Technology in Cancer Research & Treatment
Volume 21: 1-17

DOI: 10.1177/15330338221146870
journals.sagepub.com/home/tct
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Systemic and Local Effects Among Patients With Betel Quid-Related Oral Cancer

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Abstract

The major predisposing factors of developing oral cancer include smoking, alcohol drinking, and betel quid chewing. Betel quid chewing could cause the abrasion and damage of oral mucosa by crude fibers, chemical insults by additive slaked lime, and arecoline from areca nut. These would lead to the local consequence of oral submucosal fibrosis, which is regarded clinically as a precancer lesion and a major cause of trismus. In addition, the components and additives in betel quid contain chemical toxins and carcinogens, which would further affect the oral mucosa and gradually develop a malignancy. Following literature review, aside from having a greater total tumor burden and more local diseases in the oral cavity and digestive tract, patients with betel quid-related oral cancer also have more systemic diseases from metabolic syndrome, hypertension, cardiovascular disease, type II diabetes mellitus, and obesity than those without this habit. In conclusion, those patients who have the history of smoking, alcohol drinking, and betel quid chewing would present much more unique clinical characteristics than those who only have a history of smoking and alcohol drinking. More attention should therefore be paid to pretreatment evaluation, treatment strategy, and post-treatment follow-up among betel quid chewers.

Keywords

head and neck squamous cell carcinoma, oral cancer, submucosal fibrosis, betel nut, trismus, arecoline, areca nut, oral submucosal fibrosis, metabolic syndrome, cardiovascular disease

Introduction

Betel quid chewing plays a major role in the development of head and neck squamous cell carcinoma (HNSCC) in South Asia, Southeast Asia, Taiwan, and Pacific islands. The estimated highest prevalence rate of oral cancer in males is in Taiwan, followed by Papua New Guinea, Pakistan, India, Sri Lanka, and Bangladesh (Table 1), according to the available websites containing "2019 Taiwan Cancer Registry Annual Report"[1] and 2020 GLOBOCAN (Global Cancer Observatory)[2] from International Association of Cancer Registries (IACR). The clinical characteristics show some differences between the regions with betel quid chewing and those without. The components of betel quid usually consist of areca nut, betel leaf, slaked lime, and/or tobacco. Betel quid chewing is a traditional behavior, which has been prevalent in these regions for hundreds of years. The scientific name of areca palm is *Areca catechu*. Areca nut is the seed of Areca palm. Ancient findings of *A. catechu* in botanical remains were obtained from archaeological work from around 10 000 B.C. in Spirit Cave in Northwestern Thailand.[3] In fact, the areca palms could be found extensively in these warm areas.

There are several chemical components noted in areca nut. The major component, arecoline—which is a kind of alkaloid—is found to have significant effects on human organs.

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Arecoline could be classified as a psychoactive substance, which could readily cross the blood–brain barrier to stimulate the central nervous system. Aside from the partial muscarine effect, arecoline also shows part of nicotinic activity, which may play a role in the habitual use and additive character from this substance in humans.[4] The main pharmacologic effect of arecoline could raise body excitability, decrease sleep time, and improve the abilities of learning and memory physiologically.[5] Interestingly, workers or drivers in betel quid chewing regions show greater preference in betel quid chewing than taking coffee for the purposes of continuing to work more persistently and energetically. Arecoline is an alkaloid compound that can be absorbed into the body and could be detected in the saliva, blood, urine, hair, and breast milk in persons who chew betel nut.[6] Generally, the systemic absorption of arecoline may cause systemic effects over human body physiologically. The gavage studies revealed that arecoline could increase the incidence of total tumors in mice.[7] In addition, the reaction of arecoline with sodium nitrite could lead to the formation of N-nitrosamines. These N-nitrosamines, which are carcinogens to humans, could be identified in the saliva if people were to chew betel quid.[6] Regarding the tumor-promoting effect of arecoline, it induces epithelial–mesenchymal transformation and promotes the metastasis of oral cancer by SAA1 expression.[8] Therefore, chewing betel quid, or in combination with tobacco, will cause the carcinogenesis over the mucosa of the oral cavity, pharynx, and esophagus, which was well illustrated by "International Agency for Research on Cancer" (IARC) in 1978. The working group from IARC in 2003 made the conclusion that the ingredients from areca nut are carcinogenic to humans. There also exists sufficient evidence in humans for the carcinogenicity of betel quid without tobacco. Betel quid chewing alone, and without the habit of smoking, could cause oral cancer.[9] Arecoline is currently classified as a "Group 1" carcinogen to humans, according to the report from IARC in 2012.[7]

Generally speaking, multiple habits with smoking, betel quid chewing, and alcohol drinking will lead to a more complex and severe consequence in cancer formation to these patients. It is estimated that those patients who have the habits of betel quid chewing, smoking, and alcohol drinking will have 123 folds to develop the oral cancer than those without, according to a hospital-based case–control study in Taiwan.[10] The purpose of this review is to show the local and systemic conditions among patients with betel quid-related oral cancer.

Unique Molecular Characteristics of Betel Quid-Related Oral Cancer

Are the changes of genetic landscape in oral cancer cells different between those in betel quid chewing areas and those in non-betel quid chewing areas? This is an interesting issue, because the carcinogens from areca nut may cause a different genetic landscape in HNSCC. Chen *et al* reported that the most frequently mutated genes were *TP53 (65%)*, followed by *PIK3CA (16.8%), CDKN2A (12.8%), HRAS* (9.3%), *BRAF* (9.0%), *EGFR* (6.7%), and *FGFR3* (5.8%) in a series of 345 cases of advanced oral cancer from Taiwan by next-generation sequencing (NGS) for whole-exome sequencing in 2015.[11] These authors also compared these results to a dataset from The Cancer Genome Atlas (TCGA) HNSCC, which originated from the USA with a series of 279 cases.[12] They found that the frequency of genetic variations in tumor suppressor genes was similar in both studies. However, *CDKN2A* (12.8% vs 22.6% in the TCGA dataset) and *NOTCH1* (3.2% vs 18.6% in the TCGA dataset) are a much lower degree in sequence variation than those of the TCGA dataset.[11] Regarding the mutation in oncogenes, it is much more in the Taiwanese dataset than those in the TCGA dataset. These oncogenes have a more than three-fold mutation rates in the Taiwanese dataset than those in the TCGA dataset, such as *AKT1* (3.2% vs 0.7%), *BRAF* (9% vs 1.4%), *CTNNB1* (2.3% vs 0.7%), *FGFR1* (1.4% vs 0.4%), *FGFR2* (4.3% vs 0.7%), *KIT* (4.1% vs 1.1%), *KRAS* (2.3% vs 0.4%), and *MET* (4.3% vs 1.1%).[11]

Betel quid chewing is traditional and popular in India. This habit leads to a serious problem in causing the oral cancer. Therefore, the "India Project Team of the International Cancer Genome Consortium" was proposed[13] and funded by India government. In this project, 50 cases of gingivo-buccal cancer were enrolled to investigate the mutational landscape by direct exome sequencing and 60 cases were used as a validated set.[13] All these patients were classified as stage III/IV tumor and 88% patients were male. Clinically, 96% patients had the exposure of tobacco (chewing $\pm$ smoking) in this study. Accordingly, the results showed the typical signature of tobacco in a preponderance of C:G > A:T transversion. The mutation spectrum in this cohort showed 54.3% patients with *CASP8* mutations. *FAT1* (60%) and/or *NOTCH1* showed truncating mutation predominantly. Generally, TP53 was mutated in all patients. In addition, 55% patients showed mutation over MLL4 and USP9X.[13] Interestingly, the authors divided the mutation genes into several subgroups to evaluate the survival impacts. They found patients in the subclusters C1.2 (with mutations in *CASP8*, *NOTCH1*, and *FAT1*), C1.4 (with mutations in *CASP8*, *NOTCH1*, and *ARID2*), and C3.2 (with mutations in *MLL4* and other genes) had significantly better disease-free survival than other patients.[13] In another report, Liao *et al* conducted a study in an area of betel quid chewing and proposed another different nine-gene signature (*RYR1*, *HLA-B*, *TSHZ2*, *PCDH17*, *DNAH17*, *GRID1*, *SBNO2*, *KSR2*, and *GCN1L1*) to predict the survival by whole-exome sequencing among 168 patients with oral cancer in 2021. This nine-gene signature is also validated by TCGA database in the prognostic value independently.[2] These authors found that tumor cells harboring one or more mutated genes in this nine-gene panel would lead to a worse loco-regional control, a higher incidence of distant metastasis, a worse distant free survival, a worse disease-specific survival, and a worse overall survival in these patients than those without.[14]

