified. These layers take their names from their morphologic appearance [2]. This review article was prepared following the Declaration of Helsinki (1964).

Oral diseases

Maxillofacial surgeons deal with various diseases such as congenital anomaly, soft tissue tumors, viral infections, odontogenic cysts and trauma and so on. Most of the oral soft tissue diseases, however, derived from the oral squamous cells. Cancer of the

oral cavity including head and neck comprises a wide variety of histologic types of tumors, but more 80 % are squamous cell carcinoma [3]. Oral squamous cell carcinoma (OSCC) comprises 92-95% of all oral cancers [2]. Oral cancer accounts for approximately 3% of all malignancies, and found in 270,000 patients annually worldwide [4,5]. However, oral cancer is the second most common cause of death after heart diseases in developed countries, and the third leading cause of mortality following heart and diarrheal diseases in developing countries [6]. This paper then focuses on the oral suquamous cell carcinoma (OSCC) and its related disorders including upper digestive tract.

Histological and clinical features of OSCC

According to TNM Atlas [7], the sites of oral cancer is defined as buccal mucosa, upper alveolous and gingiva, lower alveolous and gingiva, hard palate, tongue and floor of mouth (Fig. 1). In Japan, the tongue margin is the most common of OSCC (Fig. 2). OSCC sometimes show the features of oral epithelial dysplasia (OED), numerous criteria exist for the diagnosis of epithelial dysplasia, and there is not always a clear-cut distinction between what presents a mild dysplasia consisting only of focal dysplasia, which may represent carcinoma in situ (CIS). OED is usually confirmed to a single tissue compartment and may progress to cancer, but does not always do so. CIS or oral intraepithelial neoplasia (OIN) are lesions that have the morphologic characteristics of cancer, including atypical cells and dysplastic tissue organization, but that, by definition, are confirmed to one tissue component and do not penetrate the basement membrane [8] (Fig. 2).

In invasive cancer, the proliferating lesion is found growing in two or more tissue compartments; that is, it shows invasion through the basement membrane (Fig. 3). These characteristics lesions have been well defined in the squamous epithelium of the uterine cervix, and similar lesions have been found in the upper aerodigestive tract (UADT) as well [2]. However, some oral malignancies show well-differentiated pattern in the most surface of the lesion, while others show basaloid pattern same as cervical squamous cell carcinoma (Figs. 4 and

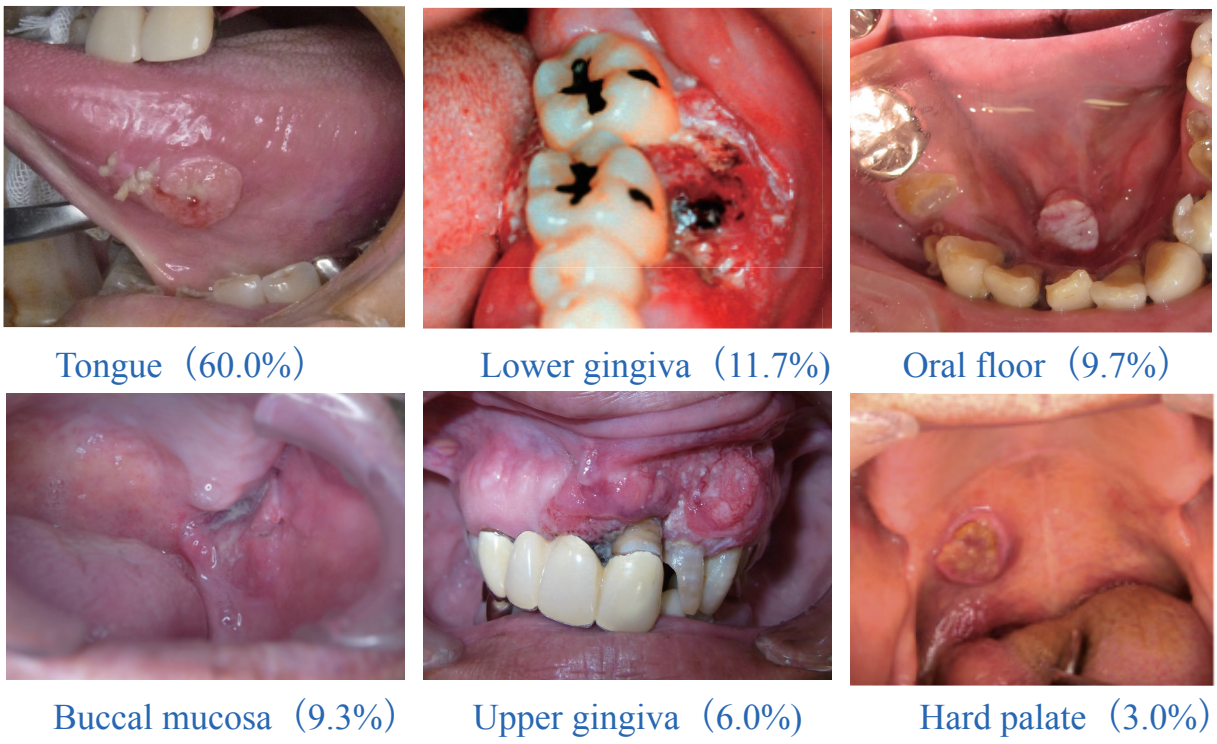


Fig. 1. Oral squamous cell carcinoma
In Japan, the tongue margin is the most common site of OSCC.

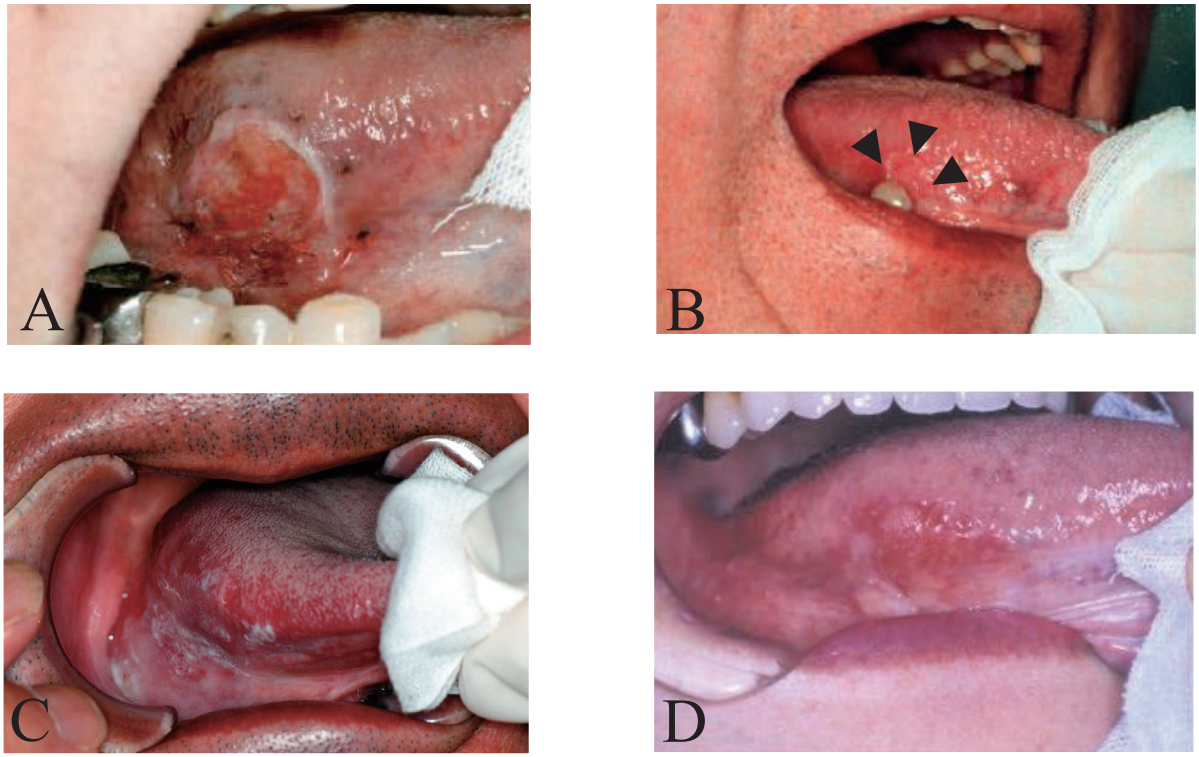


Fig. 2. Tongue squamous cell carcinoma
All are squamous cell carcinoma showing mass lesion (A), very small ulcer-like lesion (B, arrow heads), white lesion (C) and red lesion (D).

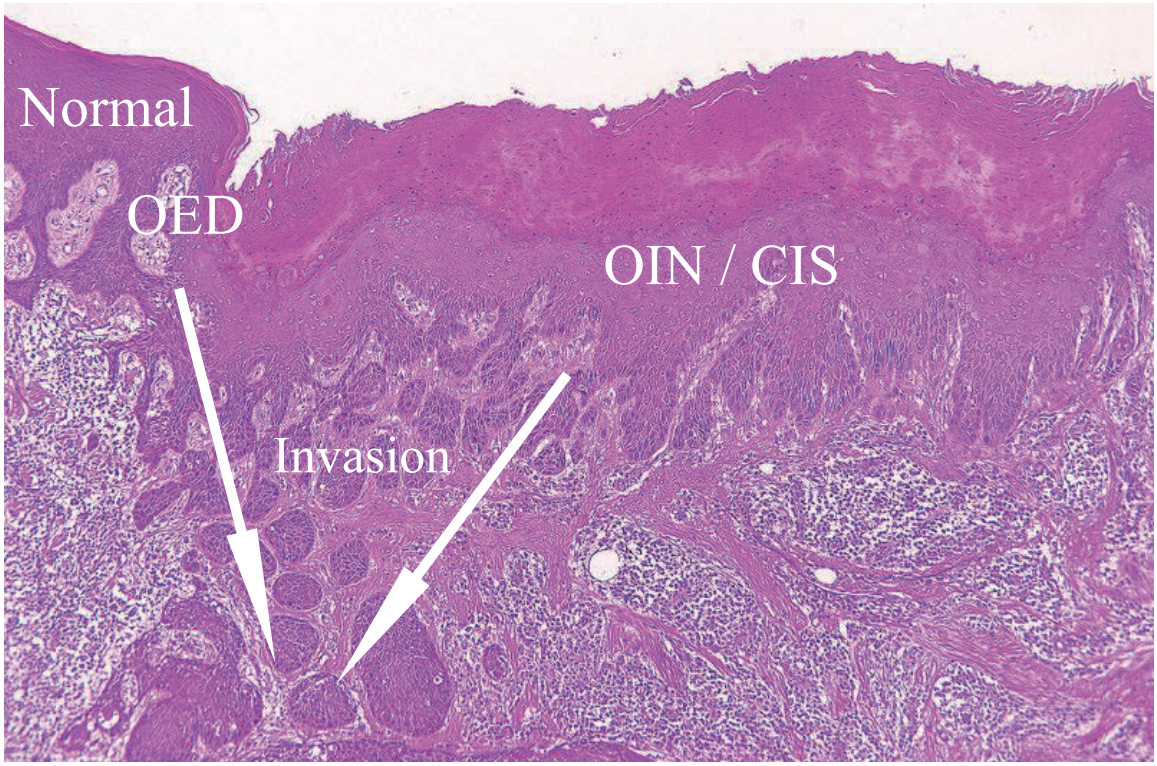


Fig. 3. Early invasive OSCC
Though invasion of submucosal tissue is seen (Arrows), the border of OED, OIN/CIS is unclear. Normal: normal mucosa, OED: oral epithelial dysplasia, OIN: oral intraepithelial neoplasia, CIS: carcinoma in situ.

