

# A Study of 63 Cases of Mouth Neoplasms in Arecanut Growing Belt of Sullia

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## Abstract

**Background:** Betel nut and betel quid chewing are from major etiological factor for oral cancer. They also increase the risk of systemic diseases such as asthma, diabetes mellitus, metabolic syndrome, myocardial infarction, hypertension, and other cardiovascular diseases.

**Methods:** Sixty three patients of oral cancer in our institution during Jan. 2007 to May 2011 were included in our study. This study included 14 cases of lip carcinoma, 41 cases of buccal mucosa carcinoma, 7 cases of tongue carcinoma, and 1 case of carcinoma of upper alveolus. Duration of use of betel quid, pan masala, and gutkha were studied as well as management.

**Results:** All patients in our study have been chewing betel-quid for 6-31 years (mean 19.42 years). All of them quit betel quid and used easily available panmasala and gutkha for 4-13 years (mean 8.28 years). Nine cases of lip carcinoma, 13 cases of buccal mucosa carcinoma and 3 cases of tongue carcinoma were treated with surgery. Seven cases of lip carcinoma, 30 cases of buccal mucosa carcinoma and 5 cases of tongue carcinoma were treated with post operative or palliative radiotherapy.

**Conclusion:** Betel nut chewing with or without tobacco and lime are proven to be carcinogens in human. Direct relationship between oral cancer and betel quid, gutkha, and panmasala use has been shown in our study. As betel quid, panmasala and gutkha chewing were proven to be carcinogens, a permanent ban on manufacturing and sale of these products should be implemented.

**Keywords:** Areca; Mouth neoplasm; Tobacco; Smoking

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## Introduction

Use of betel nut and betel quid are well known in history of India [1]. The association of this habit with oral cancer was noted over a century ago; yet the chewing of betel quid in India was considered to be a comparatively innocuous practice with complete socio-cultural acceptance [1]. In recent years it has emerged as a significant public health problem in India [1]. The normal cultural practice of betel nut ended up to a health hazard when tobacco was introduced by the European settlers four centuries ago [1]. In addition to its use for smoking, as the Europeans demonstrated, tobacco somehow got mixed with betel quid and prepared to be chewed [1]. In India tobacco was culturally accepted as it was used with a culturally accepted betel quid substance [1].

During the second half of the 20<sup>th</sup> century, the causal association between chewing of betel quid with tobacco and oral cancer was well established, so it could no longer be regarded as a completely innocuous practice [2]. The major culprit was clearly tobacco in the quid; however, probably because of its 'exotic' appeal, areca nut was erroneously thought of as playing a more important role [3]. Betel nut was reported safe in many studies where only tobacco in the quid was held responsible for oral cancers [4]. Later it was clear that betel nut chewing was responsible for Oral Submucous Fibrosis (OSMF), an established precancerous condition with trismus [5].

OSMF was a rare disease in the early 80's, occurring generally among older age groups who chew betel quid frequently [6]. A later incidence of OSMF increased amongst the Indian young



**Figure 1.** Panoramic view of x-ray mandible showing infiltration of the left 3 molar



**Figure 2.** Betel leaves and betel quid (pan) being prepared.



**Figure 3.** Gutkha being sold and anti cancer propaganda on gutkha.



**Figure 4.** Oral submucous fibrosis

population as a result of increasing gutkha chewing [6]. The frequency of oral cancer has increased among young adults as a result of increasing in number of OSMF (a precancerous condition) [7]. The increasing incidence of OSMF and oral cancers during the last two decades was due to industrial manufacturing and marketing of these chewable mixtures gutkha [7]. The younger generations were targeted with multimedia advertising [7].

The incidence of oral cancer is 12.5/100,000 and the largest numbers of oral cancer patients are present in India [8]. In India, oral cancer includes 9.4

percent of all cancers [8]. This epidemic proportion of oral cancer in India is due to the rampant use of betel nut, betel quid, and gutkha and pan masala chewing which are proven to be carcinogens [8]. Oral cancer is uncommon disease in the West but continue to be the major cause of cancer related death in Indian men [8]. Over last few decades, large funds have been spent to educate public, implement laws effectively, rehabilitate tobacco growers, build cessation facility, create health care infrastructure, etc to reduce the betel nut, betel quid,



**Figure 5.** Carcinoma of the buccal mucosa with lymph node metastasis



**Figure 6.** T4 carcinoma of the buccal mucosa and tongue



**Figure 7.** Carcinoma of the upper alveolus due to chewable raw tobacco



**Figure 8.** Post operative radiotherapy in carcinoma of the buccal mucosa

gutkha and other forms of chewable tobacco usage [8].