Another research group in Taiwan enrolled 120 cases of oral cancer from Taiwanese patients to study the mutation spectrum

by whole-exomes sequencing in 2017.[15] They found well-known mutation spectrum over *TP53* (43%; that is, 43% of tumors with TP53 mutations), *FAT1* (35%), *EPHA2* (15%), *CDKN2A* (17.5%), *NOTCH1* (29.2%), *CASP8* (23.3%), *HRAS* (11.7%), *RASA1* (5%), and *PIK3CA* (17.5%). This mutational spectrum is similar to the Taiwanese study published in 2015.[11] They also uncovered the novel mutation genes, *CHUK* (5%) and *ELAVL1* (6.7%), which are not reported before. Additionally, the copy-number alterations in several gene clusters containing *CCND1* and *MAP4K2* are enriched in tongue cancer.[15] These authors proposed the biological significance of these two genes, *CHUK* and *ENAVL1*, in the carcinogenesis of these Taiwanese patients. *ELAVL1* is encoded an RNA-binding protein, which could stabilize many cancer-related genes.[16] *CHUK* acts as the tumor suppressor and is involved in the activation of nuclear factor κB (NF-κB) by controlling the turnover of cyclin D1.[17,18]

Chai *et al* conducted the genome-wide Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) screens among 21 oral cancer cell lines in 2020.[19] They used this gene editing technology to find the genes, which were essential for these oral cancer cells to survive. The authors identified 918 genes, which were essential in survival and spread of oral cancer cells in this study. Interestingly, 110 fitness genes were found to be unique in betel-quid-associated oral cancer cell lines and some fitness genes were significantly related to NF-kB signaling pathway, including *NFKB2*, *TNFAIP3*, *CSNK2A1*, and *TRIM25*.[19] These results from oral cancer cell lines are compatible to the studies of tumor tissues from Taiwan and India where the betel quid-related oral cancer is common. Particularly, the extracted components from areca nut of betel quid could directly activate the NF-kB signaling pathway to promote the tumor survival according to the past studies.[20,21] In another report from Malaysia, the authors investigated the genomic alterations among oral cancer cell lines.[22] Aside from well-known mutated genes, *TP53*, *CDKN2A*, *EPHA2*, *FAT1*, *NOTCH1*, *CASP8*, and *PIK3CA*, the authors also identified mutations over *MLL4*, *USP9*×, and ARID2 in oral cancer cell lines, which were derived from betel quid users. These results are similar to those found in "India Project."[13]

Zhang *et al* conducted a study about the mutational signatures and the genomic landscape of betel quid-related tongue cancer (BQ-TC) by whole–exome sequencing technique in China. They also compared with the differences between the results of this study and those of TCGA. They found the mutation rate of *TP53* in BQ-TC (47%) is much lower than that in TCGA-TC (77%). The *RASA1* is a kind of tumor suppressor gene which mutation rate in this Chinese cohort (20%) is much more than that in TCGA dataset (4.48%). The genetic feature of BQ-TC showed the unique one in tongue cancer. Namely, the GCG (to GTG) pattern of the C > T mutations is the major mutation pattern in BQ–TC, but not in TCGA–TC. Furthermore, this pattern of C > T mutations contributes to more mutation rate over CpG islands in BQ-TC.[23]

Su *et al* also showed the similar results. The elevated BQ-related mutation rate was noted in tongue cancer, but not in overall oral cancer in a Taiwanese study, which is a quantitative survey of mutational signatures and genomic aberrations in BQ-related oral cancer by whole–exome sequencing technique. In addition, the numbers of small insertions and deletions and breakpoints derived from structural variations were increased but the extent of loss of heterozygosity was decreased in the genomes of BQ-related oral cancer.[24] Additionally, Adhikari *et al* conducted a study about genome-wide analyses and quantitative methylation-specific PCR in oral cancer and they showed the methylation levels of *DUSP4* were significantly higher in the betel quid-related oral cancer than those in the nonrelated one and controls. The authors concluded that hypermethylation of *DUSP4* could be regarded as a specific marker in betel quid-related oral cancer.[25]

Clinical Characteristics

Age and Gender. There are 5340 cases of first diagnosis as oral cancer in Taiwan. The median age is 57 years in males and 65 years in females in 2019. The age-standardized rate is extremely high (Table 1) and is up to 27.01 per 100 000 persons in males, but only 2.79 per 100 000 persons in females. The male-to-female ratio is up to 9.68 to 1, according to "2019 Taiwan Cancer Registry Annual Report from the website of Health Promotion Administration, Ministry of Health and Welfare."[1] The mean age of oral cancer in most Asian countries between 2000 and 2012 is 51-55 years, according to a review from Rao *et al*.[26] However, Ariyoshi *et al*[27] reported that the mean age of oral cancer in Japan is 65.2 years. On the other hand, the mean age of diagnosis of oral cancer in USA is 64.2 years, and the younger patients (0-39 years) with oral cancer showed an increased trend, according to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (USA) database between 1975 and 2016.[28] Interestingly, the mean age of oral cancer would be 7 to 10 years younger among those patients who have the habit of betel quid chewing. The male-to-female ratio in USA is around 2.23 to 1, according to the SEER data between 2000 and 2010.[29] Regarding the gender ratio in India, the male-to-female ratio is 135 989 to 48 849, which is around 2.78 to 1, according to the 2020 India National Cancer Registry Programme.[30] In addition, the male-to-female ratio is only 1.45 to 1 in Japan, according to an epidemiologic report.[27] However, the male-to-female ratio is extremely larger, at 9.68 to 1, in Taiwan.[1] This accounts for the male patients who have very high prevalence rate in betel quid chewing than female patients. Indeed, most female patients do not have the habit of betel quid chewing in Taiwan. This reflects the fact that the female mean age of oral cancer in Taiwan is remarkably similar to that of countries of nonbetel quid chewing. Nonetheless, the male mean age of oral cancer in Taiwan is similar to that of countries of betel quid chewing in South Asia.

Local Conditions from Betel Quid Chewing

Oral Submucosal Fibrosis with Trismus. Oral submucosal fibrosis (OSMF; Figure 1) is common among patients who have the

Table 1. The Estimated Prevalence of Oral Cancer in Male in 2020.

Region	Case Number	ASR/100 000
Taiwan	4776*	27.01[a]
Papua New Guinea	758	21.18
Pakistan	11 395	10.14
India	104 661	9.76
Sri Lanka	2202	9.67
Bangladesh	9356	9.5
Namibia	64	6.58
Australia	1862	6.46
Hungary	792	6.32
Slovakia	466	6.13
Latvia	183	6.01
Poland	2985	5.99
Cabo Verde	20	5.98
Romania	1607	5.37
France	4244	5.35
Portugal	804	5.26
Cuba	782	5.21
United Kingdom	3931	5.1
Russian Federation	9582	5.06

Abbreviation: ASR, age-standardized rate.
[a]The report in Taiwan is the updated information in 2019.
Data source:
1. 2019 Taiwan Cancer Registry Annual Report. Website Available from: https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=14913
2. 2020 GLOBOCAN (Global Cancer Observatory) from International Association of Cancer Registries (IACR). Website Available from: https://gco.iarc.fr/

habit of betel quid chewing. Chewing betel quid for a long period of time would cause damage of oral mucosa significantly by the crude fibers in areca nut, the toxic effect from arecoline, and the corrosive character of slaked lime. Gradually, good compliance of oral mucosa will be replaced by stiff fibroblastic tissue, and this consequence may develop OSMF, which even leads to severe trismus in some patients (Figure 2). OSMF is a kind of oral potentially malignant disorder, and the pathological finding commonly reveals squamous cell hyperplasia with/without dysplasia. Patients with OSMF may develop a malignancy with an incidence of 4.5% after the initial diagnosis, in a report from India patients with a period of 8-year follow-up.[31] The malignant transformation rate of OSMF in Taiwanese patients is 1.99% at a period of 10-year follow-up.[32]