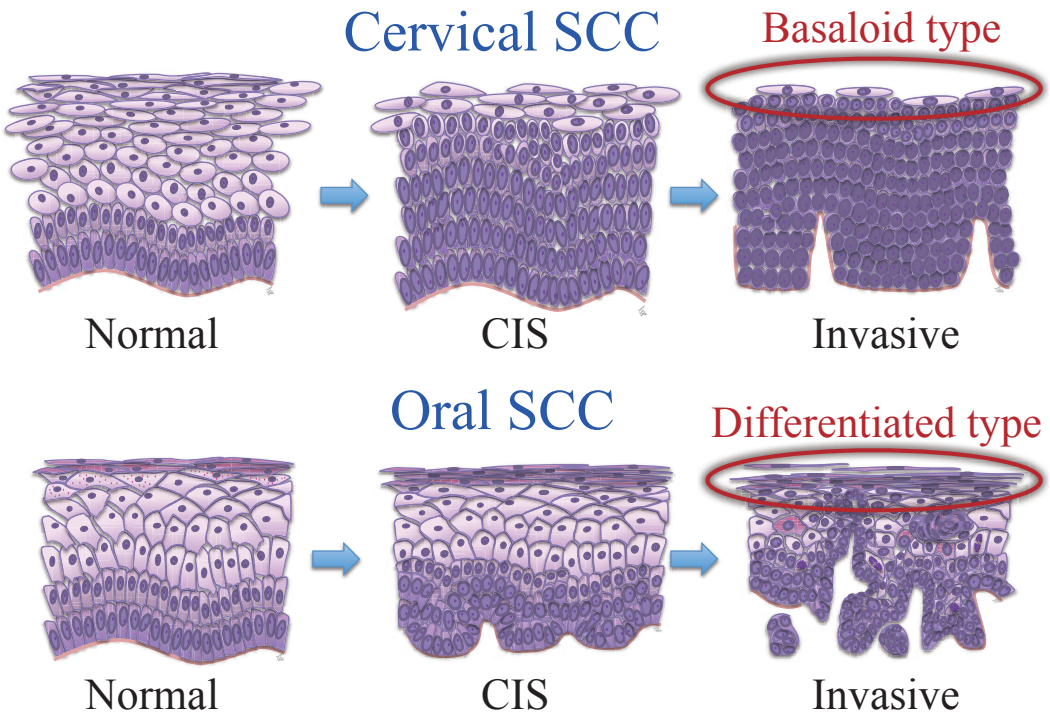


Fig. 4. Schematic illustration of cervical and oral squamous cell carcinoma
The upper shows basaloid type, the lower differentiated type.

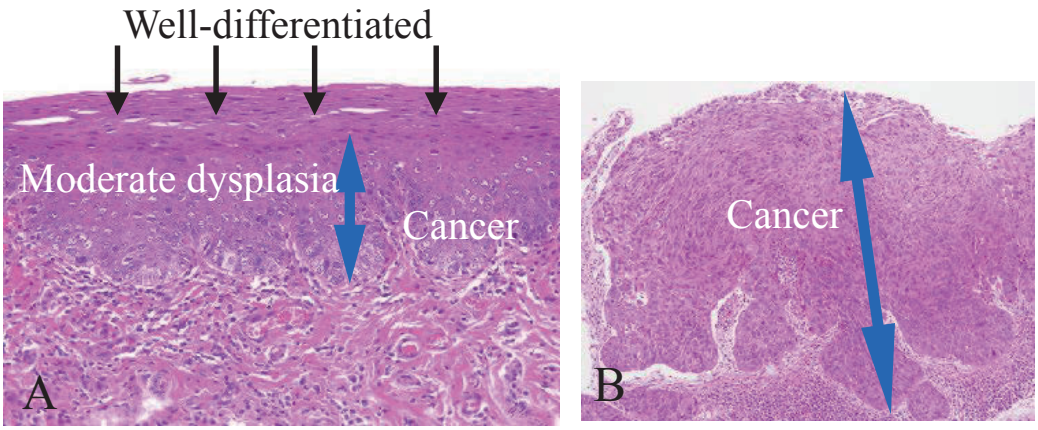


Fig. 5. Histopathological findings of two types of OSCC
A: Diffewrentiated type showing well-differentiated surface of the epithelium B: Basaloid type showing micro invasion

5). As for the clinical change of differentiated type looks like normal or slight change of the color such as red and/or white (Fig. 6). As with most white oral lesions, the color is derived from the thickened keratin layer or thickened spinous layer, which masks the vascularity (redness) of the underlying connective tissue [2]. Clinicians pay special attention to such cases, and palpation of the lesions is feasible to clinical diagnoses of malignancies.

The possible presence of dysplasia must be diagnosed histopathologically; thus, a biopsy must be taken of all cases of oral leukoplakia and erythroplakia, because it is not possible to determine clinically as well as histopathologically which cases are

precancerous or dysplastic (Table 1).

Table 1. Classification of oral epithelial dysplasia

2005 WHO Classification	*JSHNC	**JSOO
Mild dysplasia		OED
Moderate dysplasia	Low-grade dysplasia (Inc. reactive change)	Unclear!
Severe dysplasia	High-grade dysplasia	OIN
Carcinoma in situ (CIS)	CIS	CIS

*Japanese Society for Head & Neck Cancer
**Japanese Society for Oral Oncology

There is controversy regarding the detailed classification of OED in Japan.

Feasibility of oral cytology

Exfoliative cytology is a reliable tool for assessing malignant change in various organs [9]. Cytology has been also applied to the diagnosis of oral lesions [10, 11]. Accurate cytological diagnosis of oral lesions, especially in distinguishing benign lesions from malignant ones, is essential for treatment as well as for clinical and epidemiological research including the study of prognosis [12].

With respect to oral cytological diagnosis, the classification of cervicovaginal smears into five classes was initially proposed by Papanicolaou, who formulated a series of guidelines for smear interpretation [13]. In December 1988, a committee of experts who convened under the auspices of the National Cancer Institute (USA) in Bethesda, Maryland, proposed a diagnostic system for the interpretation of cervicovaginal smears. The resulting Bethesda System (modified in 2001) was officially accepted by the federal authorities in the United States [14]. Recently, this system has been used in various fields such as thyroid, renal, and female genital cytology [15].

The author's group investigated the clinical applicability of oral cytology following Bethesda System [14, 15] by exploring the diagnostic accuracy of oral cytology using histological diagnoses of 327 cases were classified as Negative, Borderline lesion –, Borderline lesion +, oral intraepithelial neoplasia/

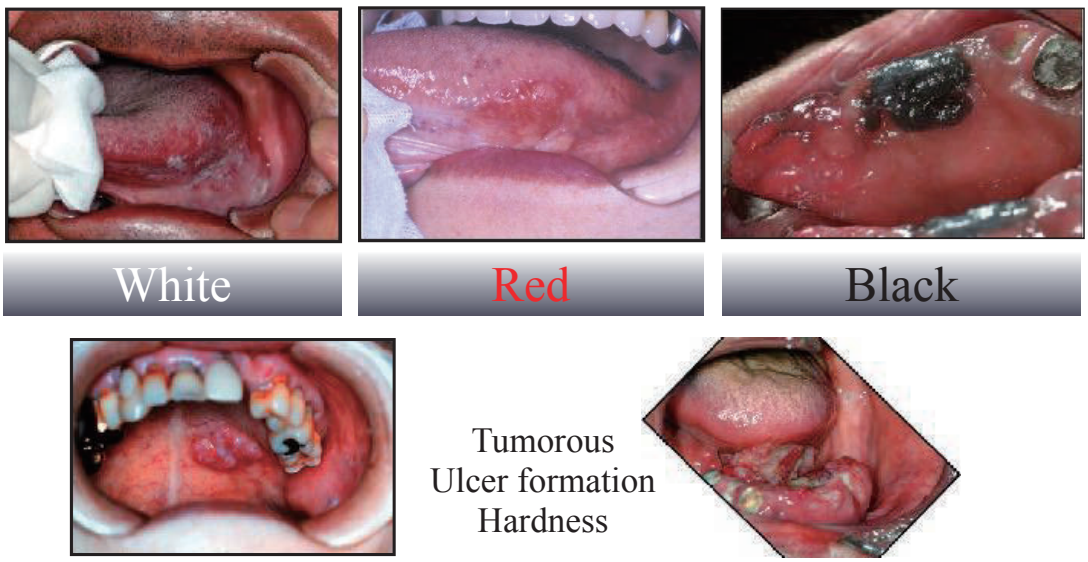


Fig. 6. Clinical features of oral tumor
Upper shows the color of lesions. White and Red lesions are OSCC. Black lesion shows malignant melanoma. Lower two lesions show tumorous and ulcer lesions.

carcinoma in situ (OIN/CIS), or Positive (Fig. 7) [16].

Sensitivity, specificity, and positive predictive and negative predictive values were 93.5%, 50.6%, 62.4%, and 89.8%, respectively, when the cytological diagnosis of Negative was assumed to be NILM; they were 77.8%, 83.9%, 81.0% and 81.1%, respectively, if the cytological diagnosis of Negative was assumed to be NILM and LSIL. The number of false-positive and false-negative diagnosis affected cases with LSIL and HSIL may indicate the difficulty in the cytological diagnosis of borderline lesions. While the negative predictive value was relatively high (89.8%) when the cytopathological diagnosis of Negative was assumed to be NILM only (Fig. 8).

Table 2 shows histopathology of cytological borderline lesions, showing the necessity of biopsy. Recently, such a borderline lesions including leukoplakia, Lichen Planus and erythroplakia has been categorized to potentially malignant disorders (PMDs), and most of the squamous cell carcinoma are thought to develop from PMDs [9]. The borderline lesions such as PMDs diagnosed as LSIL and HSIL are then indicated for biopsy and/or surgical resection in our hospital [12, 17].

Table 2. Histopathological examination of cytological diagnosed as borderline lesions

Subclassification	LSIL	Borderline	HSIL
Number of cases	168	244	45
Histopathology	61	118	28
(%)	36.3%	48.4%	62.2%
Number of OIN	13	30	9
Number of Malignancy	17	54	17
(%)	27.9%	45.8%	60.7%

Even diagnosed as LSIL, 27.9% showed malignancy. Biopsy is recommended in the cases cytological diagnosed with SIL. LSIL: low grade squamous intraepithelial lesion, HSIL: high grade squamous intraepithelial lesion.

All procedures performed in this study were approved by the ethical committee at Shimane University (Approval no. 1270; March 29, 2013).

Conception of PMDs

Table 3 shows conception of PMDs. Most of the early oral cancers and PMDs show the color of 'white' and/or 'red' and typical white lesion is leukoplakia, red is erythroplakia or Lichen Planus. Leukoplakia is a white, plaque-like lesion that can spread over wide areas, particularly in the oral cavity. This lesion, which may expand and connect over time, consists of mucosal cells that exhibit aberrant keratinization. Leukoplakia have a 1.5% to 6% annual rate of neoplastic progression and are frequently associated smoking, oral tabacco or betel nut use and diet lacking in vitamins of the carotenoid family [18].

