

REVIEW ARTICLES

Management of Oral Sub-Mucous Fibrosis: An update

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Abstract:

Oral submucous fibrosis (OSMF) is a complex, debilitating, and precancerous condition. Formerly restricted to the Indian subcontinent, it is now frequently seen in the Asian communities of the United Kingdom, the United States, and other developed countries, and thus constitutes a severe global health problem. Areca-nut, the well-known causative agent of the disease, is now recognized as a group one carcinogen. Several grading systems and management protocols have been published in the literature to deal with this progressive

disease. Despite the numerous medical methods used in oral sub mucous fibrosis management, sometimes surgical intervention becomes inevitable. Here, we extensively reviewed existing literature to discuss about incidence, presentation, aetio-pathogenesis, medical and surgical management with outcome of OSMF.

Keywords: Areca nut, Arecoline, Fibrous Band, Oral Sub-mucous Fibrosis, Reconstruction.

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Introduction:

Oral sub mucous fibrosis (OSMF) is a chronic progressive debilitating disease most frequently seen in South and South East Asia or emigrants from these areas.¹ The presentation of oral sub mucous fibrosis is now called a “potentially malignant disorder”. The progressive irreversible fibrosis of the submucosa leads to trismus, an inability to consume the average spicy food that people in the subcontinent are used to, and carries a high risk of malignant transformation.² The most widely accepted definition of the disease by Pindborg and Sirsat² is one of an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx. The definition by the World

Health Organization (WHO) of a precancerous oral condition: “a generalized pathological state of the oral mucosa associated with a significantly increased risk of cancer” fits well with the characteristics of OSMF.^{3,4} The disease is believed to be multi-factorial in origin with an elevated prevalence in individuals who chew areca-nut and a substantial rate of malignant transformation (7–30%) presents worldwide public health issues.^{5,6}

Most treatment options in OSMF focused on relieving the burning sensation and releasing fibrotic bands to help with oral opening. The release of fibrotic bands has been predictably the foundation of all surgical methods, while medical procedures focused on suppressing the inflammatory response and preventing progressive fibrosis⁷. The medical management includes multiphase injections of hyaluronidase, hydrocortisone, placental extract, and triamcinolone plus vitamin and iron supplements while various surgical modalities include release of fibrous bands and covering of the raw areas with split thickness skin grafting, bilateral nasolabial flaps, palatal island flaps, tongue flaps, temporalis myotomy and coronoideectomy.^{8,9} The purpose of this review is to discuss all of OSMF’s elements including terminology, epidemiology, etiopathogenesis and provide a short summary of medical and surgical management.

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Terminology

More than half a century has passed since **Schwartz** described oral sub-mucous fibrosis in Indian tobacco-chewing females in East Africa.¹⁰ In 1952, Schwartz described a condition in 5 Indian women that he called “atrophiaidiopathies (tropica) mucosae oris”¹¹; Joshi established the term “sub-mucous fibrosis of the palate and pillars”.¹² Pindborg and Sirsat used the term “submucousfibrosis” although they recommended that a more appropriate name would be “juxtaepithelial fibrosis”.² Other names suggested include “diffuse oral submucous fibrosis”, “idiopathic scleroderma of the mouth”, “idiopathic palatal fibrosis”, and “sclerosingstomatitis”.^{2,4} Paymaster first described its pre-malignant nature in 1956.¹³

Epidemiology

Geographically, OSMF has a specific distribution and affects predominantly Asians (and particularly Indians) from the southern states, and Taiwanese.^{14,15} Other series of OSMF in Europe, the Far East, and the Pacific Rim have also been reported.^{5,14,15} An estimate from 1996 stated that around 2.5 million individuals worldwide have OSMF.^{5,16} Furthermore, it is estimated that up to 20% of the world's population consumes betel nut in some form, so the incidence of OSMF is likely greater than in the literature released.¹⁷