### Materials and Methods

This is a retrospective study of 63 cases of oral cancer patients who were managed in KVG Medical College Sullia. The study was conducted during January 2007 and May 2011. Sixty three patients, 38 males and 25 females, were included in our study. The youngest patient was 47 years old and the oldest was 73. A detailed history of the patients

was taken plus oral and oropharyngeal examination. Baseline investigations were done along with routine blood and urine examinations.

Chest x-ray along with AP neck x-ray, lateral view and panoramic view were taken (Figure 1). The biopsy of the ulceroproliferative mass was taken; histopathology of all specimens showed squamous cell carcinoma. TNM staging (Tumor size, Lymph nodes, Metastasis) showed most of the cases were in advanced stages.

All of 63 patients were managed according to the oral cancer management protocol and all signed written informed consent.

All patients aged 47-73 (mean 61.67) years. The mean age in males was 61.20 years and female median age was 59.92 years. The mean duration of betel chewing in males was 18.56 years and in females was 20 years (Figure 2). All patients in our study changed to chewing packaged panmasala and gutkha which were easily available. The mean duration of panmasala and gutkha chewing in males was 8.66 years and in females was 7.36 years (Figure 3).

Thirteen males (mean 11.2 years) in our study were tobacco smokers and 12 males (mean 9.4 years) were occasional alcohol drinkers. Twelve males (mean 10.3 years) and 14 females (mean 8.4 years) were workers in tobacco processing industry.

Ischemic heart disease and hypertension were seen in 22 patients (16 males and 6 females). Diabetes mellitus was seen in 11 cases (4 females, 7 males). No other malignancies were seen in all cases. Thromboangiitis obliterans were seen in 15 male patients. Oral submucous fibrosis and leukoplakia were excluded from the study after histopathological examination (Figure 4).

Out of 63 cases, 14 had lip carcinoma, 41 with carcinoma of the buccal mucosa and 7 had carcinoma of tongue and there was 1 case of carcinoma of upper alveolus. Out of 14 cases of carcinoma of lip, 2 cases were in stage 1, 3 cases in stage 2, 7 cases in stage 3, and 2 cases in stage 4.

Out of 41 cases of buccal mucosa carcinoma, 4 were in stage 1, 11 in stage 2, 18 in stage 3, and 8 cases in stage 4 (Figure 5). Out of 7 cases of tongue carcinoma, 2 were in stage 1, no cases in stage 2, 2 cases in stage 3, and 3 cases in stage 4 (Figure 6). The case of carcinoma of upper alveolus refused treatment and was lost in follow up (Figure 7).

## Results

All Stage 1 oral cancer patients in our study were treated by wide excision only and followed up for 6 months to 2 years. Three cases of lip carcinoma with stage 2 were treated by wide excision and postoperative radiotherapy (Figure 8). Two cases of buccal mucosa carcinoma with stage 2 were widely excised and were sent for postoperative radiotherapy, 8 patients were sent for radiotherapy as they refused surgery and 1 refused radiotherapy (Table 1). Out of 7 cases of lip carcinoma with stage 3, 3 patients refused treatment and 4 had wide excision with neck dissection and postoperative radiotherapy.

Out of 18 cases of carcinoma of buccal mucosa stage 3, 7 patients underwent wide excision with neck dissection plus radiotherapy, 11 refused surgery so they were referred to radiotherapy. One case of carcinoma stage 3 had wide excision with radiotherapy and the other refused surgery but took radiotherapy. Two cases of lip carcinoma with stage 4 refused surgery so they were given radiotherapy. All buccal mucosa carcinoma patients with stage 4 refused surgery but only 2 of them received radiotherapy. All 3 cases of tongue carcinoma with stage 4 refused both surgery and radiotherapy. All patients were followed up every month.

A direct relation between oral cancer and duration of betel quid, gutkha and panmasala chewing was seen in our study. The incidence was earlier if the patient was alcoholic and smoker.