Table 3. Conception of potentially malignant disorders (PMDs)

Normal *Dysplasia Malignancy

World Health Organization Classification of Tumors

*Epithelial precursor lesions

Potentially malignant disorders

Pathology & genetics. Head and neck tumours.

International Agency for Research on Cancer (IARC).
Head and neck tumors, IARC Press, Lyon, 2005

Dysplasia locates between normal and malignancy, however, dysplasia contains due to malignancy and/or inflammation. Leukoplakia and erythroplakia are also included in the category of PMDs.

Erythroplakia is a red lesion that can exhibit severe dysplasia. This type of lesion is less common than leukoplakias, but has a higher probability of progressing to invasive carcinoma. Leukoplakia and erythroplakia as histologic terms are to be discouraged, as they are clinical terms [18].

Unfortunately, oral PMDs are usually misdiagnosed due to lack of adequate knowledge among the general population and even medical professions. Therefore, improvement of physicians' or dentists' level of knowledge about oral PMDs may play a key role in saving patients' life [19].

How to distinguish PMDs in histopathological specimens

Numerous criteria exist for the diagnosis of OED, and there is not always a clear-cut distinction of what represents mild dysplasia—consisting of only

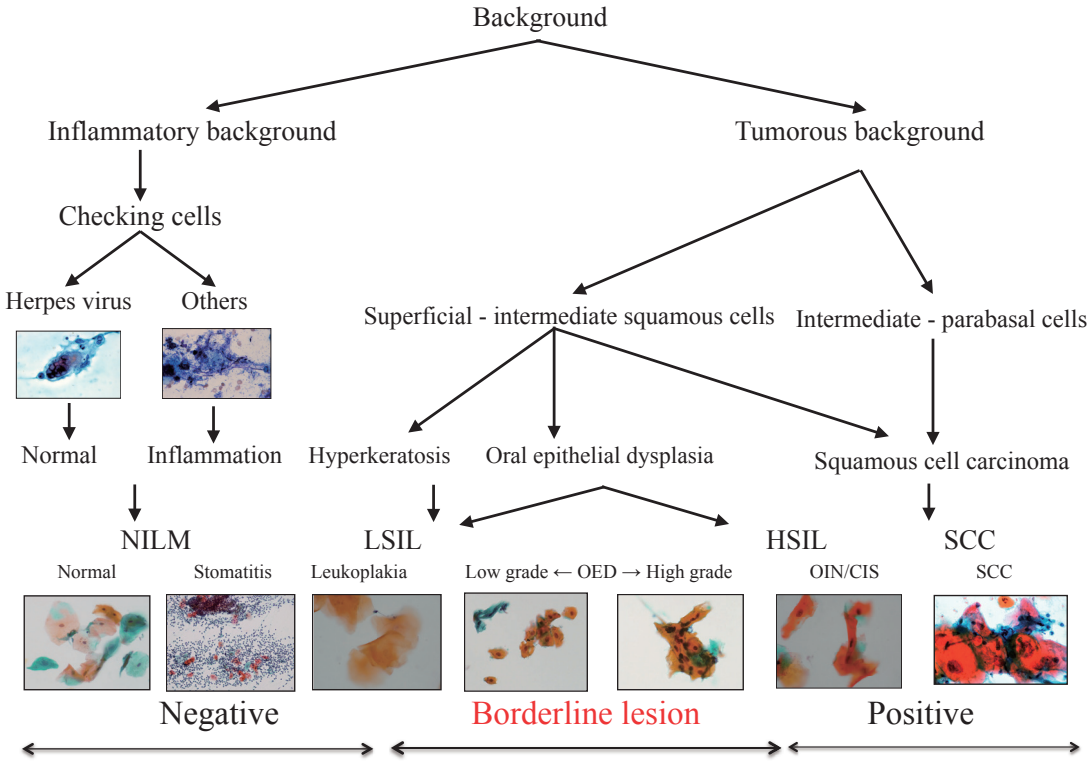


Fig. 7. Algorithm of oral cytology
NILM: negative for intraepithelial lesion or malignancy, LSIL: low grade squamous intraepithelial lesion, HSIL: high grade squamous intraepithelial lesion, SCC: squamous cell carcinoma. Borderline lesions are considerable as potentially malignant disorders (PMDs).

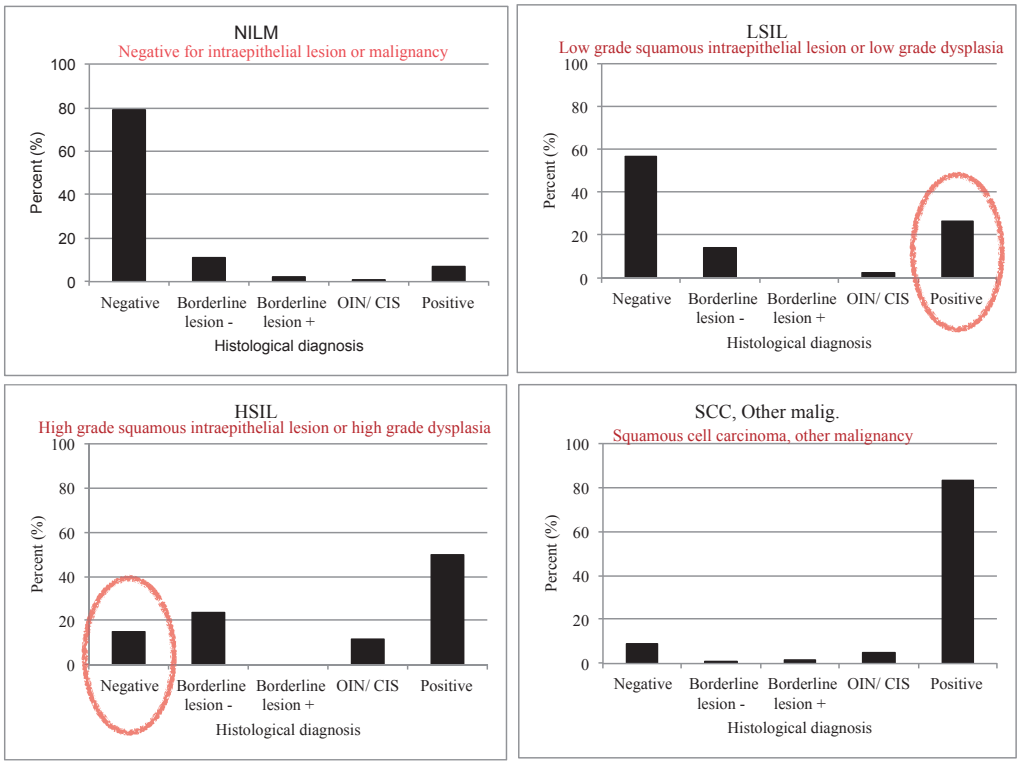


Fig. 8. Distribution of the 327 cases with a histological diagnosis in each cytological diagnostic category.
The percentages are shown above the columns. Cited and modified from Ref. #16

focal atypia, moderate dysplasia, and severe dysplasia—which may present as OIN and CIS [20]. Clinically, Lugol's solution is feasible to detect PMDs (Fig. 9). On the other hand, cytokeratin 13 and 17 are reportedly suitable for such a distinction between non-neoplastic tissue and a dysplastic or neoplastic (malignant) oral lesion; however, a clear distinction between OED/OIN and CIS is currently unavailable (Fig. 10)[21]. Here, the preliminary investigation by the author's group is shown to distinguish between these states.

Expression of NAC1 expression

Recently, Sekine et al. [17] reported that nucleus accumbens-associated protein 1 (NAC1) has the potential to be used as a biomarker for distinguishing OED from CIS/OSCC. This preliminary investigation is the first to study NAC1 expression in oral lesions [22] (Fig. 11). The study included 114 patients (64 men, 50 women). There were 67, 10, and 37 patients with OED, CIS, and OSCC, respectively. NAC1 labeling indices (LIs) was evaluated (Fig. 12). The NAC1 LIs cut-off values which discriminated between OED and CIS/OSCC were 50% (Fig. 13). For NAC1 LIs with > 50% positivity the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 0.766, 0.910, 0.857, and 0.847, respectively. The study protocol approved by the Ethics Committee of Shimane University Hospital, Japan (Approval No.995; March 26, 2012).

Expression of HPV 16, 18 and p16

The natural history of the human papilloma virus (HPV) has been characterized extensively in the uterine cervix [23, 24], whereas less data are available on the difference phases of HPV infection and oncogenesis in the oral, head and neck regions [25]. The identification of HPV in oropharyngeal carcinoma has prognostic significance, with longer survival and a higher rate of response to therapy in cases positive for HPV [25, 26]. In the field of OSCC, HPV infection was found to be present in 26.0% of cases, and high risk (HR)-HPV-positive cases have similar clinical characteristics as HR-HPV-negative cases, but had a significantly worse prognosis [27, 28].

The author's group thus evaluated the association between the expression of HPV16, HPV18, and p16 (Fig. 14) and various lesions derived from the oral epithelium (Fig. 15), testing the hypothesis that the expression of HPV16, HPV18, and p16 could be feasible biomarkers to distinguish PMDs in the oral cavity.

Age, the LIs of HPV18, and the status and LIs of p16 had increasing trends in the order of NOE, OED and OIN; therefore, age and the variables related to p16 and HPV18 were used further as covariates in regression tree analysis for predicting OED/OIN against NOE. As a result, 4 stratified groups (100.0%, 90.0%, 60.0%, and 30.0% of OED/OIN) by age, p16 status, and HPV18 status were provided. The p16-positive group included all OED/OIN cases; the p16-negative, age ≤ 60 years, and HPV18-positive group included 90.0% of OED/OIN cases; the p16-negative, age > 60 years, and HPV18-negative group included 60.0% of OED/OIN cases; and the p16-negative and age ≤ 60 years group included 30.0% of OED/OIN cases (Fig. 16).

In conclusion, the expression of HPV18 and p16 and participants' age are factors that distinguish NOE from OED/OIN [20]. All participants provided informed consent to participate, following approval of the study protocol by the Ethics Committee of Shimane University Hospital, Japan. (Approval No. 996; March 26, 2012)

Treatment of OSCC

Oral tumor surgery can result in dysfunctional and cosmetic problems. Reconstructive surgery is then recommended to improve patients' quality of life. The purpose of reconstruction of oral cavity defects is to facilitate healing, prevent wound breakdown and fistula formation, cover exposed bone with full thickness tissue, and promote normal function and facial esthetics as much as possible. However, patients who underwent reconstruction of mandibular continuity were left without dentition or were rehabilitated with removable dentures.