Oral cancer in those who chew betel quid is one of the most prevalent malignancies in the nations of South and Southeast Asia^{18,19} and with immigration from the Indian subcontinent to the UK, USA, and South Africa, oral and maxillofacial surgeons in these countries are likely to encounter the disease.⁵ According to a 2009 survey targeting all men and women aged 15 years or more in Bangladesh, betel was used by both men (23.5%) and women (25.2%).²⁰ Recent investigations into betel quid chewing in the UK have found the habit to be widespread among Bangladeshis.^{21,22} Previous studies showed that 95% of Bangladeshi women in West Yorkshire chewed betel quid, of whom 89% added tobacco where in Birmingham, 96% of Bangladeshi women and 92% of Bangladeshi men reported chewing betel quid, of whom 81% of the women and 37% of the men added tobacco.^{22,23}

Epidemiological data and intervention studies suggest that areca nut (Supari) is the main etiological factor for OSMF.²⁴⁻³⁸ Areca nut is believed to be the fourth most

addictive substance in the world⁽¹⁷⁾. Other etiological factors suggested are chilies, lime, tobacco, nutritional deficiencies such as iron, zinc, and copper, immunological disorders, collagen disorders, and genetic predisposition.

There is a wide variation in the range of ages as reported by various authors. Pindborg et al. reported average age range as 53.6 years for males and 37.7 years for females²⁹ however, recent authors, report incidence of OSMF mostly in the younger population age ranging from 20 to 30 years.^{12,30-33} In a study reported by Babu et al. and Trivedy et al. on OSMF, 23% of patients were of ages between 14 and 19 years.^{34,35} In another study by Anuj Jain⁽³⁶⁾ stated that the youngest patient reported to be suffering from OSMF was of 2.5 years old. The precancerous nature of oral sub-mucous fibrosis has been observed with development of slowly growing squamous cell carcinoma in one-third of oral sub-mucous fibrosis patients according to Paymaster.¹³ Recent studies have shown that as many as 19% of oral sub-mucous fibrosis patients develop oral carcinoma^{37,38} but other studies claim that the malignant transformation rate of OSMF is 7 to 30 percent.^{2,39,40}

Etiopathogenesis

OSMF was initially believed to be idiopathic, but epidemiological data and intervention studies suggest that it has multifactorial in origin and areca nut (Supari) is the main etiological factor for OSMF.²⁴⁻²⁸ Areca nut is believed to be the fourth most addictive substance in the world.¹⁷ Other etiological factors suggested are chilies, lime, tobacco, nutritional deficiencies such as iron, zinc, and copper, immunological disorders, collagen disorders, and genetic predisposition. A possible autoimmune role and genetic predisposition for the disease (OSMF) with demonstration of various auto-antibodies and an association with specific HLA antigens A10, DR3, DR7, and probably B7, along with haplotypic pairs A10/DR3, B8/DR3, and A10/88, has been found.^{42,43}

However, there have been overwhelming proof from multiple epidemiological studies, large cross-sectional surveys, case-control studies, and cohort and intervention research that areca-nut is the major etiological factor in OSMF.^{25-28,30,43-50} Four alkaloids have been conclusively identified in biochemical studies, arecoline, arecaidine, guvacine, and guvacoline,

of which arecoline is the main agent. Arecoline an alkaloid component of areca nut, stimulates fibroblastic proliferation and collagen synthesis. Flavonoids (tannins and catechins) inhibit collagenase, stabilize fibrils of collagen and make them resistant to collagenase degradation.^{14,43,51-53}

An initial epithelial inflammation is followed by fibro-elastic changes in the lamina propria.^{18,45} Dense fibrotic bands are formed by epithelial atrophy and collagen deposition. Over activity during chewing creates ischemic changes. The subsequent fibrosis and scarring of the masticatory muscles further lead to the formation of fibrotic bands and trismus. These bands are visible in the palate, buccal and labial areas and, in later stages, in the pharyngeal and oesophageal areas.⁵⁴

Clinical Features

Initially, most patients present with a burning sensation or intolerance to spicy food, and they may have vesicles, particularly on the palate. Ulceration and dryness of the mouth is later followed by fibrosis of the oral mucosa, which leads to rigidity of the lips, tongue, and palate, and trismus.¹⁴ Petechiae, in the absence of blood dyscrasias or systemic disorders, are found in about 22% of patients with OSMF, occur most often on the tongue followed by the labial and buccal mucosa.^{4,55}

A useful clinical sign is pain on palpation in the sites where submucosal fibrotic bands are developing, and trismus is caused mostly by fibrosis in the dense tissue around the pterygomandibular raphe.⁵⁵ Fibrosis of the eustachian tube may lead to deafness.^{5,56} When the fibrosis involves the nasopharynx or esophagus, patients may experience referred pain to the ear, a nasal voice, and dysphagia to solids; usually these are features of more advanced disease.^{5,55}

The most obvious clinical signs include blanched, opaque oral mucosa with palpable fibrous bands.^{14,57,58} Furthermore, the overlying epithelium may become dysplastic and malignant.