It is necessary to bring about long-term awareness in the mucosal change of the oral cavity among patients with OSMF, although the malignant transformation rate is less than 5% in a long period of follow-up.[31,32] However, the persistent smoking, betel quid chewing, and liquor drinking will further increase the malignant transformation rate of OSMF. Clinically, the definition of trismus in patients with head and neck cancer is the maximal distance between upper and lower incisors, with a maximal interincisal opening (MIO) of less than 3.5 cm.[33,34] Transoral excision of oral cancer or full inspection of oral lesion will be hampered if the distance of MIO is too short (Figure 2). The approach to oral cancer in this scenario is advised to shift to an external approach. It includes the lip splitting to remove buccal/buccogingival sulcus cancer and mandibulotomy or pull-through approach to remove tongue cancer. The oral rehabilitation in the dental field after treatment of oral cancer is a challenge in some patients because of the limitation in MIO due to OSMF and the consequences of treatment in oral cancer. Proper reconstruction for oral defect after ablation of oral cancer is essential in preventing further trismus after surgery. Local tongue flap[35] (Figure 3), submental island flap,[36] and radial forearm free flap (RFFF) (Figure 4)[37] or trimmed anterior lateral thigh free flap[38] (Figure 5) could be used for the defect of oral inner lining. Nasolabial myocutaneous flap[39,40] is another reconstructive option for a buccal mucosal defect over anterior to middle part, although the facial scar is often a concern from patients. Wei *et al* reported that bilateral coronoidectomy, together with the oral reconstruction by RFFFs could, add more distance in the MIO after surgery in his series.[37] However, the donor site morbidity is more by using RFFF for reconstruction of oral cavity defect.

There are clinical reports to evaluate the prognosis of oral cancer between those patients with OSMF and without. Chaturvedi *et al* suggested that oral cancer originating in background of OSMF reveals a distinct disease clinicopathologically. They found most patients of oral cancer arising from OSMF were young males. Their tumors showed thinner lesions, earlier tumor stage (pT), lesser incidence of neck metastases, better differentiated tumors, and lesser incidence of extracapsular spread (ECS) of lymph node than those patients without the OSMF. In addition, patients of oral cancer with OSMF even in advanced tumor stage (pT) would show lesser incidence of neck metastasis and ECS of lymph node than those without OSMF. All these distinct characters would contribute the better survival chance among patients with OSMF than those without.[41,42] Another report from India confirmed the similar results that patients with oral cancer coming from OSMF have better survival chances than those without.[43] Zhou *et al* also reported the similar findings. There is no lymph node metastasis in oral cancer among Chinese patients with OSMF. Additionally, the histologic type was also the well differentiated one.[44] The lesser incidence in neck lymph node metastasis among patients with OSMF may come from the blockage of submucosal lymphatic channels and vascularity in fibrotic tissue.[41] In fact, survival studies performed in different regions produced inconsistent results. Regarding the comparison of prognosis of oral cancer between betel quid chewers and nonbetel quid chewers, there is an interesting study of systemic review and meta-analysis focusing in this issue. Compared with nonchewers, the pooled hazard ratio (HR) among betel quid chewers was 1.26 for 5-year overall survival and 1.40 for 5-year disease-specific survival. Yang *et al* concluded that betel quid chewing is significantly associated with poor prognosis among patient with oral cancer. Of course, regarding the role of betel quid chewing on the prognosis of oral cancer, the current evidence is not adequate and controversial. Further studies are warranted.[45]

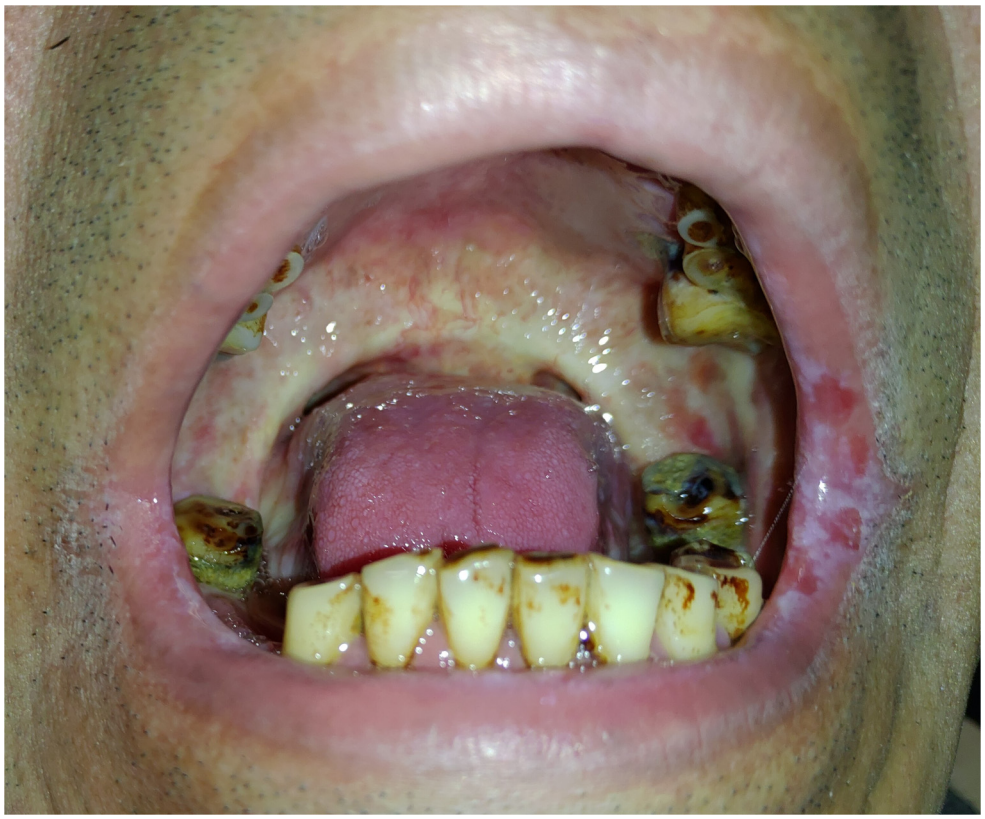

Figure 1. This patient shows submucosal fibrosis over the oral cavity and soft palate. Erythro-leukoplakia over mucosa of the left upper and lower lips is also noted. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.)

The treatment strategy among patients with OSMF is recommended to have a proper reconstruction as mentioned above after the removal of oral cancer to prevent further trismus, which would cause a worse condition in the quality of life and hamper a detailed inspection over oral mucosa after surgery clinically. Furthermore, the long-term follow-up of oral mucosa is necessary to detect the progressive change of abnormal mucosa in oral cavity or upper aerodigestive tract. Regarding the issue of surgical margin of oral cancer in patients with OSMF, the surgical margin is recommended to have 1-2 cm and the goal of pathological margin over 5 mm is also mandatory to achieve a better clinical outcome. Clinically, the application of intra-operative chemodetection for mucosal margin control by Lugol's staining is feasible and convenient for surgeon to detect abnormal mucosal margin with moderate dysplasia, carcinoma in situ or even early squamous cell carcinoma in Logol-voiding area.[46]

Chronic Periodontitis. Long-term betel quid chewing, smoking, and poor oral hygiene would lead to chronic periodontitis (Figure 6). Loosening of teeth due to periodontitis and gradual loss of teeth—or even becoming edentulous—is not rare, if patients do not keep oral hygiene and undergo adequate treatment of this disease. Currently, the association between betel quid chewing and periodontitis is well reported in the literature.[47–49] Clinically, periodontitis is demonstrated to have a positive association with coronary artery disease[50] and cerebrovascular disease[51] in the epidemiological reports. These two medical conditions are advised to be thoroughly evaluated prior to treatment of oral cancer among these chewers. Furthermore, a recent report showed that chronic inflammatory status in chronic periodontal disease might have an association with oral cancer.[52] Treatment of this chronic periodontal disease by a periodontist or an oral and maxillofacial surgeon following the complete treatment of oral cancer is essential among these patients.