Our policy to establish treatment goal in oral tumor patients is to achieve functional oral rehabilitation with implant-supported osseointegrated prostheses following anatomical reconstructive surgery (Fig. 17). The author describes our surgical strategy for

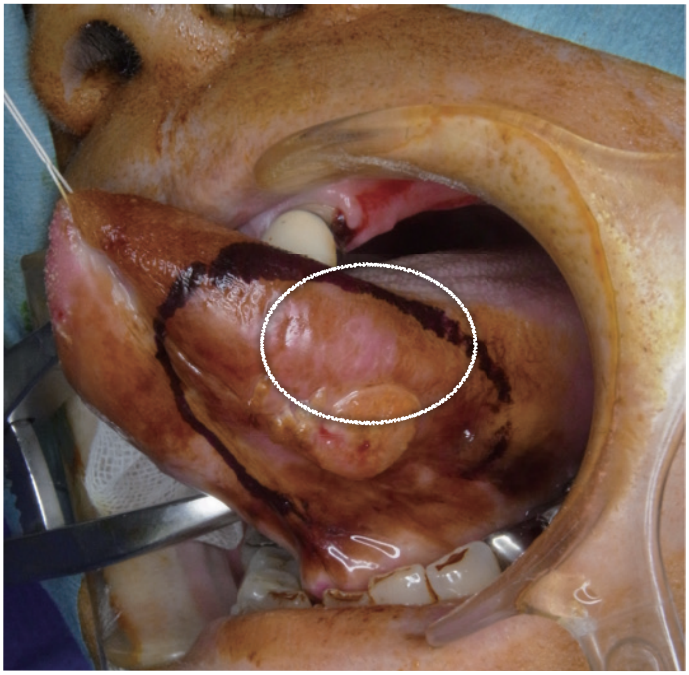


Fig. 9. Lugol's solution
White circle shows unstained (white) are, which is strongly considerable as NOT normal epitheilium. Histopathologically, these areas showed the feature of dysplastic cells, but not clearly of malignancy.

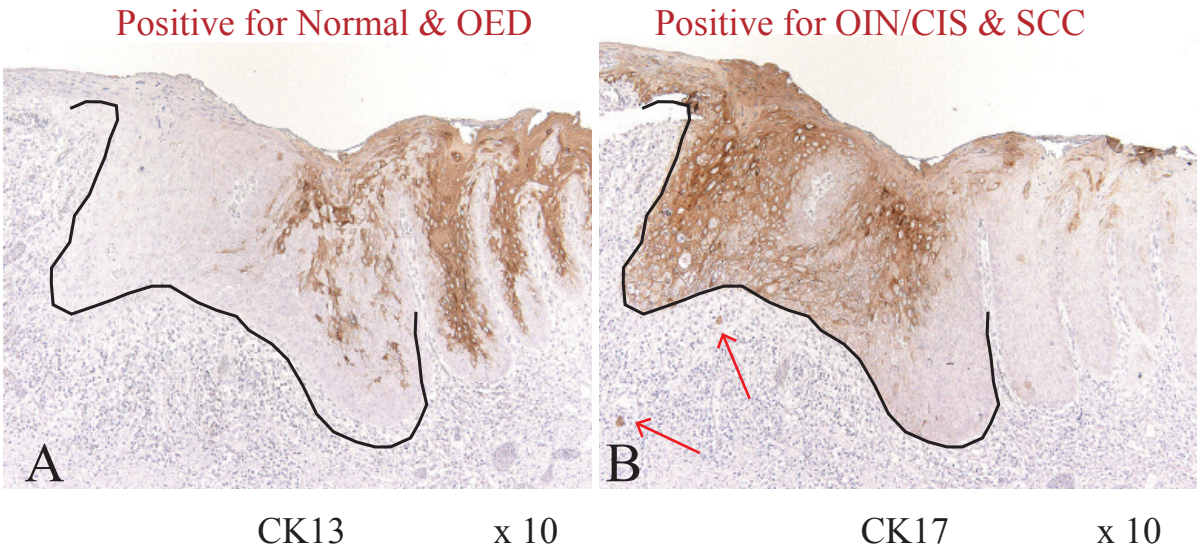
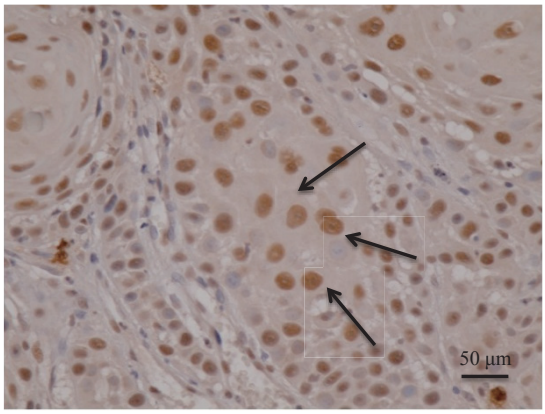
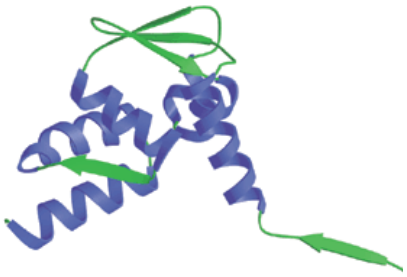


Fig.10. Cytokeratine expression
A: CK13 is positive for normal and OED. B: CK17 is positive for OIN/CIS and OSCC, but the border of both staining results are unclear. Red arrows show cancer cells. Black lines show the basement membrane. Squamous cell carcinoma, 23-yrs-old, Japanese female.



NAC1 Immunostaining of OSCC
1:1,000, 4°C, overnight



The BTB domain
from human PLZF

Fig. 11. NAC 1 immunostaining results
A: NAC 1 positive cells（arrows）are expressed in the tumor cells of OSCC（×40, Cited and modified from Ref. #22）.
B: Nucleus accumbens-associated protein 1（NAC1）is a member of the Pox virus and Zinc finger/Bric-a-brac Tramtrack Broad complex family of proteins that mediates several cellular functions including proliferation, apoptosis, transcription control, and cell morphology maintenance. Furthermore, NAC1 is reported to be significantly overexpressed in several types of other human carcinoma.

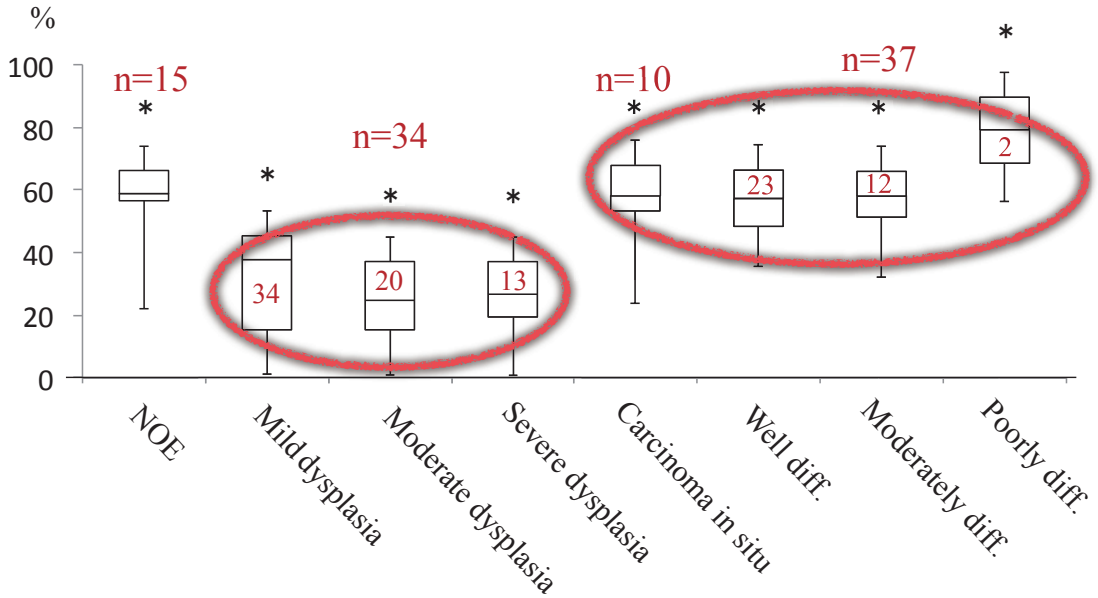


Fig.12. Comparison of NAC1 LIs in normal oral mucosa, epithelial dysplasia, carcinoma in situ, and oral squamous cell carcinoma by histological severity and tumor differentiation.（Cited and modified from Ref. #22）
NAC1 LIs of mild dysplasia were significantly higher than those in moderate and severe dysplasia. The NAC1 LIs of carcinoma in situ and well, moderately, and poorly differentiated oral squamous cell carcinoma（red circle）were higher than those of dysplasia cases, with poorly differentiated oral squamous cell carcinoma（red circle）showing the highest LIs（$p<0.001$, ANOVA）. NOE: normal oral epithelium, Well diff.: well differentiated, Moderate diff.: moderately differentiated, Poorly diff.: poorly differentiated.

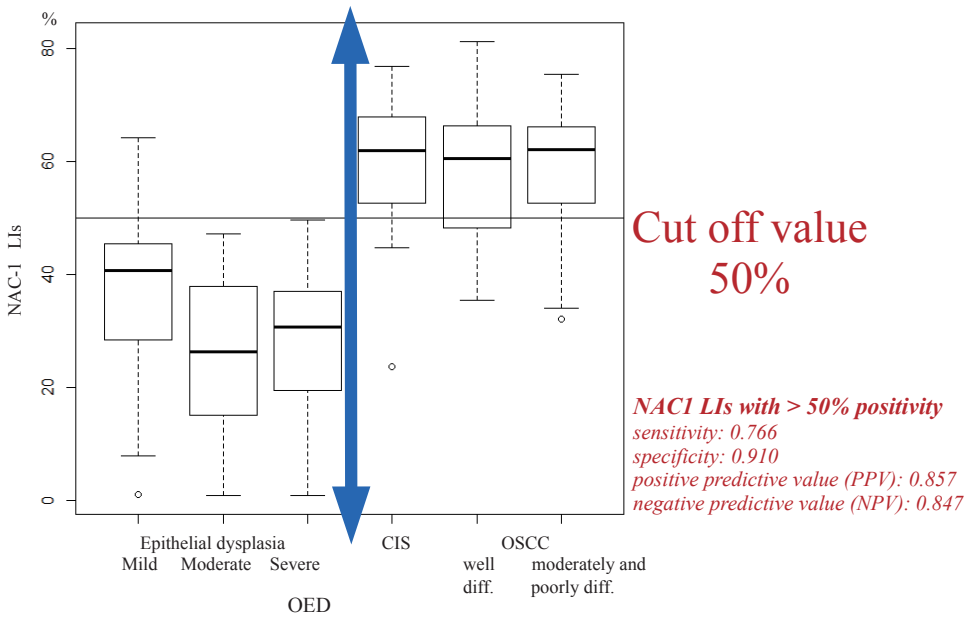


Fig. 13. Cut off value of NAC 1 for distinguishing OED from CIS/OSCC
NAC1 LIs cut-off values which discriminated between OED and CIS/OSCC were 50%. For NAC1 LIs with > 50% positivity, the sensitivity, specificity, PPV, and NPV for CIS/OSCC were 0.766, 0.910, 0.857, and 0.847, respectively, by multivariate analysis. Cited and modified from Ref. #17