Histopathology

Histopathology (HP) does not seem to play a much significant role in the diagnosis of OSMF as most clinicians diagnose OSMF based on clinical findings. However, this does not undermine in any way importance of HP studies. The early histological changes present as chronic inflammatory cell infiltration of sub

epithelial connective tissues. This otherwise non-specific infiltrate usually contains a number of eosinophils, which are not usually found in oral inflammation.⁵⁹ This is followed by a strong fibro-elastic response resulting in the formation of fine, fibrillar collagen bundles. The histological changes in established cases include atrophy of the epithelium, together with a keratinizing metaplasia and the accumulation of hyalinized subepithelial collagen and a progressive loss of vascularity.⁵⁹ Canniff⁶⁰ found that 87% of 44 patients with oral sub mucous fibrosis showed an atrophic epithelium, the epithelium in 67% had undergone a keratinizing metaplasia, 27% showed mild atypia and 100% showed presence of juxta-epithelial collagen.

Very affordable immunohistochemistry in the form of Silver binding nucleolar organiser regions (AgNORS) also known as "poor man's Immuno" can be used for prognostication of Oral Submucous fibrosis (M A Nusrath 1997, Thesis Masters Course, University of Gujarat, India). Comparison of moderate OSMFS with advanced OSMF was significant with a t value of 3.62 and p being <0.005. Comparison of advanced OSMF with moderately diff SCC was significant with a t value of 3.02 and p being <0.005. The study along with other numerous studies showed that AgNORS can be used for prognostication of OSMF and were good alternative for immune especially for developing countries.

Staging

To aid in treatment planning Khanna and Andrade⁶¹ developed a classification system of OSMF based on inter incisal opening (MIO) as follows:

& Group I: This is the earliest stage and is not associated with mouth opening limitations. It refers to patients with an inter incisal distance of greater than 35 mm.

& Group II: This refers to patients with an inter incisal distance of 26-35 mm.

& Group III: These are moderately advanced cases. This stage refers to patients with an inter incisal distance of 15-26 mm. Fibrotic bands are visible at the soft palate, and pterygo-mandibular raphe and anterior pillars of fauces are present.

& Group IV: Trismus is severe, with an inter incisal distance of less than 15 mm and extensive fibrosis of all the oral mucosa.

& 'Group IVB: Disease is most advanced, with premalignant and malignant changes throughout the mucosa.

Pindborg et al⁶² described consecutive stages of oral sub mucous fibrosis based on histologic findings: very early stage, early stage, moderately advanced stage, and advanced stage.

S. M. Haider et al⁶³ gave the following staging system:

Clinical and Functional Staging

Clinical Stage

1. Faucial bands only
2. Faucial and buccal bands
3. Faucial, buccal, and labial bands

Functional Stage

- A Mouth opening 20 mm
- B Mouth opening 11-19 mm
- C Mouth opening 10 mm

Management

The management of an OSMF patient depends on the degree of clinical involvement. It comprises of: discontinuation of areca-nut related habit, nutritional support and antioxidants, physiotherapy, immuno-modulatory drugs (steroids) for local/systemic application, intra-lesional injections of steroids,

hyaluronidase, human placental extracts etc, either singly or in combination for early/milder form of disease and surgical measures for advanced cases with post-operative nutritional support and anti-oxidants along with active physiotherapy to prevent contracture at the surgical site and recurrence.⁵⁴