Extensive Tumor Burden Over Digestive Tract. Oral cancer patients with a combination of habits including betel quid chewing, smoking, and alcohol drinking would develop more extensive damage to the mucosa of aerodigestive tract than those with only the habits of smoking and alcohol drinking. Impressively, betel juice staining would soon coat over the mouth after betel quid chewing (Figure 7). In addition, the betel juice staining and residues of betel quid are swallowed all along the food pipe and the coatings are found all over the mucosa of base of tongue, epiglottis, pyriform sinus, whole esophagus, and stomach (Figure 8). Among patients with oral

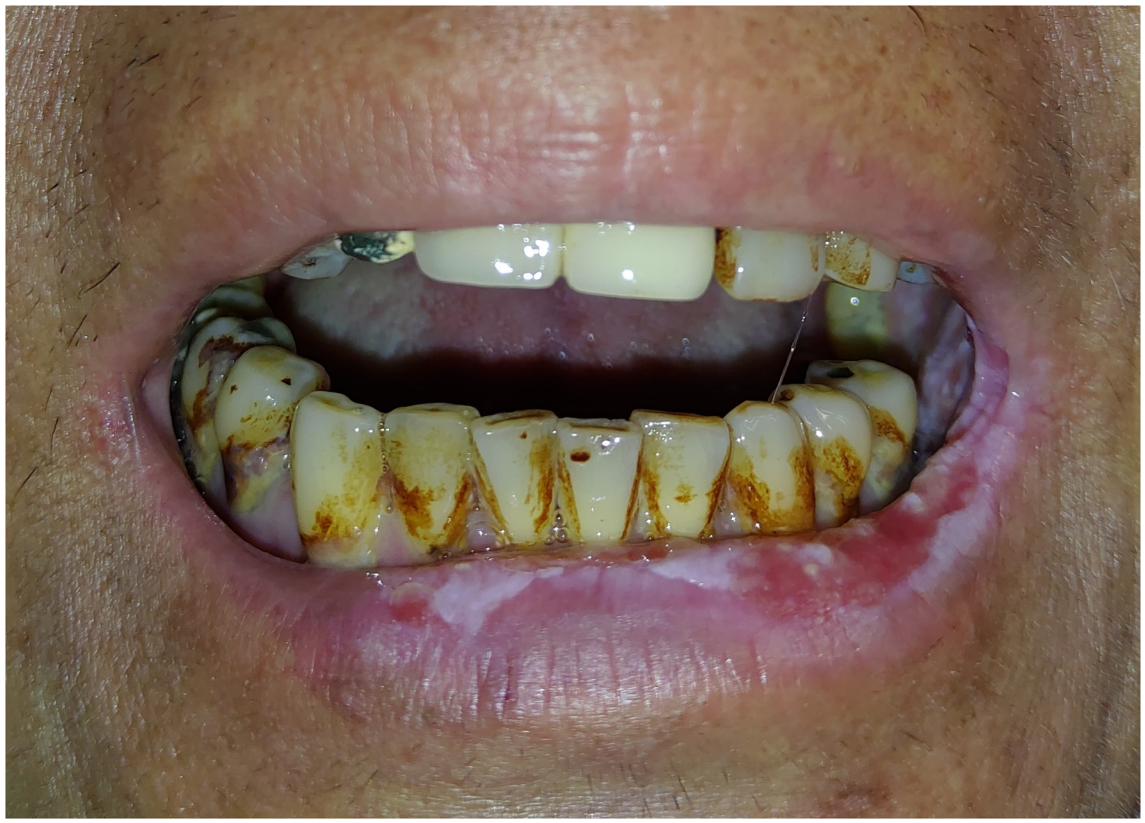

Figure 2. This patient shows submucosal fibrosis with trismus over the oral cavity with limited maximal interincisal opening. Erythro-leukoplakia over mucosa of the lower lip is also noted. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.)

cancer, second primary site over esophageal cancer is poor prognosis in the late stage. In fact, the key component of areca nut—arecoline—could cause carcinogenesis over esophagus in mice.[6] One population-based study in Taiwan shows that those patients who have the esophageal cancer diagnosed as the second primary cancer after the initial diagnosis of oral cancer in Taiwan are not rare. Compared with the general population, the standardized incidence ratio is up to 5.15 folds after a period of 5–10 years of follow-up.[53] The other reports also revealed that the incidence of synchronous esophageal cancer would be 0.79%,[54] and metachronous one would be 1.6%[55] among patients with oral cancer in Taiwan. Betel quid chewing is also a risk factor for developing esophageal cancer, according to the reports from India.[56,57]

The most common second primary site from oral cancer is the oral cavity itself, or the mucosa of pharynx. Compared with the general population, the standardized incidence ratio is up to 14.67 folds to develop second primary site over the oral cavity/pharynx after a period of 5–10 years follow-up.[53] Another report, which is a population-based study with one-million randomized sample size from Taiwan's National Health Insurance Research Database, showed that those patients with HNSCC in Taiwan would have a significantly higher incidence to develop esophageal cancer (HR: 12.34), gastric cancer (HR: 3.54), and colorectal cancer (HR: 1.51) compared to those who are not HNSCC.[58] Generally, more than 75% patients who develop HNSCC in Taiwan would have the habit of betel quid chewing.[59] The number of oral cancer accounts for nearly 60% of HNSCC in Taiwan annually, according to 2019 Taiwan Cancer Registry Annual Report. This large sample size with one-million population-based study could roughly reflect the higher incidence rate of second primary site development among patients with oral cancer in Taiwan. Regarding the carcinogenetic effect over the liver, the report from Taiwan showed that betel quid chewing would increase the risk of hepatocellular carcinoma (HCC) in a case–control study. Those persons who chewed betel quid would have a higher incidence (OR: 3.49) to develop HCC compared to those without betel quid chewing. Furthermore, there was a synergetic effect between betel quid chewing and the infection of chronic hepatitis B virus or hepatitis C virus.[60] Basically, most studies illustrated in this manuscript are case–control studies from Taiwan. The data is produced from the oral cancer patients compared with the general population, but not from the comparison between the betel quid-related oral cancers and betel quid non-related oral cancers. The evidence was not enough to convince the readers. Indeed, it would be worthwhile to conduct the international multi-institute study in comparison of the conditions of