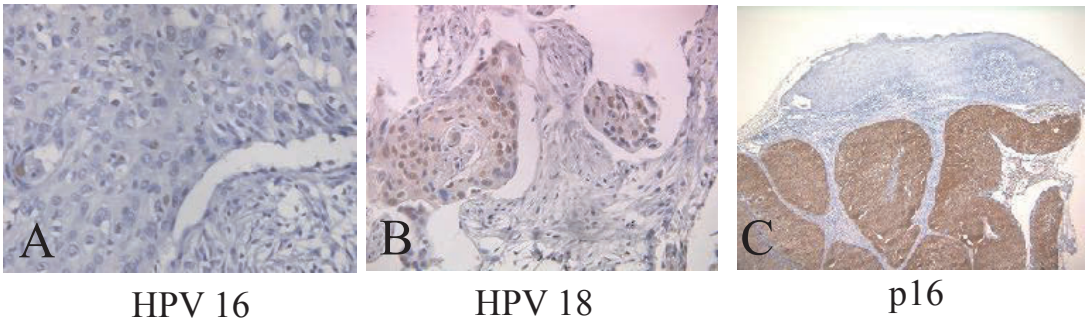


Fig. 14. Expression of HPV16, HPV18, and p16 in oral squamous cell carcinoma（OSCC）
In OSCC, staining for HPV16-positive cells was distributed in the nucleus of dysplastic or tumor cells（A, ×40）. Staining for HPV18-positive cells was distributed predominantly in the nucleus of dysplastic or tumor cells（B, ×40）, and staining for p16-positive cells was distributed predominantly in the nucleus and/or cytoplasm of dysplastic or tumor cells（C, ×40）. Detection of p16 could substitute for investigation of HPV. Cited and modified from Ref. # 29

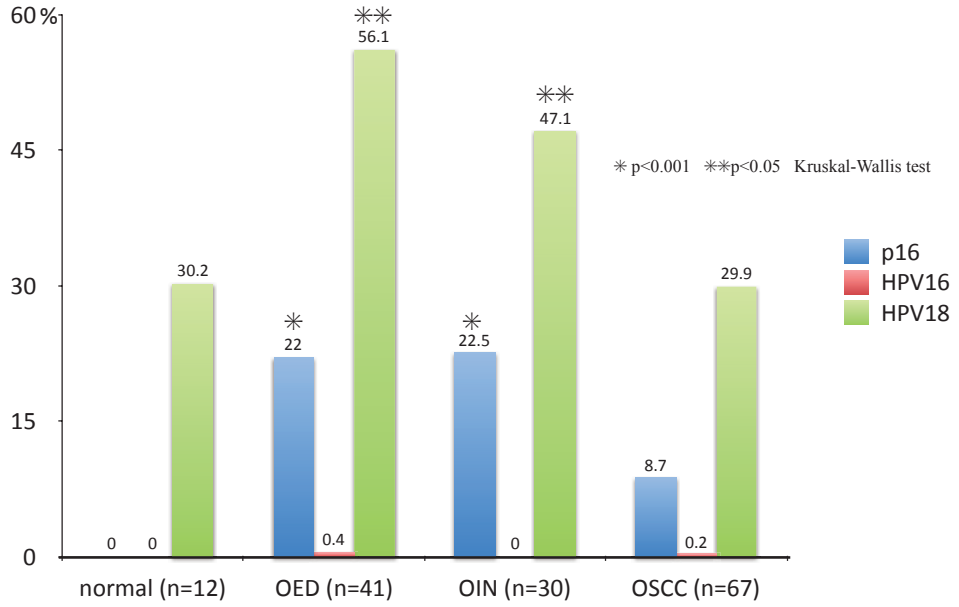


Fig. 15. Positive indices of HPV and p16
HPV16 was not expressed in normal and OIN, but slightly did in OED and OSCC. On the other hand, HPV18 and p16 were clearly expressed. Cited and modified from Ref. # 29

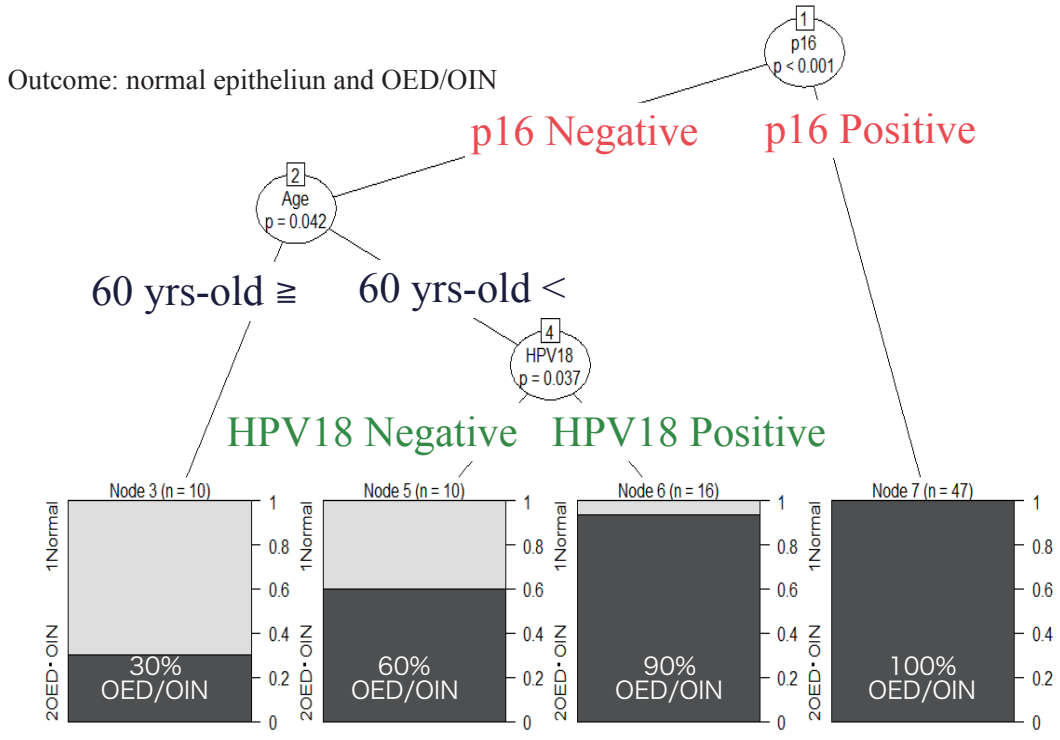


Fig. 16. Result of regression tree analysis for discrimination between NOE and OED/OIN
The independent variables were p16, HPV16, HPV18, and age. To predict OED/OIN, the primary variable for the hierarchical tree was p16 status, the secondary variable was age（60 years）, and the tertiary variable was HPV18 status. Cited and modified from Ref. # 29

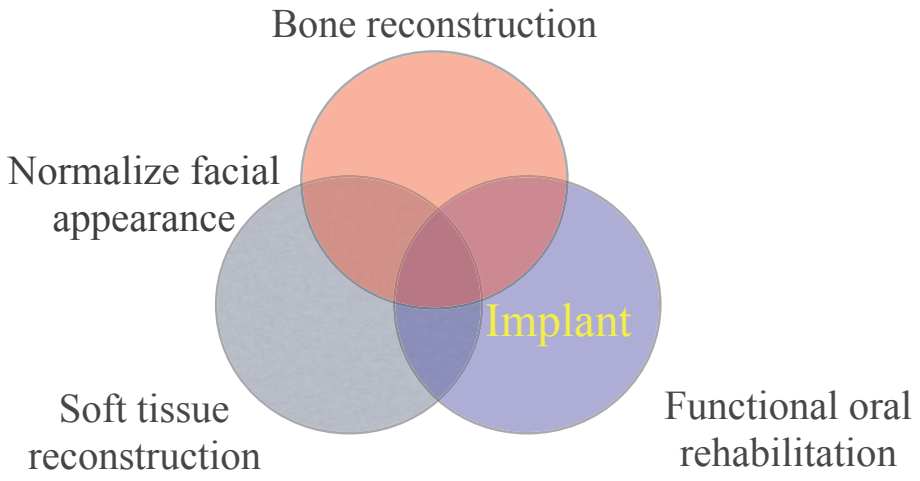


Fig. 17. Our treatment policy in oral tumor patients
Following complete resection of the tumor, functional reconstruction of oral function is achieved.

functional oral rehabilitation using osseointegrated implants following many kinds of bone augmentation procedures [30].

Radical resection and reconstructive surgery

First, the most important point of surgery is complete resection of the lesion including metastasized lymph nodes (Fig. 18). Regarding the application of neck dissection, the preoperative quantitative estimation of nuclear features using morphometrical analysis established by the author's group [12, 31]. Reconstructive surgery should be then indicated following radical resection including bone, soft tissue and teeth. With regard to the reconstruction, combination of free iliac bone grafting and free flap such as free forearm flap or pedicled flap, or osseocutaneous flap is the most common technique (Figs. 19 and 20) [32, 33].

Oral rehabilitation using osseointegrated implants

The timing of fixture placement is important in non-vascularized bone cases, and certain consideration must be taken into account. Successful osseointegration is dependent on the existence of viable bone cells for osteogenesis at the bone-to-implant interface. The periosteum, which supplies nutrition to the bone and plays important roles in mineralized tissue generation and support, is employed as a recipient tissue for therapeutic transplantation for reconstructive surgery including implant placement [34, 35]. In a non-vascularized bone transplant, adequate time is then needed for creeping substitution of the non-vital bone to occur. In our hospital, the waiting period between non-vascularized iliac bone grafting and fixture placement was at least 8 months; a longer waiting period might result in unexpected resorption of non-vascularized bone transplants (Fig. 21) [36].

Maxillofacial surgeons have to make an extra effort to improve the quality of life in patients who are suffering form masticatory disturbance due to oral tumor surgery using osseointegrated implants as well as many kinds of bone augmentation .

Related disorders including upper digestive tract

Associated factors for second primary tumor of the esophagus in oral tumor patients

Development of a second primary tumor (SPT) contributes to a poor prognosis, even if the primary oral tumor (OT) was adequately managed. SPT develops as synchronous or metachronous esophageal cancers in 1-20% patients with oral squamous cell

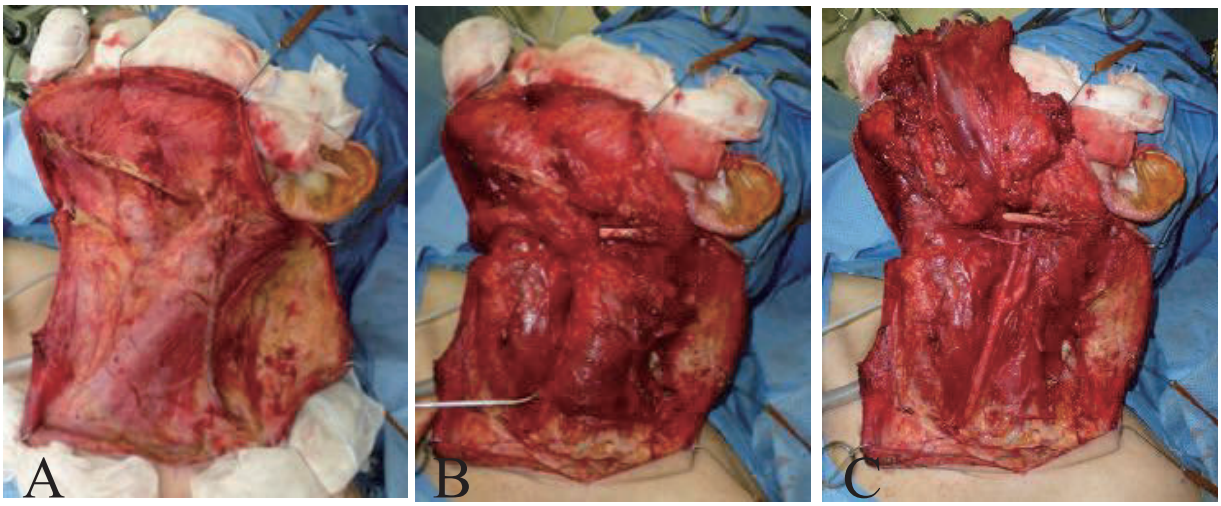


Fig. 18. Radical neck dissection
A: Operating field is exposed. B: Radical neck dissection is completed. C: Reflection of dissected specimens, which are also resected with primary lesion（tongue squamous cell carcinoma）.

carcinoma（OSCC）. This study aimed to evaluate the prevalence of and associated factors for SPT of the esophagus in OT（OSCC, oral intraepithelial neoplasia/carcinoma in situ: OIN/CIS, and verrucous carcinoma: VC）patients. Neoplastic diseases in the upper digestive tract were esophageal carcinoma（EC）and intraepithelial neoplasia（IN）, gastric carcinoma（GC）, epithelial dysplasia（ED）, and other diseases. Univariate analysis showed that Brinkman index（BI）was a candidate associated factor. In the multivariate analysis, BI as a continuous variable was also a significant associated factor. We strongly suggest that endoscopic screening be performed to identify malignancies of the upper digestive tract in patients with OSCC, OIN/CIS and VC［37］.

