Oral carcinoma associated with betel nut chewing in the Pacific: An impending crisis?

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Abstract:

In Western populations, tobacco and alcohol use are the major etiologic factors associated with oral cavity cancers. In developing countries of Asia and the South Pacific, however, oral cancer is increasingly associated with the chewing of betel nut. As the population of Asia and the South Pacific immigrates, Head and Neck surgeons in North America are likely to see more patients with oral carcinoma induced by betel nut chewing.

Tumor Registry records from 1977-2003 from a tertiary care, referral medical center were reviewed. All patient charts (27) demonstrating betel quid use of greater than 20 years and carcinoma of the upper aerodigestive tract were entered into the study.

Five-year disease-free rates by stage were as follows: Stage I: 100% (2/2); Stage II: 50% (2/4); Stage III: 36% (4/9): Stage IV: 25% (3 /12).

Despite the prevalent misperception in the Pacific region that betel nut chewing is a harmless habit, betel nut-induced oral carcinomas are aggressive malignancies requiring aggressive treatment and long-term follow-up.
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REVIEW PAPERS

Introduction

While tobacco smoking and the consumption of alcohol are the major etiologic factors associated with oral cavity cancers in Western populations, the chewing of betel nut quid has recently emerged in the Pacific as a potent inducer of oral neoplasia. In Asia, betel nut use has long been implicated as a risk factor for oral carcinoma1. It is estimated that between 10% and 20% of the world's population now chews betel quid, and this habit appears to be spreading from Asia throughout the Pacific[2,3]. As the population of Asia and the South Pacific immigrates, physicians in North America are likely to see more patients who chew betel quid.

Although the chewing of betel quid is practiced in several different ways in various countries, the major components are relatively consistent[2]. The areca nut, more commonly known as betel nut, is the fruit of the Areca palm tree (Areca catechu). The Areca palm is found throughout South and South-East Asia and many Pacific Island nations. The shell of the nut is removed and the seed is used either fresh or after being sun-dried. Betel nut accounts for a major portion of betel nut quid, which is composed of areca nut, betel leaf (from Piper betel) and lime, with or without tobacco[2]. The betel vines are easily cultivated in hot and humid climates. Lime is prepared from either grinding of seashells or misshapen pearls in coastal regions or from quarried stone[4]. The betel quid is prepared by mixing chopped fresh green betel nut with a paste of slaked or shell lime. The mixture is wrapped in the betel leaf. Dried tobacco may be wrapped as well or may be placed next to the quid in the mouth. The quid is chewed and kept compressed against the oral mucosa in the gingivobuccal sulcus for periods from 5 minutes to several hours. Some patients report keeping the quid in the gingivobuccal sulcus overnight while sleeping.

The constitutional effects of betel nut quid are similar to those seen in tobacco smokers. The active ingredient of areca nut is arecoline, a lipoid soluble alkaloid, which acts like nicotine[5]. Betel nut quid is reported to induce a feeling of euphoria, which overcomes sensations such as hunger, fatigue, and irritability6. It has been reported that the consciousness of habitual chewers of betel nuts remains unimpaired and their capacity for work in the hot, humid climate is substantially improved[7]. Betel nut has also been used to treat dental caries, as an antiemetic, antacid, and anthelmintic[5]. The Piper betel leaf contains an ether oil, which is responsible for the aroma and taste of the quid and the anesthetic-like effect on the oral mucosa[5]. The lime acts to release the aromatic oil from the Piper betel leaf and the arecoline from the areca nut. It also promotes the release of the red

coloring of the areca nut which gives the characteristic red lips and excess saliva production5. The lime is also the major source of the severe abrasions found on the buccal mucosa of betel nut chewers.

The prevalence and composition of betel nut quid chewing demonstrates geographic variation[2]. The prevalence of betel nut quid chewing has been reported to be as high as 90% in Papua New Guinea, with daily frequency of use ranging from 1 to 25 quid per day[8]. A survey of 10,000 patients in India reported 22 different betel quid compositions and habits[9]. The habit is more prevalent among women and is generally acquired between the age of 8 and 20, although lactating mothers have been reported prechewing quid for their infants[2]. The use of betel nut chewing is usually a habit learned from parents or coworkers[10].

The association between betel quid chewing and oral cavity malignancy is undisputed. However, due to the strong association between tobacco and site specific carcinoma, only
tobacco has been held responsible for causing cancer [11]. Unfortunately, this has led to the
erroneous belief that betel quid without tobacco is risk free. Recent studies have demonstrated genomic damage caused by areca nut consumption without tobacco[11]. Further study has demonstrated that the combination of lime with areca nut leads to the formation of reactive oxygen species[12].