## Discussion

Betel nut may be consumed alone or as a betel quid in combination with betel leaf and slaked lime and may contain other substances like tobacco, catechu, spices or sweeteners [9, 10]. Betel leaf that is commonly consumed with this nut contains a known carcinogen named safrole [9, 10]. The lime in the betel quid enhances the extraction of the betel nut alkaloids by salivary degradation and promotes carcinogenesis [9, 10]. The alkaloids in betel nut which are responsible for the biological actions in humans are arecoline, arecaine, guvaine, and guvacoline [9, 10]. Asians and Indians even after immigrating to western countries still continue the habit of betel nut chewing which show an addiction among these populations [9, 10].

The betel nut derived alkaloids are cholinergic agonists and they affect nervous system via acetylcholine [11]. Prolonged use of betel nut causes peculiar facial and systemic features, staining of teeth, attrition of teeth, and creation of wear facets with higher incidence of periodontitis [11]. Betel nut for consumption is obtained from areca catechu which is the fourth most common addictive substance after tobacco, alcohol, and caffeine. It has 600 million users in the world [12]. It is possibly the second most consumed carcinogen after tobacco in the Indian subcontinent [12].

In India, betel nut is chewed for variety of reasons such as stress reliever, mouth freshener, improving concentration, and for digestion after food [13]. Addiction withdrawal symptoms are mood swings, anxiety, and irritability, loss of concentration, sleep disturbance and craving which were seen in most cases in our study [14]. Betel nut psychosis has been reported in heavy users following sudden cessation

**Table 1.** Incidence and management of carcinoma of the oral cavity

Stage	Carcinoma of lip	Carcinoma of buccal mucosa	Carcinoma of tongue	Total
1	2 cases	4 cases	2 cases	8 cases
	2 wide excision done	4 wide excision done	2 wide excision done	
2	3 cases	11 cases	0 cases	14 cases
		1 refused treatment		
	3 wide excision + radiotherapy	8 sent for radiotherapy as they refused surgery		
		2 wide excision and post – op radiotherapy		
3	7 cases	18 cases	2 cases	27 cases
	3 refused treatment	11 refused surgery so radiotherapy	1 wide excision + radiotherapy	
	4 wide excision + neck dissection with radiotherapy	7 wide excision + neck dissection with radiotherapy	1 refused surgery so radiotherapy	
4	2 cases	8 cases	3 cases	13 cases
	2 refused treatment so radiotherapy	6 refused treatment	3 refused surgery and radiotherapy	
		2 refused surgery so radiotherapy		
Total	14 cases	41 cases	7 cases	62

of the habit [14]. India is the greatest producer of betel nut something like 330,000 million tonnes per year (nearly half of global betel nut production) [13].

The total area under betel nut cultivation in India is estimated to be around 372,000 hectares and total production is 340,000 tonnes [13]. It is estimated that nearly 10 million people depend on betel nut industry for their livelihood in India [13]. Most of the betel nut production is consumed within India because it has limited export potential [13]. Betel nut products (gutkha, panmasala) are being advertised as mouth fresheners which are misleading Indian youth [15].

Gutkha and panmasala are more dangerous than betel nut alone because they are kept in mouth for a longer time [13]. The other promoting factors in this industry are lack of statutory warning, low cost, easy availability, attractive packaging and aggressive marketing [13]. This has increased new generation of users who are innocent adolescents and youth [13]. Panmasala is basically a preparation of betel nut, catechu, cardamom, lime and a number of natural, artificial perfuming and flavoring materials [16]. Gutkha is a variant of panmasala, in which in addition to these ingredients flavored chewing tobacco is added. Both products are often sweetened to enhance the taste [16]. Betel leaf is perishable and preparation of betel quid is somewhat complex or requires visits to shops selling Pan/BQ. With the emergence of commercial pan

masala and gutkha about three decades ago, not only did the Indian market witness massive growth in the sales of smokeless tobacco and betel nut products, but also a huge worldwide export market developed [16,17]. All our patients earlier chewed betel quid but turned to gutkha, pan masala chewing over the last two decades.