This study protocol was approved by the Ethics Committee of Shimane University Hospital, Japan（Approval No. 1779, 11 March 2015）.

Relationship between Oral symptoms and gastroesophageal reflux disease (GERD)

The author's group evaluated the effects of salivary flow volume and swallowing function on oral symptoms including dental erosion in gastroesophageal reflux disease（GERD）. Subjects were 40 GERD patients and 30（15 younger, 15 older）healthy controls. Detailed medical, dietary, and dental histories were obtained to identify individual behavioral habits potentially associated with dental erosion. Oral examination evaluated dental erosion and determined scores for the decayed, missing, filled（DMF）index, the papillary, marginal, attached（PMA）index for gingivitis, and the Simplified Oral Hygiene Index（OHI-S）. Salivary flow volume and swallowing function were evaluated by the Saxon test and repetitive saliva swallowing test（RSST）, respectively.

DMF index and OHI-S scores differed significantly between all 3 groups. PMA index was significantly different between the GERD group and the two control groups. Prevalence of dental erosion was 24.3 % among the GERD group（0% in the control groups）. No specific relationship was found between the incidence of dental erosion and dietary history or behavioral habits. The Saxon test results were significantly lower in the GERD group than in both the control groups. Frequency of swallowing was significantly lower and time to first swallow was significantly longer in the GERD group than in the two control groups.

Oral symptoms in GERD would likely be associated with impaired salivary flow volume or swallowing function. Treatment for oral dryness induced by reduced salivary flow volume and rehabilitation for

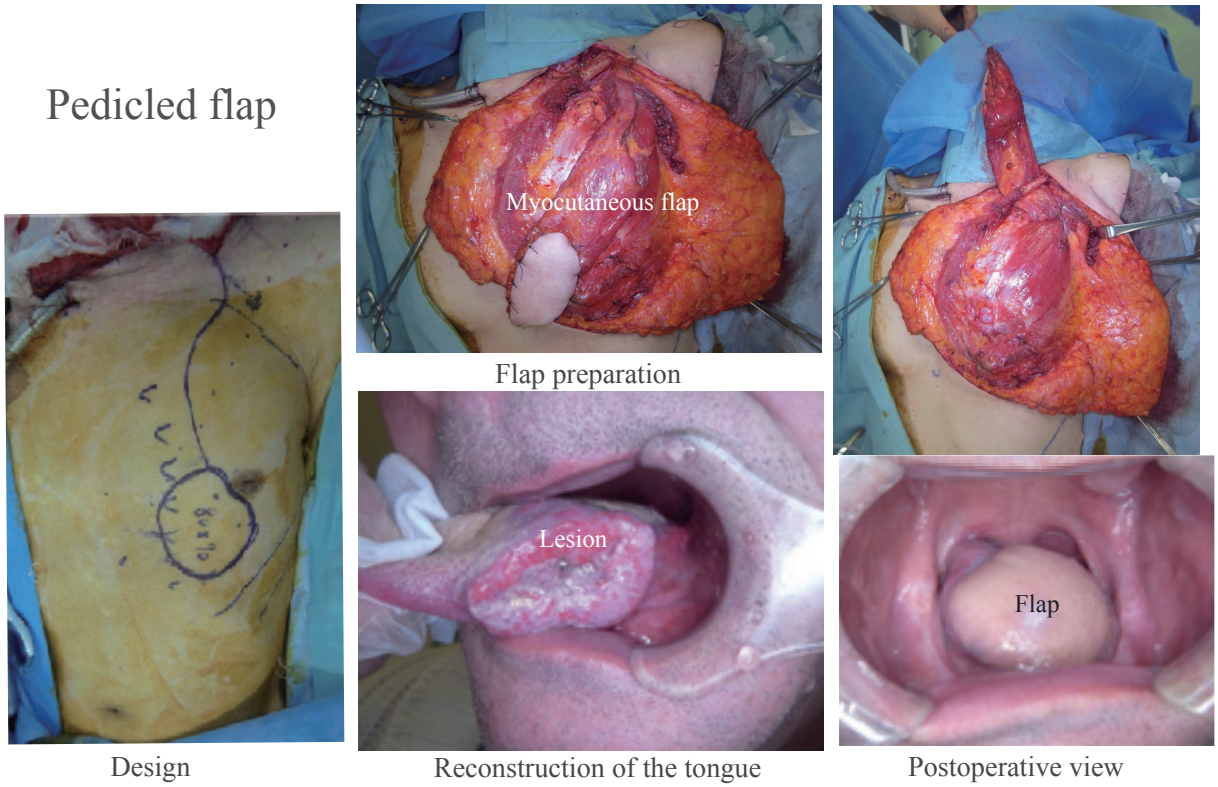


Fig. 19-1. Soft tissue reconstruction materials (Pedicled flap)
Pedicled flap (pectoralis major muscle cutaneous flap) is shown for reconstruction of soft tissue defect of the tongue.

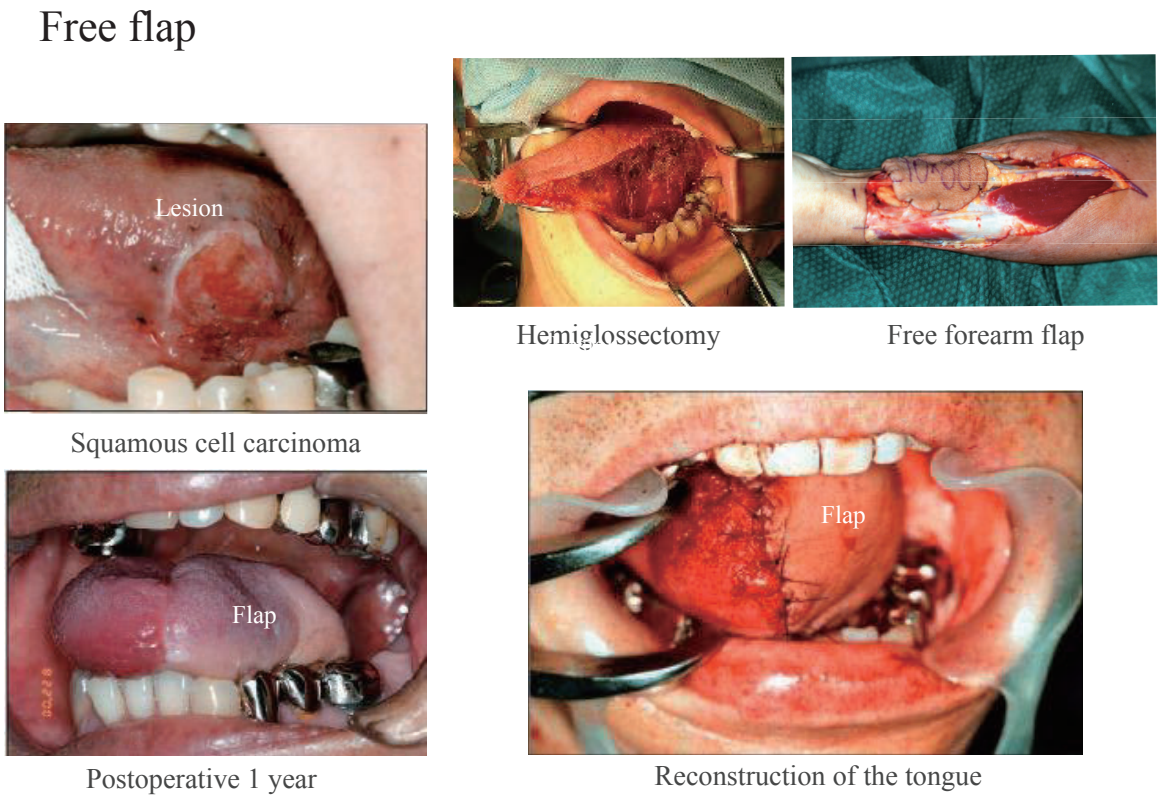


Fig. 19-2. Soft tissue reconstruction materials (Free flap)
Free vascularized forearm flap is shown for reconstruction of the soft tissue defect of the tongue.

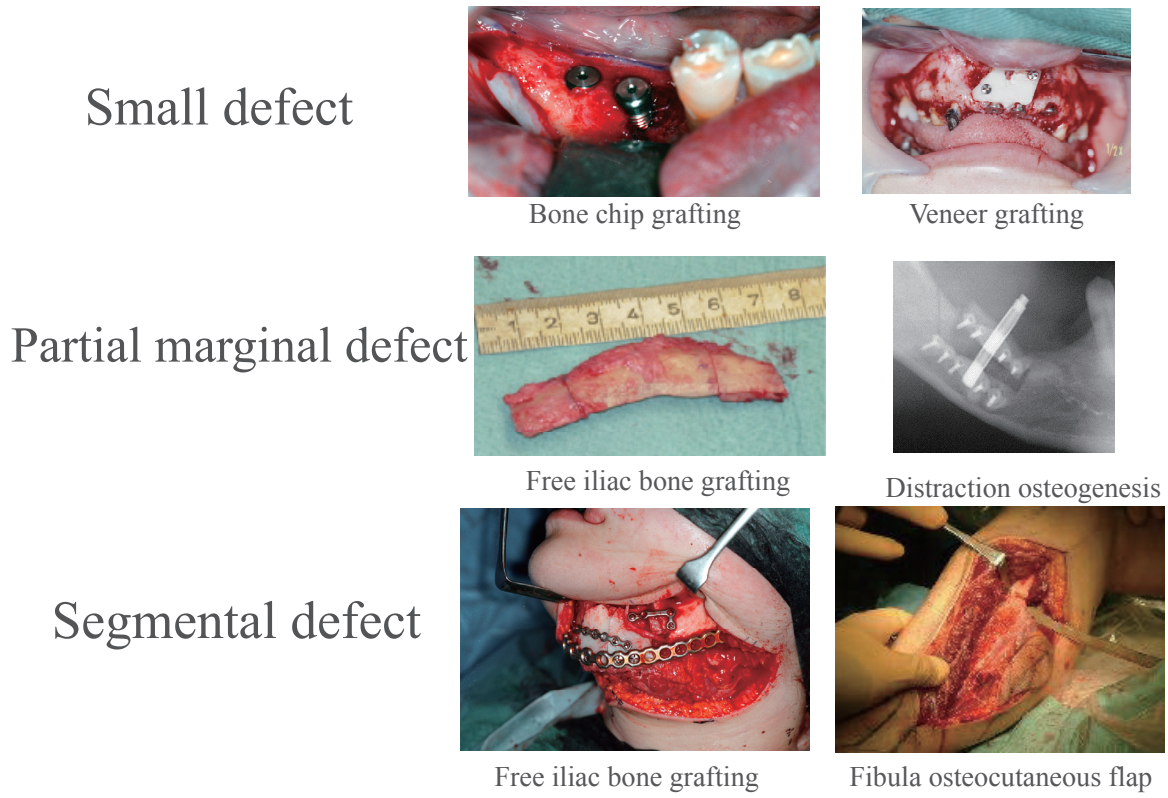


Fig. 19-3. Bone tissue reconstruction materials
Many options are available for the size of the defect.