A review of the English literature reveals only isolated cases of oral cavity malignancy associated with betel nut chewing Epidemiological studies have demonstrated the extensive prevalence of oral cavity carcinoma associated with betel quid chewing in Asia[2]. These studies, however, have not reported the biologic behavior of the disease and management of oral cavity carcinoma associated with betel quid chewing[2,13,14,15,16,17]. This report addresses a series of patients with betel nut-induced oral carcinoma who were treated at a Western, tertiary care referral medical center in the Pacific Region.

Materials and Methods

The Tumor Registry records of Tripler Anny Medical Center from 1975 through 2003 were reviewed. All patient charts demonstrating betel quid use of greater than 20 years and carcinoma of the upper aerodigestive tract were entered into the study.

Results

A review of the Tumor Registry charts revealed that 27 patients with oral cavity carcinoma and ahistory of betel quid chewing were treated at Tripler Army Medical Center between 1975-2003. The age range at diagnosis was 29 through 86, with the average being 53.6 years. Twenty patients were female and 7 were male. MI of the patients were from Pacific islands. Four patients were from Saipan, 11 from Yap, 11 from Palau and 1 from Pohnape. At the time of presentation, 2 patients were Stage 1, 4 were Stage II, 9 were Stage III and 12 were Stage TV. Two patients presented with bilateral disease (Table I). Eight patients had no history of substance abuse aside from betel nut quid. Seven patients additionally abused only tobacco, 4 only alcohol and 8 abused both alcohol and tobacco.

Table 1. Distribution by Clinical Stage

Stage*	No. (%) of Patients
I	2(7.41)
II	4(14.8)
III	9(33.3)
IV	12(44.4)
Total	27 (100)

**If a patient had 2 primary tumours, the higher stage was used*

The most common site for the primary tumor was the buccal mucosa (16/27). Other primary sites included the tongue (4/27), lower lip (4/27), alveolar ridge (1/27), tonsil (1/27), and the floor of the mouth (1/27). Associated sites included the mandible in 3 patients, maxillary sinus in 1 patient, hard palate in 1 patient, and retromolar trigone in 1 patient (Table 2).

Table 2. Primary and Associated sites of Tumour

Primary Sites	No. Patients
Buccal Mucosa	16
Tongue	4
Lip	4
Floor of Mouth	1
Alveolar Ridge	1
Tonsil	1
Total Patients	24

Associated Sites	No. Patients
Mandible	3
Retromolar trigone	2
Palate	1
Maxillary Sinus	1

Well-differentiated squamous cell carcinoma (SCC) was the most common pathology consisting of 13 patients. The pathology was moderately differentiated SCC in 9 patients, poorly differentiated SCC in 1 patient, verrucous carcinoma in 3 patients, and exophytic papillary SCC in 1 patient (Table 3). Fifteen patients received postoperative radiation therapy and 12 did not. At the time of the chart review, 18 patients had died of their disease and 9 patients had no evidence of disease. The average time of follow up was 43.3 months, although patients with no evidence of disease had an average follow up of only 9.4 months. The average time of survival was 35.4 months for the patients who died of their disease (Table 4). The average survival for patients who died of their disease based on staging at time of diagnosis was 75.5 months for Stage I, 21.5 months for Stage II, 24.2 months for Stage III, and 20.4 months for Stage 4.

Table 3. Pathology

Type of Pathology	No. of Patients
Well differentiated Squamous Call Carcinoma	13
Moderately differentiated Squamous Cell Caricoma	9
Verrucous Caricoma	3
Poorly differentiated Squamous Cell Caricoma	1
Exophytic Papillary Squamous Cell Caricoma	1
Total Patients	27

Discussion

The twenty-seven patients presented in this series represent the largest case series of patients with oral carcinoma associated with betel nut chewing reported in the English literature. The patients treated at Tripler Army Medical Center are referred from multiple Pacific Islands. Tripler Army Medical Center provides tertiary care for these remote island nations and therefore the population is skewed towards more advanced disease. Table 1 demonstrates that 718% of the patients treated were either Stage III or Stage IV, which probably represents late referrals from developing countries.

The most common location for oral carcinoma associated with betel quid chewing is the buccal mucosa. This is consistent with the location of the quid during chewing, which can last from 5 minutes to overnight. Direct absorption of the contents of the quid likely leads to malignant transformation of the mucosa in contact with the quid. For instance, two patients in this series had bilateral primary site disease and each patient reported chewing betel nut quid on both sides of the oral cavity.