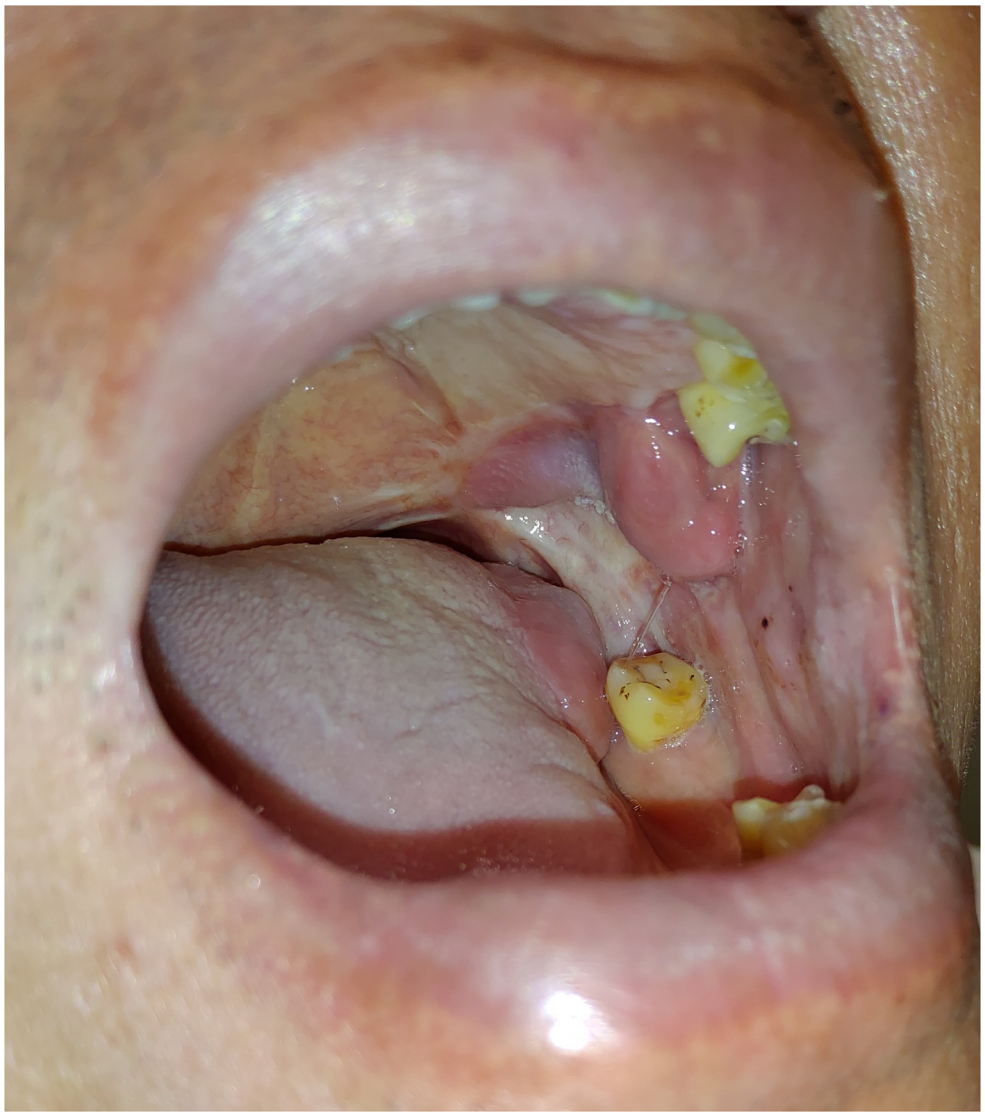

Figure 3. This patient underwent excision of the left retromolar trigone cancer and reconstruction of oral soft tissue defect by tongue flap, which was divided about 6 weeks later. Transferred tongue tissue could be found over the left retromolar trigone. Original maximal interincisal opening is well preserved. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.)

digestive tract between patients with betel quid-related oral cancer and those with betel quid nonrelated oral cancer.

Medical Conditions from Betel Quid Chewers

Increased Incidence of Gastroesophageal Diseases. Betel quid chewers have a higher chance of causing irritation over the gastroesophageal mucosa directly. This could be observed in Figure 7 in a patient who swallowed the betel juice and residues into a food pipe. Hung *et al* reported in 1994 about the phenomenon of gastric mucosa damage by betel quid chewing.[61] Additionally, the behavior of betel quid chewing would have a chance to bring these nondisinfected and raw substances with the notorious bacteria, *Helicobacter pylori* into gastrointestinal tract.[62] Such kinds of bacteria may further aggravate the condition of gastric mucosa. A gastric ulcer—or even a gastric cancer—could happen several years later if patients do not undergo treatment. However, there is no exact data reported till now about the prevalence rate of *H. pylori* infection in gastric mucosa or peptic ulcer among persons who are chewers. Notably, most patients who have the habit of betel quid chewing also have the habit of smoking, and even alcohol drinking, in Taiwan. Clinically, patients who have concomitant these three habits will have 2.99-fold risk of Barrett's esophagus, 1.60-fold risk of grade A-B erosive esophagitis, 2.00-fold risk of gastric ulcer, 2.12-fold risk of duodenitis, and 1.29-fold risk of duodenal ulcer than those without, according to a large series of cross-sectional study.[63]

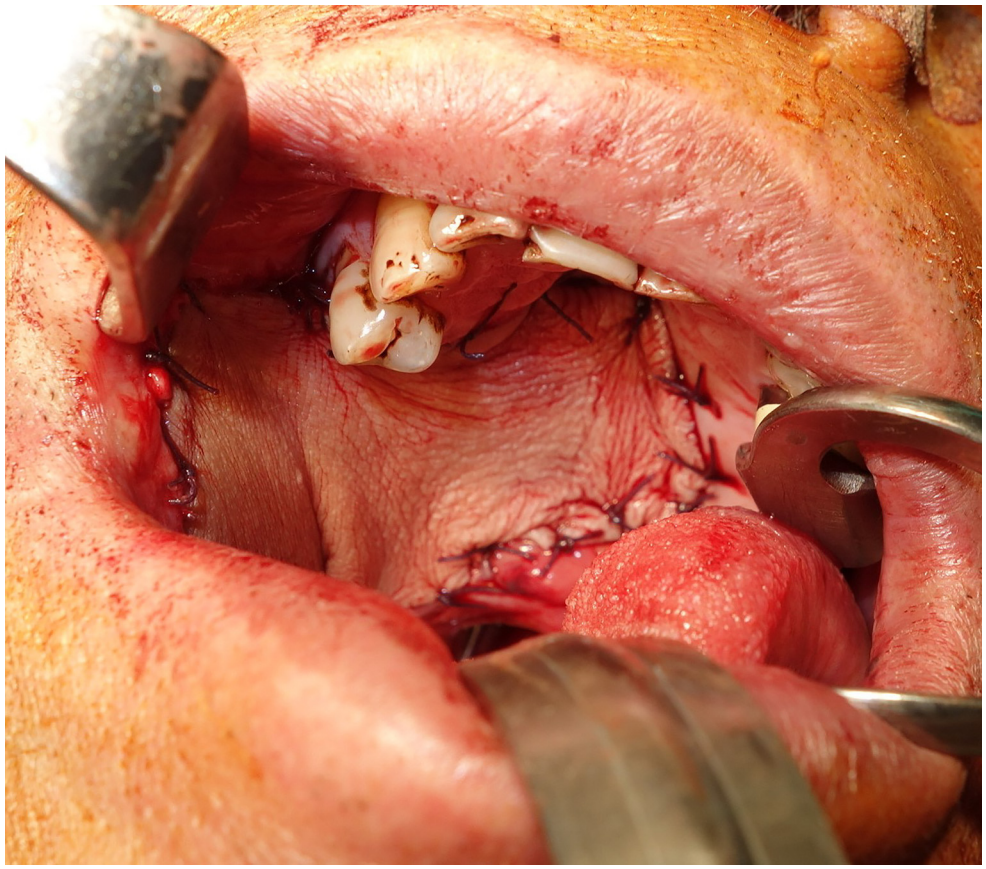

Figure 4. This patient underwent excision of right buccal cancer, which extended to mucosa of the soft palate and hard palate. Radial forearm free flap was applied to reconstruct this defect. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.)

Increased Incidence of Hypertension and Cardiovascular Disease. Arecoline is a kind of partial agonist of muscarinic acetylcholine receptors and nicotinic receptor.[4] Physiologically, the binding of arecoline to muscarine receptors would lead to parasympathomimetic effects. The behavior of betel quid chewing would increase the heart rate and systolic pressure in chewers due to central sympathetic response. However, decreased diastolic blood pressure could be noted among chewers due to peripheral cholinergic effects.[64] The study from Bangladesh showed that chewing betel quid without tobacco was associated with general hypertension and systolic hypertension after adjusting other explanatory variables.[65] Another epidemiologic report from Taiwan showed that betel quid chewing was significantly associated with hypertension in Taiwanese patients with type II diabetic mellitus and that the association was stronger in women.[66] The chewers having a higher systolic blood pressure was based on a cross-sectional study in Taiwan.[67] In addition, most betel chewers have the habit of smoking in Taiwan, and this is also a synergetic factor in leading to a higher incidence of hypertension in this cohort.