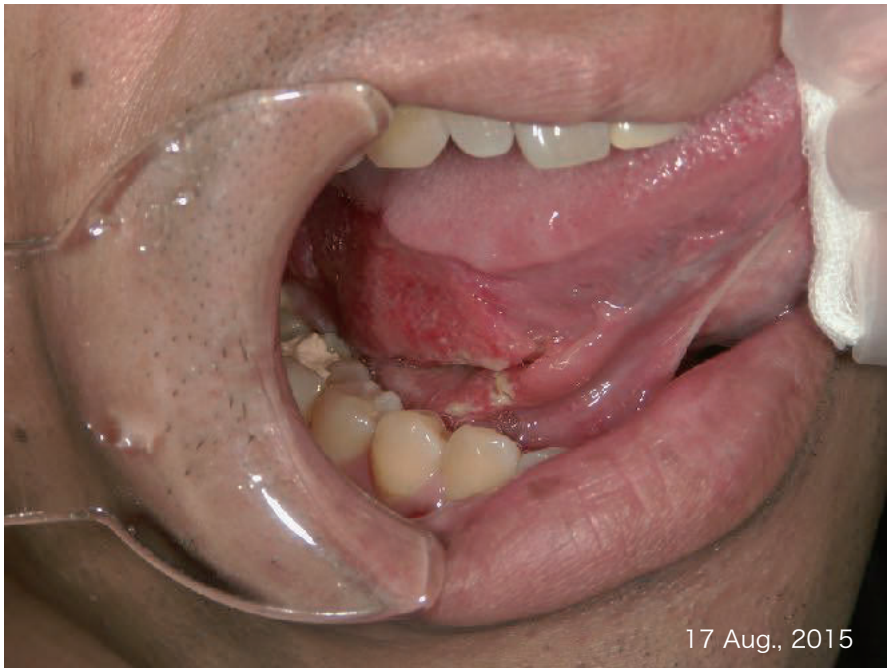


Fig. 20-1. A case of tongue squamous cell carcinoma
A 40-yrs-old Japanese male, T4aN2bMo, Stage IVA.

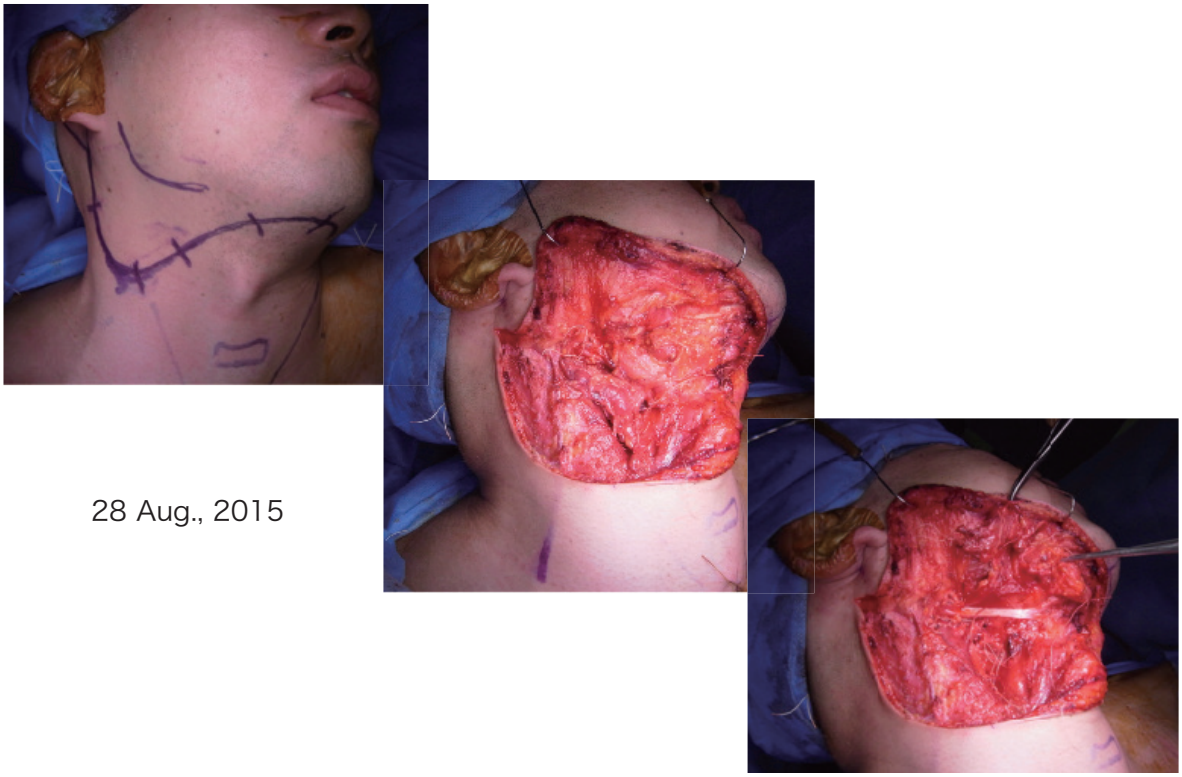


Fig. 20-2. Supraomohyoid neck dissection
Modified neck dissection was done in this case.

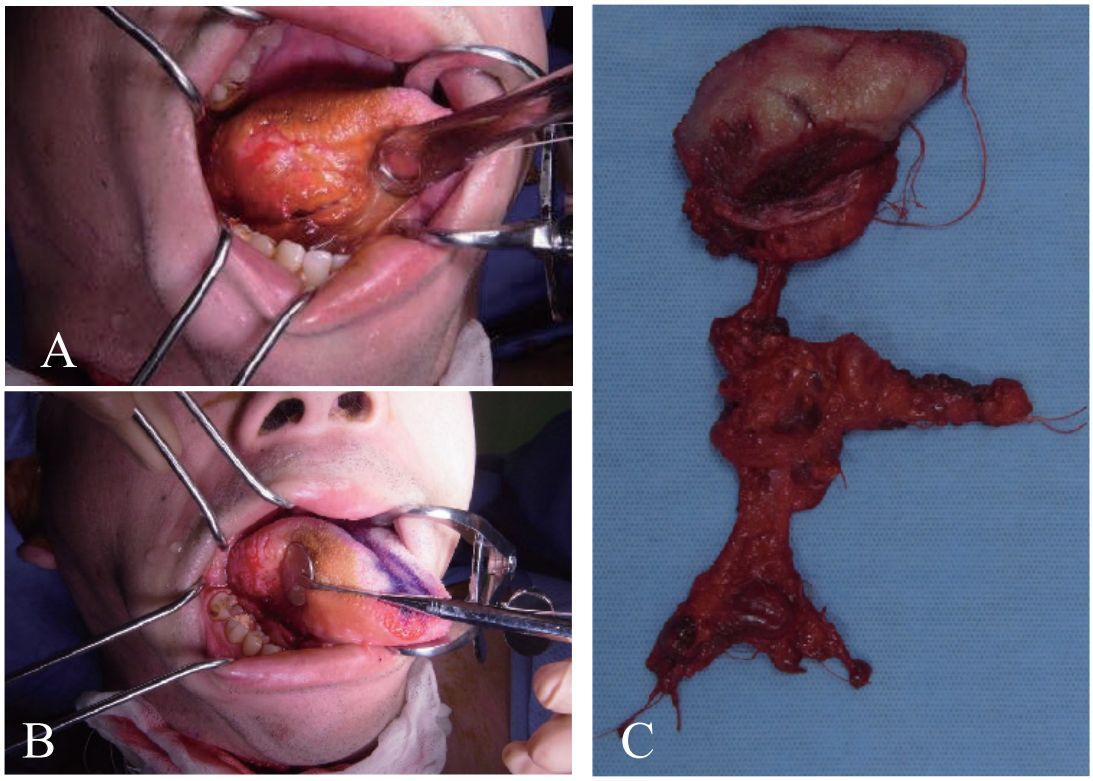


Fig. 20-3. Resected specimen
Neck dissection specimens were also resected together with primary lesion（hemiglossectomy）.

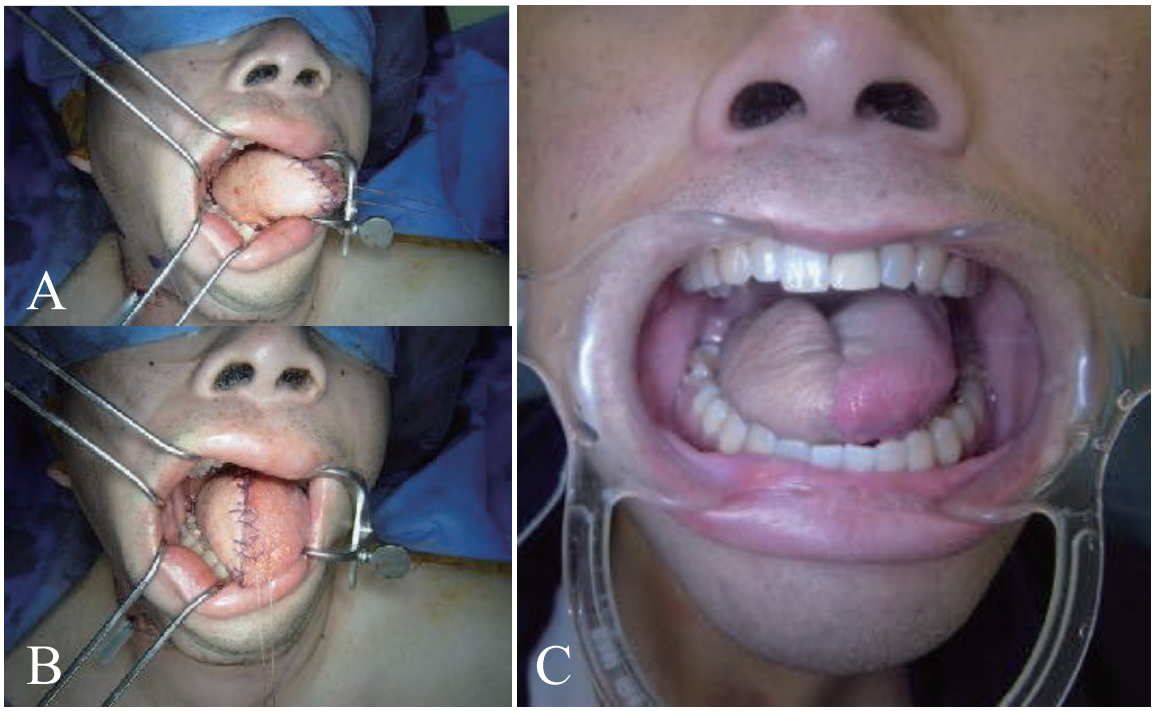


Fig. 20-4. Reconstruction using free forearm flap
A and B: Just after the operation. C: Postoperative 1 year and half. Patient can talk clearly and eat every kind of food, as he did not loose his teeth.