Just like tobacco, betel nut is a psychostimulant, an addictive substance and a carcinogen [13]. The cancer causing properties of betel nut have been well-reported in animal, human and epidemiologic studies [13]. Cancers caused by betel nut chewing also shows a strong dose–response relationship for frequency and duration of chewing [13]. N-nitroso compounds converted from betel nut alkaloids are responsible for oral and pharyngeal cancer [13]. Also betel nut chewing (with or without tobacco) is associated with hepatocellular carcinoma, cholangiocarcinoma, cancers of the larynx, stomach, lung and cervix in humans [13]. Betel nut is a synergistic carcinogen along with tobacco with which it is commonly consumed in India [13]. All patients in our study had betel quid and gutkha panmasala chewing as the etiology with smoking, alcohol consumption and working in tobacco processing factories as other etiologies.

The WHO and International Agency for Research on Cancer classified betel nut as a Group 1 human carcinogens with sufficient evidence of increased risk of OSMF (precancerous oral lesion) and cancers of



the oral cavity, pharynx and esophagus [17-20]. Cancers caused by betel nut chewing also shows a strong dose-response relationship for frequency and duration of chewing [18]. It is postulated that betel nut-specific N-nitroso compounds converted from alkaloids are responsible for oral and pharyngeal cancer [18]. There are several other reports that have linked betel nut chewing (with or without tobacco) with hepatocellular carcinoma, cholangiocarcinoma, laryngeal cancers, stomach, lung and cervix in humans [18].

Studies in mice have shown that, betel quid extract given by gavages produced carcinoma of lung, stomach, liver and salivary gland [18]. Fibrosarcomas at the injection site were observed by subcutaneous injections of betelnut extracts in mice [18]. Animal research has shown that panmasala in the diet led to tumors in various organs, most frequently adenocarcinoma of lung [18]. In another experiment, Arecoline was given as gavage and it produced carcinoma of lung, stomach and hemangiomas of liver [18]. Esophageal cancers increased 195 times, pharyngeal cancers 96.9 times and laryngeal cancers 40.3 times when betel quid chewers had habits of smoking and drinking [21]. Fortunately none of our patients had synchronous cancers. Betel quid chewing resulted in a statistically significant increase in the risk of overall mortality and cerebrovascular deaths in the elderly population [22, 23].

Betelnut addiction has also been found to be associated with heart attacks, arrhythmia, metabolic syndrome and diabetes [24-27]. There are reports of acute exacerbation of asthma and hypertension in betel nut chewers [28]. Chronic betel nut chewers' women give birth to low weight babies similar to smoker women [29, 30]. Betel nut and betel quid chewing has been a popular oral habit in India and many other Southeast Asian countries for a long time [31, 32]. Betel nut, betel quid and gutkha chewing habit has become the top five oral habits (including smoking, alcohol, tea, coffee, and betel chewing) in the world. There are about 200-600 million betel nut, betel quid and gutkha chewers in the world [28, 29]. They are proven carcinogens resulting in oral cancer, oral precancerous lesions, hepatocarcinoma, diabetes mellitus (DM), cardiovascular diseases and other systemic diseases [31, 32].

India accounts for 1/3 of an estimated 3 million betel and tobacco related deaths in the world per year [32]. In 2001, the sale of cigarettes was banned to people under 18 [32]. In view of high usages of betel nut, betel quid and other tobacco containing products such as gutkha and their proven

role as a carcinogen, it is necessary to look into the hazardous effects of these addictions and their impact on health and society [32]. So a ban on betel nut, betel quid and tobacco in any form is immediately necessary to eradicate the menace of the morbidity [32].

## Conclusion

Panmasala and gutkha have flooded the Indian market as cheap and convenient betel quid substitutes and become popular across all age groups wherever betel nut is abundantly used. There is sufficient evidence that chewing of betel nut with or without tobacco and lime are carcinogenic in humans.

Some restrictions on the manufacture and sale of these products are being implemented but because of seriousness of the situation, a permanent ban on gutkha and panmasala is necessary as they are well-established oral cancer causing agents. An emphasis on health education aiming to reduce and later eliminating betel nut and tobacco products should be placed.

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## Conflict of Interest

The authors have no conflict of interest in this article.

## Authors' Contribution

SMN designed the study, analyzed the data and wrote the paper. SSN contributed to data entry, literature review, writing up process, study design and analysis.

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