Oral examination of patients with betel nut induced carcinoma demonstrates leukoplakia at the site of quid chewing, a physical finding similar to patients who chew tobacco. The examination of a patient with a history of long-term betel quid chewing will generally demonstrate poor dentition. An unmistakable sweet smell can also be detected when a patient chewing betel nut quid enters the office.

This series of patients has a female predominance, which is consistent with the increased prevalence of betel nut chewing among women. Tobacco and alcohol abuse is also often associated with chewing. However, females are more likely to chew betel nut quid without tobacco or alcohol use as compared to males in this series. Interestingly, females in this series having Stage HI disease survived an average of 16.5 months whereas males in this series survived an average of 46.5 months. Further, females in this series with Stage IV disease survived an average of 28.5 months whereas males with Stage IV disease survived an average of 80.6 months. These data suggest either a different tumor biology or disparate referral and treatment patterns in women compared to male patients.

The survival statistics for both genders combined do not directly correlate with the Stage of the disease (Table 4).

Table 4. Survival by stage

Stage	Number of Patients	Number Dead of Disease	Average Time Until Death (months)	Number Evidence of Disease	Average Time of Survival (months)
I	2	2	75.5	-	-
II	4	2	21.5	2	136
III	9	5	24.2	4	23.75
IV	12	9	20.4	3	104.67
Total	27	18	-	9	-

**If a patient had 2 primary tumours, the higher stage was used*

In fact, while 2/2 Stage I patients died of disease, 3/12 patients with Stage IV disease were alive at an average of 104 months. This counterintuitive finding suggests that early stage betel nut induced oral carcinomas, especially those located in the buccal region, should be treated very aggressively. (Table 5) indicates that Stage III patients with NO neck disease have a shorter survival than N+ necks. This is due to an 86-month survival of one patient with stage III disease and an N+ neck and a relatively small sample size. If this patient is excluded, the survival for the three remaining Stage III N+ neck patients is an average of 11.6 months. The Stage III NO neck patients had an average survival of 19 months. As expected, Stage IV patients with NO disease survived much longer than patients with N+ disease.

Stage I and Stage II carcinomas are usually treated successfully by perioral excision18. Because of this, the use of radiation therapy (RT) is most commonly reserved for management of advanced cancers (Stage III and Stage IV). The results of this study demonstrate that in the case of squamous cell carcinoma from betel nut use, especially those located in the buccal region, these recommendations may be insufficient. Review of the data indicates that patients with Stage I disease had diminished survival when compared to data on Stage I disease based on the statistics from the American Joint Committee on Cancer 19 (Table 5). Although Stage I patients in this series of betel nut chewers had a 100% survival rate by 1 and 5 years (versus 93.3% for 1 year and 68.1% for 5 years reported by AJCC21, both of the patients in this series died of disease by 75.5 months (6.29 years).

Table 5. Survival by Stage and Node Status (Average time of survival in months)

Stage*	N0	N+
III	5(19)	4(30.25)
IV	5(73.4)	5(25.2)

Betel nut chewers with Stage II disease not treated with radiation demonstrated a more rapid progression of their disease as well (Table 5). The published 1 year and 5 year survival rates for patients with Stage II oral cavity squamous cell carcinoma is 88.1% and 52.9% respectively19. In this series 50% of patients (2/4) had a 1 year survival rate and 0% had a 5 year survival rate, again suggesting possible under treatment due to the decision not to add radiation therapy to the treatment plan of these patients.

Stage IV patients in this series demonstrated relatively dismal survival statistics as well (Table 5). Survival rates at 1 and 5 years were 44% and 11% compared to 4 statistics for typical patients with Stage IV disease, which show 60.3% and 26.5% of patients alive at 1 and 5 years. It should also be noted that the patients in this series returned to their remote Pacific islands after treatment, and thus did not receive the normal, intensive follow-up (monthly visits and complete head and neck examinations) that normally occurs in patients treated for head and neck cancer.

Conclusion

Betel nut induced oral cavity carcinomas appear to be aggressive tumors. In particular, Stage I and II betel nut-induced oral carcinomas, especially those located in the buccal region, should be treated aggressively and adjunctive treatment modalities such as post-operative radiation therapy should be strongly considered. Given the propensity for late recurrent disease (>5 years from the time of initial treatment), continued long-term surveillance of these patients should be stressed. Perhaps most importantly, patients and physicians in the Pacific Region should not be lulled into the false preconception that betel nut chewing is an innocuous and risk-free habit.

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