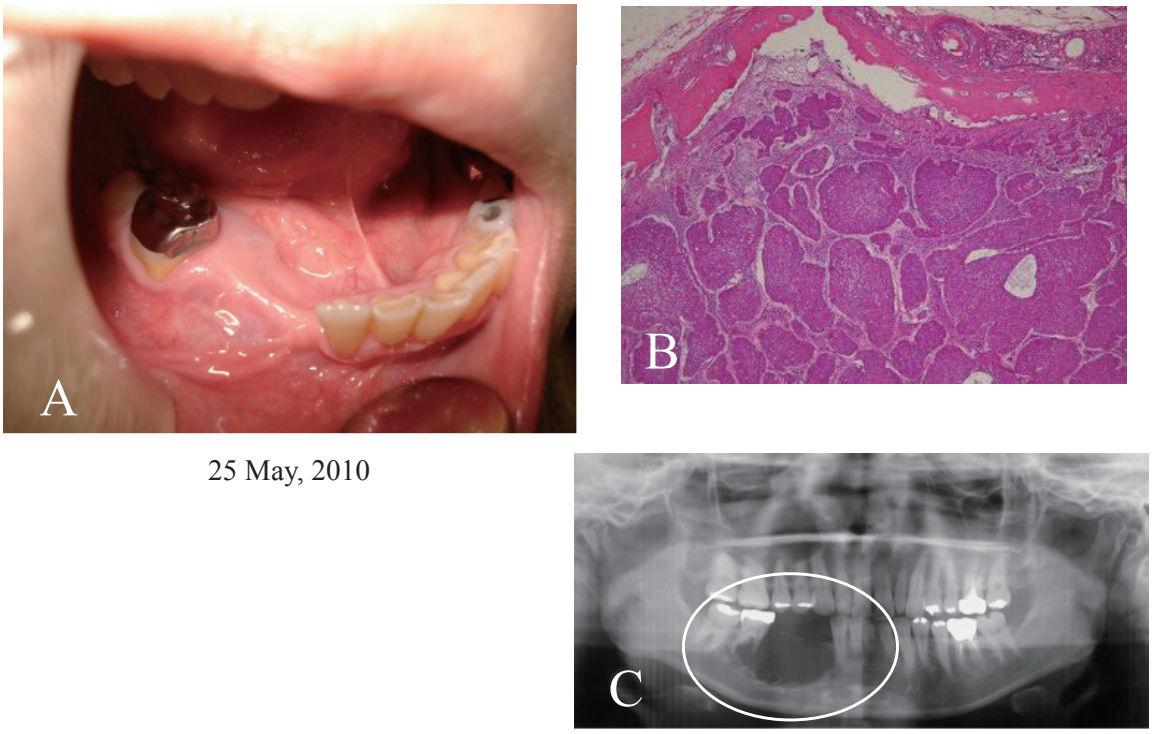


Fig. 21-1. A case of mandibular squamous cell carcinoma
A 38-yrs-old Japanese female. Her chief complaint was discomfort of the right side mandible. A: Intraoral findings. B: Histopathological findings show the feature of squamous cell carcinoma. C: Panoramic X-ray findings. White circle shows the primary lesions.

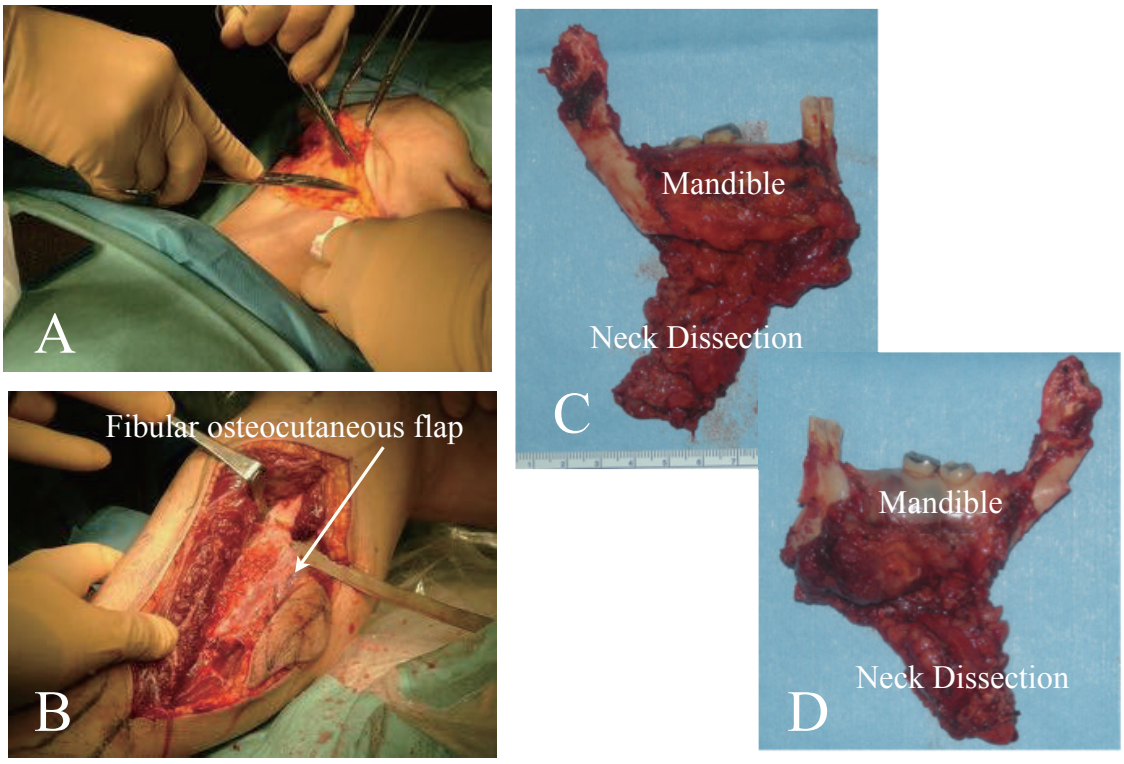


Fig. 21-2. Primary surgery and harvesting free fibular osteocutaneous flap
A: Intraoperative findings. B: Havesting of fibular osteocutaneous flap. C and D: Resected specimens.

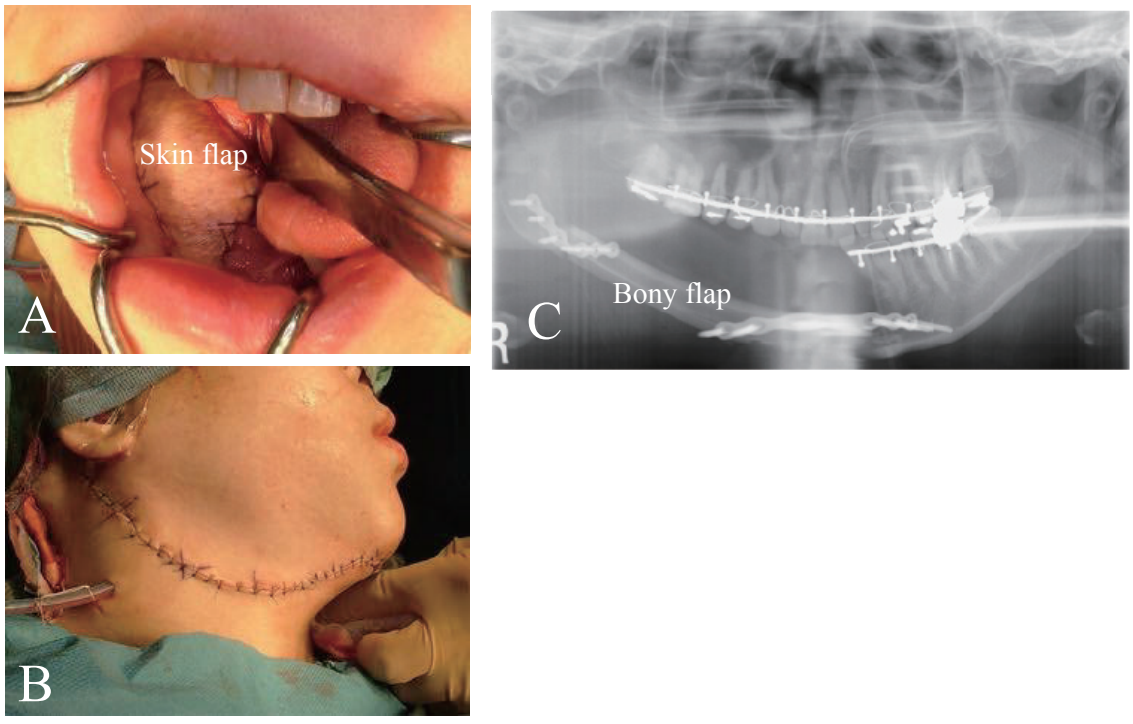
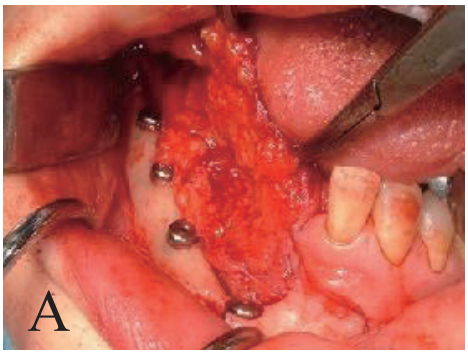
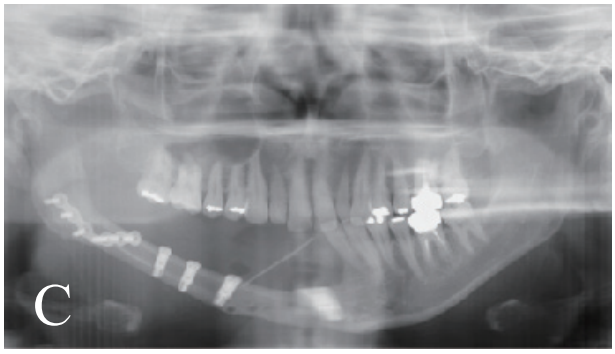


Fig. 21-3. Postoperative view and panoramic X–ray findings
A and B: Just after the operation. Bone and soft tissue defects were reconstructed by free flap. X-ray shows excellent reconstruction of the mandible.





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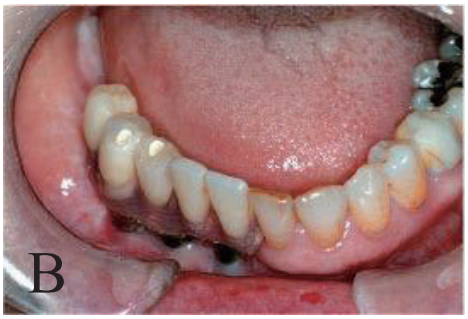

Fig. 21-4. Oral rehabilitation using implant supported fixed denture
Oral rehabilitation is needed, as this patient lost 7 teeth in the right side mandible. A and B: Implant placement. B: Final prosthesis supported by osseointegrated implants.

swallowing function could be indicated in patients with GERD [38].

All participants of this study provided informed consent to participate following approval of the study protocol by the Ethics Committee of Shimane University Hospital, Japan (Approval No.398; 18 Sep., 2008).

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