Betel chewers showed a higher incidence of cardiovascular diseases, which are shown in some epidemiologic reports. One epidemiologic study, which enrolled 56 116 participants with an 8-year follow-up, showed that relative risk of cardiovascular disease among the former betel quid chewers and current chewers was 1.56 and 2.02, respectively, compared to those without this habit after the adjustment of many variables. These authors concluded that betel nut chewing was independently associated with a greater risk of cardiovascular disease and all-cause mortality in Taiwanese men.[68] Other reports also showed the similar result that betel chewers are independently associated with heart disease among women[69] and men[70] in Taiwan. Furthermore, chewers showed a significantly higher risk of having cardiovascular disease up to 24% after further adjustment for age, education, and other significant confounders in a community-population-registry-based integrated screening program in Taiwan.[71] In the evidence from an animal model, the in vivo studies showed that arecoline from areca nut could lead to significant cardiotoxicity, heart damage, and cardiac fibrosis by inducing several hypertrophy-related signaling pathways in rats.[72,73]

Northeast India is one of the most prevalent in betel quid chewing region. Choudhury *et al* found that there may be a link between betel quid chewing and cerebral vascular disease

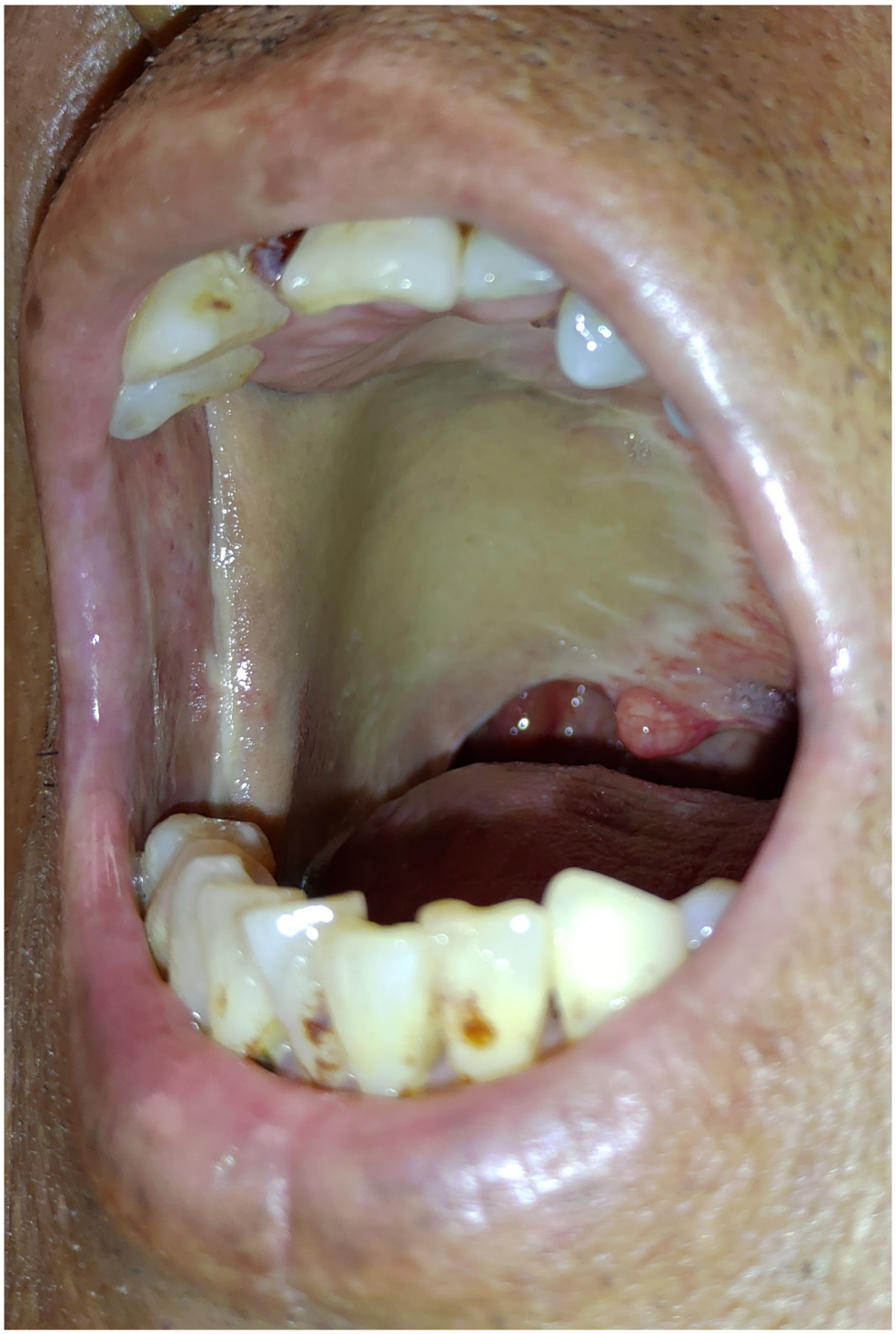

Figure 5. This patient underwent excision of right buccal cancer, which extended to mucosa of the soft palate and hard palate. Trimmed anterior lateral thigh free flap was applied to reconstruct this defect. Original maximal interincisal opening is well preserved after surgery. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.)

such as stroke in Northeast India based on clinical observation. They conducted a computational study about arecoline and showed that arecoline has the potential to block the high-density lipoprotein (HDL) receptor. These authors suggested that arecoline may have a role in the contribution of atherosclerosis.[74] This computational study for development of atherosclerosis

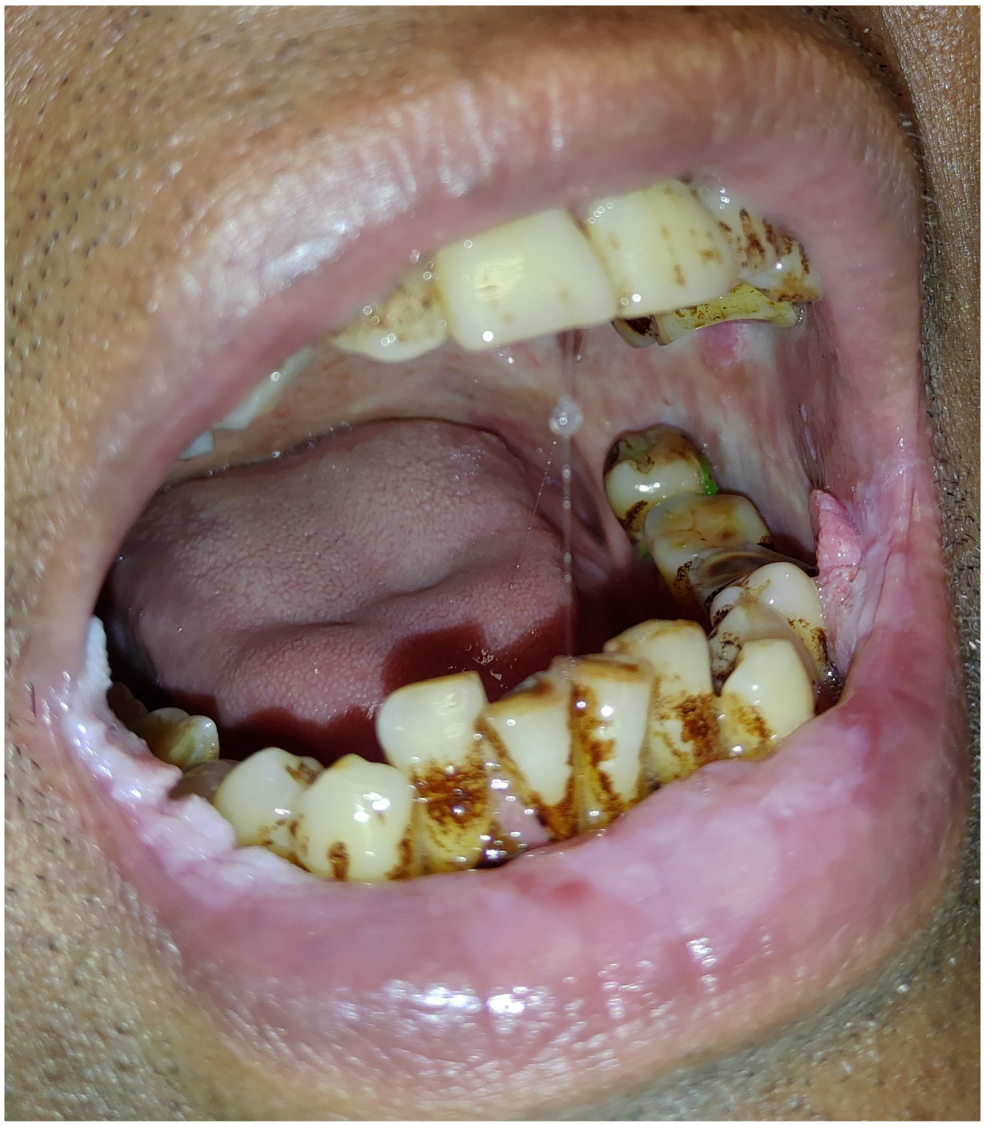

Figure 6. This betel quid chewer shows chronic periodontitis. Notably, submucosal fibrosis of oral mucosa with trismus is recorded. Right lower lip thick leukoplakia, central lower lip thin leukoplakia, and left anterior buccal small cancer are also noted simultaneously. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.)

model by arecoline should be further validated by in vivo and clinical studies.

Increased Incidence of Obesity, Metabolic Syndrome, and Type II Diabetes Mellitus. Patients with metabolic syndrome would have the concomitant conditions of higher levels of blood sugar, blood pressure, cholesterol, and triglyceride. The body shape with excess adipose tissue over the waist is also noted. In essence, those patients who have metabolic syndrome would have a greater chance of developing diabetes mellitus, stroke, and coronary artery disease. Regarding the obesity issue in betel chewers, this habit would increase the risk of obesity noted by a "2001 National Health Interview Survey" in Taiwan with an enrollment of 6126 males. In this cohort, 16.2% cases showed that the cause of obesity was suspected to be from the increased appetite after betel quid chewing.[75] Another report from Taiwan also confirmed the relation between central obesity and betel chewers.[76]

Generally, betel chewers have a higher chance of developing metabolic syndrome. There are some case–control and epidemiologic studies aiming at this issue so far. A report of a case–control study showed that betel quid chewing was an independent risk factor for having the metabolic syndrome, with the odd ratio of 1.92 in males, and 1.60 in females.[77] The case–control study from "National Cholesterol Education Program Adult Treatment Panel III" showed similar results in Taiwanese adults. The authors concluded that betel quid chewing could lead to a metabolic syndrome.[78] Furthermore, the large series of population-based study with an enrollment of 19 839 Taiwanese participants also showed that there were

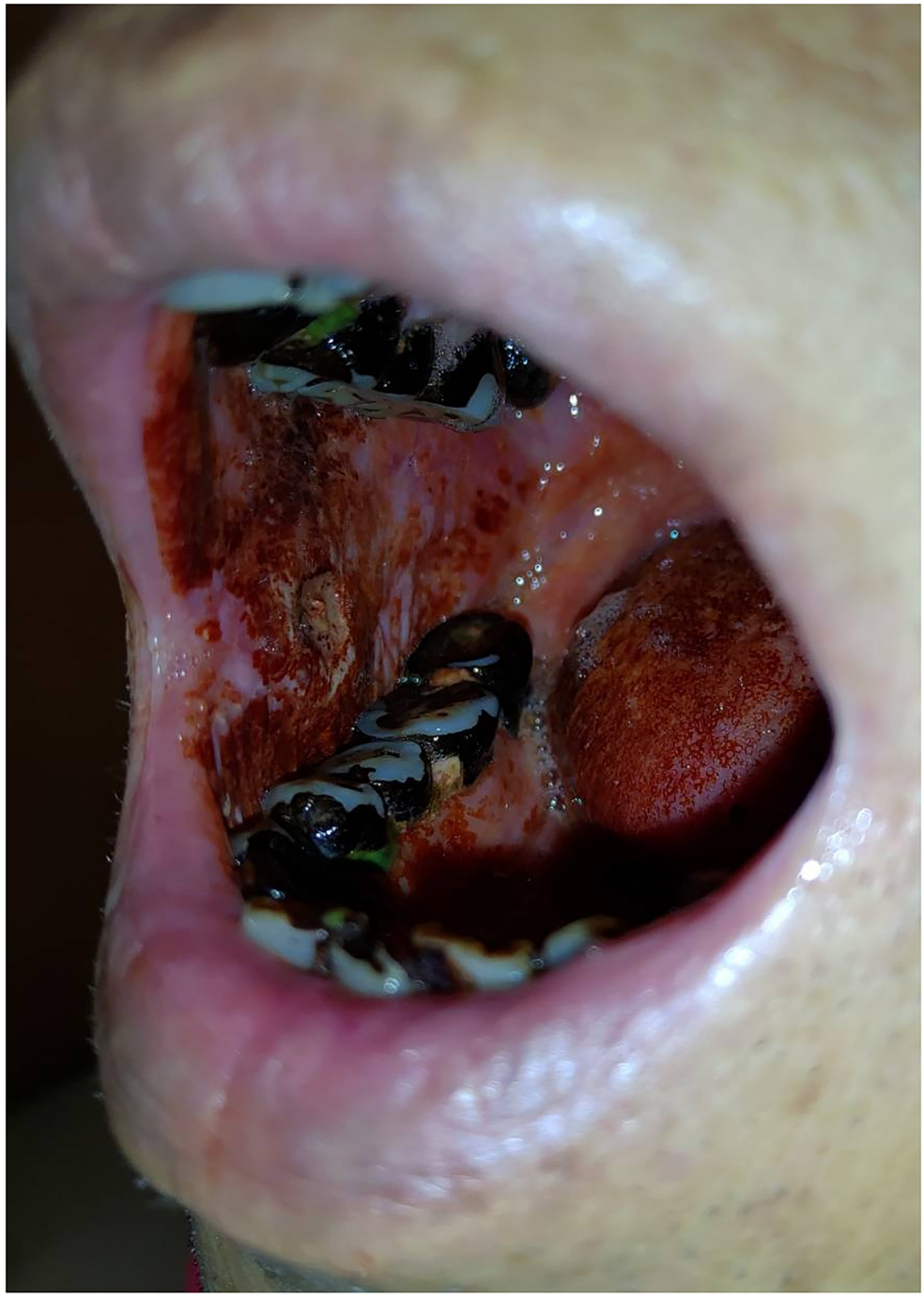

Figure 7. This betel quid chewer had right side buccal cancer. He still chewed betel quid before his visit at our outpatient office for his malignancy. The betel juice could readily coat over the oral mucosa and this ulcerative tumor. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.).

independent predictive dose-response effects in betel-quid chewing to develop metabolic syndrome after adjustment of well-known risk factors.[79] Hsu *et al* conducted an in vitro study, and they showed that arecoline could inhibit adipogenic differentiation and interfere with insulin-induced glucose uptake, which would further lead to hyperlipidemia and hyperglycemia/insulin-resistance due to fat cells dysfunction. These findings could provide more evidence about the development of metabolic syndrome from the habit of betel quid chewing.[80]

Essentially, those patients with metabolic syndrome would have a higher chance of developing type II diabetes mellitus.

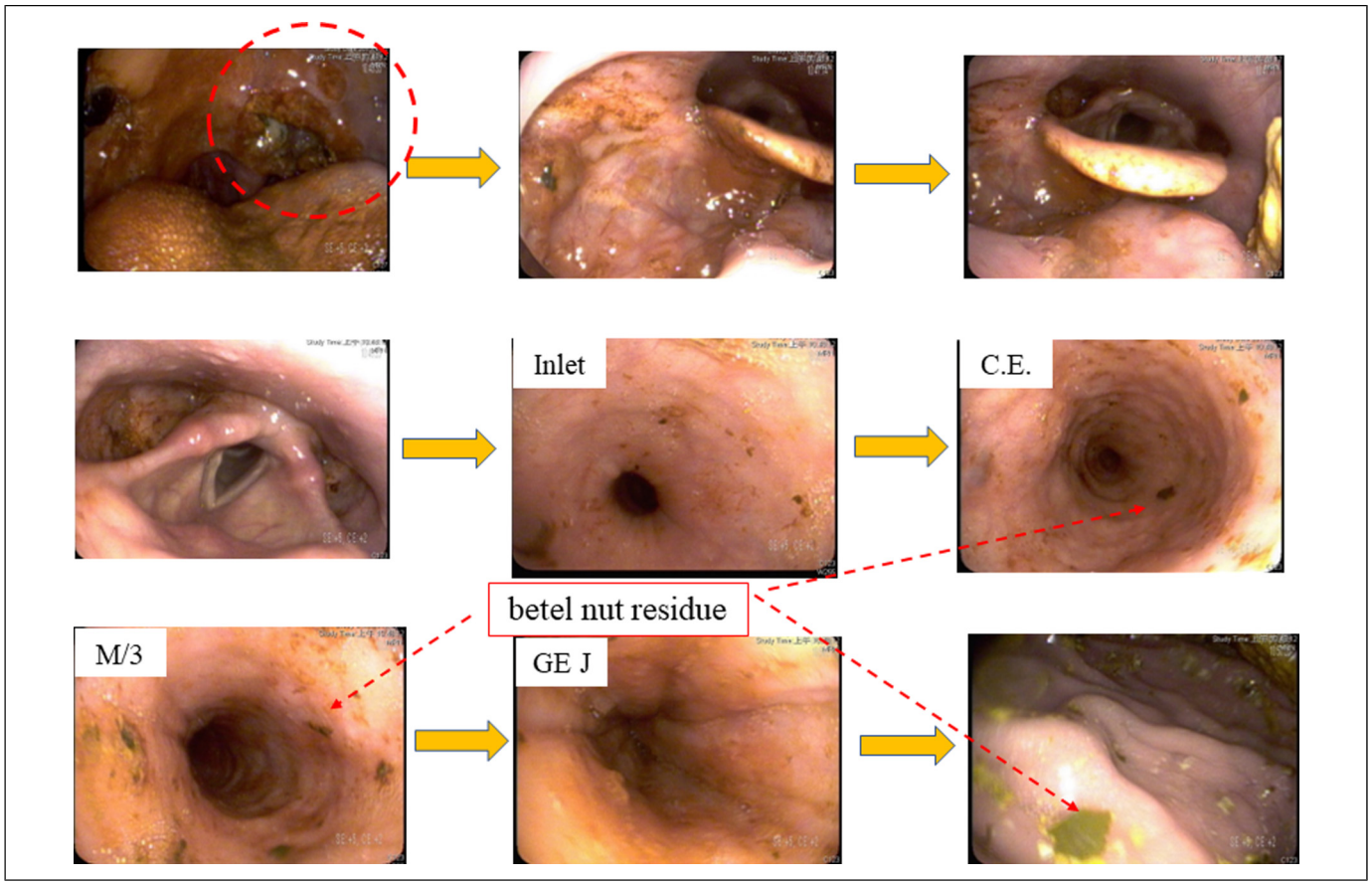

Figure 8. This betel quid chewer had left tonsil cancer with p16 negative tumor. He still chewed betel quid before his visit at our outpatient office for his malignancy. The betel juice and residues of areca nut could readily coat over the mucosa of base of tongue, epiglottis, hypopharynx, whole esophagus, and stomach. C.E., cervical esophagus; GE J, gastroesophageal junction; M/3, middle third esophagus. (This is an original figure and unpublished data. Informed consent was obtained for image use, although no personal identifying information is visible in the image.)

Tung *et al* conducted a population-based cross-sectional survey in Taiwan and showed that betel chewers had higher prevalence rates to have type II diabetes (10.3% vs 7.8%) than those without. Furthermore, this habit was an independent factor in developing type II diabetes with dose dependence and duration of chewing in Taiwanese males.[81] Another population-based study in Taiwan revealed that betel chewers among patients with diabetes mellitus were younger and more obese than never-chewers. The author concluded that this betel chewing habit is diabetogenic.[82]

Increased Incidence of Liver Cirrhosis and HCC. Aside from hepatitis B virus, hepatitis C virus, and other chemical toxins, areca nut and betel quid would also cause a significant burden of liver diseases, because the main ingredient of areca nut—arecoline—is not only a carcinogen to the oral cavity mucosa, but also may have a role in the association with a higher risk in liver diseases such as liver cirrhosis[83–86] and HCC.[60, 86–88] This risk could be synergistically additive to those of hepatitis B or C virus infections.[86] In fact, all of these studies mentioned above are community-based studies to support the relationship between liver diseases and betel quid chewing. In vitro and in vivo studies to further confirm the hepatocytes damage and carcinogenesis directly by this toxin from areca nut are few in the literature. In 1992, India researchers reported on the liver toxicity by pan masala (betel quid without betel leaf) from gavage studies in rats.[89] They found that chronic feeding of pan masala could lead to the impairment of liver function. The mechanisms of liver toxicity by arecoline are not well known. In an in vivo study, arecoline induces hepatoxicity through the induction on rat hepatic CYP2E1 and 2B.[90] Dasgupta at al. conducted an in vivo study about the arecoline toxicity in mice and found that arecoline could cause hepatotoxicity by disrupting the hepatocyte ultrastructure in mice and increase the hepatotoxic marker enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), in serum.[91] Furthermore, Wang *et al* reported an in vitro study about the toxicity of arecoline and its oxidative metabolite, arecoline N-oxide, which is ingested by chewers and is a kind of primarily oxidized substance, in the normal liver cell lines. They found that arecoline N-oxide can produce a higher incidence of liver cells cytotoxicity, DNA damage, and mutation than its parent compound, arecoline, in liver cells.[92]

Clinical Implications

Patients with betel quid-related oral cancer suffer from the local and systemic conditions from betel quid chewing including the increased risk in developing metabolic syndrome, coronary artery disease, type II diabetes mellitus, and cerebral artery disease. An increased cancer burden is also noted clinically. Basically, these comorbidities are related to chewing dose and duration but the exact dose and duration in developing these comorbidities is not fully investigated. Pretreatment evaluation is recommended to have a more detail in systemic review for these medical conditions. Regarding the surveillance over digestive tract, gastro-esophagoscopy with narrow band image (NBI), and positron emission tomography (PET) are the recommended measurements for the detection of synchronous primary sites. Abdomen sonography is helpful to survey the liver or biliary tract diseases. Swallowing and speech problems are also common among these patients after oral cancer treatment. Earlier intervention through the assistance of speech pathologist is advocative. Additionally, synchronous cancer over aerodigestive tract and undetected coronary artery disease are not rare in these patients. Multidisciplinary consultation with other cancer team members, cardiologist, neurologist, or even endocrinologist is necessary to seek for the optimal treatment strategy.

Worse survival could be observed among patients with betel nut-related oral cancer if comorbidities and synchronous cancer[93] happen in these patients. The metachronous cancer would show clinical impacts in the overall survival rate. Patients with metachronous cancer over oral cavity would be observed to have a decreased 10-year overall survival rate from 61% to 30% (calculated from the diagnosis of each primary site) if the fourth primary tumor is noted.[94] Long-term follow-up are necessary among these patients to actively survey the possible recurrent tumor or metachronous tumor to increase the long-term overall survival. The follow-up period is recommended once per year among patients who complete the treatment of oral cancer for 5 years according to the American National Comprehensive Cancer Network (NCCN) guideline. However, the field of cancerization over oral mucosa is so extensive in these patients with betel quid-related oral cancer. The return visit is suggestive to be 6 months or sooner even after the 5-year treatment in these patients. In addition, the integration of cardiologist, endocrinologist, gastroenterologist, and neurologist to form a medical team for these patients after treatment is recommended for the survivorship care if the related comorbidities develop.

The target measurements in the return visit are suggestive to follow the NCCN guideline in Head and Neck Cancers (Version 2. 2022) among patients with betel quid-related oral cancer although there are unique clinical presentations among these patients. Besides the cessation program of smoking and drinking, this program is recommended to include the betel quid chewing. In another point, active endoscopy in surveillance of the mucosa over laryngo-pharynx, esophagus, and stomach among these patients is recommended at a 6-month interval if there is a precancer lesion noted by NBI before treatment.

Conclusions

The clinical characteristics of oral cancer among betel quid chewers exhibit highly unique presentations, either locally or systemically. Aside from the local problems of trismus, periodontitis, and submucosal fibrosis of the oral cavity—which would cause poorer quality of life after treatment—patients who are betel quid chewers would also experience much more tumor burden, either synchronous or metachronous cancer, and a higher incidence of medical conditions such as hypertension, cardiovascular disease, gastrointestinal diseases, type II diabetes mellitus, metabolic syndrome, obesity, and liver diseases than those without this habit would. In clinical implication, more attention should be paid to pretreatment evaluation, treatment strategy, and posttreatment follow-up among patients with betel quid-related oral cancer due to the local and systemic conditions from betel quid chewing.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Statement

Not Applicable. Informed consent was obtained by patients for image use, although no personal identifying information is visible in any images.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Ministry of Science and Technology, ROC (grant number: MOST 108–2314-B-182A-112-MY3, MOST 107–2314-B-182A-085, and MOST 101–2314-B-182A-075-MY3).

Author's Contribution

Hui-Ching Chuang wrote this manuscript. Ming-Hsien Tsai, Yu-Tsai Lin, Ming-Huei Chou, and Kun-Lin Yang edited and reviewed this manuscript. Chih-Yen Chien designed and reviewed this manuscript. All authors gave final approval of this manuscript for submission.

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