Medical management

The noninvasive treatment regimens include dietary supplementation with iron, Vitamin A or Vitamin B and anti-inflammatory agents like steroids as well as injection of degradative enzymes to facilitate fibrous tissue removal. This may give temporary relief but aggravates fibrosis because of the multiple needle insertion and irritation from the drug.⁶⁴ The medical management is palliative therapy which is not going to reverse the condition completely.⁶⁵ Patient has to quit the habit, along with long duration of medication will benefit in mild to moderate way which is not up to the satisfaction of patient or original mouth opening^{66,67} It will be useful in some extent only; if patient is in stage I transition where the burning sensation for hot spicy foods is started but no limited of mouth opening will be benefited.⁶⁸

The medical management has been summarized in the following table given by Auluck et al⁶⁹

Table-I

Treatment modality for OSF (Auluck et al. 2008)

Treatment	Treatment Details
Micronutrients and minerals	Vitamin A, B complex, C, D and E, iron, copper, calcium, zinc, magnesium, selenium and others
Milk from immunized cows	45 g milk powder twice a day for 3 months
Lycopene	8 mg twice a day for 2 months
Pentoxyfilline	400 mg 3 times a day for 7 months
Interferon gamma	Intralesional injection of interferon gamma (0.01- 10.0 U/mL) 3 times a day for 6 months
Steroids	Submucosal injections twice a week in multiple sites for 3 months/ Topical for 3 months
Placental extracts	
Turmeric	Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months
Chymotrypsin, hyaluronidase and dexamethasone	Chymotrypsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4mg), twice weekly submucosal injections for 10 weeks

Micro nutrients and minerals

Few studies conducted in the previous decade observed that Vitamin A given at a concentration of 50,000 IU would cause symptomatic improvement^{64,70,71} On the other hand Reddi⁷² suggested that Vitamin E given concomitantly with the Hyalase and betamethasone was better than as compared with Hyalase and betamethasone alone. It was believed that Vitamin C reduces the edema between the collagen bundles and helps in regeneration of new collagen bundles with good approximation.⁷³ Other than vitamins several minerals also have been used as an adjunctive in treatment of OSMF. Anil et al.⁷⁰ administered Zinc (220mg) in combination with vitamin A and observed good results. Zinc plays essential role in DNA synthesis and cell division.

Antioxidants

Gupta et al.,⁷⁴ carried out a study on 34 cases of OSMF. They have advocated one tablet of antioxidants thrice daily for 6 weeks and observed improvements and amelioration of the symptoms. Kumar⁷⁵ advocated Lycopene (16mg) and concluded that it produced better response. The process of carcinogenesis is known to occur through the generation of Reactive Oxygen Species, which acts through the initiation of lipid peroxidation (LPO). Antioxidants are used to prevent LPO-mediated harm and it has also been reported that antioxidant supplementation can effectively treat oral premalignant lesions.⁷⁷

Steroids

Sinha and Jain⁷⁷ have tried local injection of hydrocortisone 1.5 cc and found hydrocortisone to be effective. Moreover Kakar et al.,⁷⁸ found that injection of Dexamethasone (4 mg) and 1500 IU of hyaluronidase locally for 7 weeks gave superior results if it is followed by 3 weeks of hyaluronidase.

Enzymes

Collagenase is a lysosomal enzyme, Lin and Lin⁷⁹ found that intralesional injection of collagenase resulted in significant improvement. Gupta and Sharma⁶⁶ gave injected Chymotrypsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg) twice weekly for 10 weeks sub-mucosally and observed good results.

Vasodilator

Occlusive blood vessels encountered in OSMF restrict nutrients and therapeutic substances from reaching the affected tissue, which may be one of the reasons for the unsatisfactory therapeutic effect of drug treatment of OSF. Lai (1995)⁸⁰ has carried out treatment for OSMF using buflomedial HCL (3 tablets of 450 mg each per day) and topical trimacoloneacetone 0.1% on mucosal ulcers at bed time and observed positive results. Rajendran (2006)⁸¹ used pentoxifylline, a methylxanthine derivative that has vasodialating properties. It was administered as 400 mg thrice daily for a period of more than 12 months and observed improvement in symptoms of OSMF. Buflomedial HCL (peripheral vasodialator) has been found to affect the tissues in diffuse fibrosis to a noticeable degree by the relief of local ischemic effect.⁸²

Placental extract

The injection placentrax is an aqueous extract of human placenta. The action of placental extract is essentially biogenic stimulation and its use is based on the tissue therapy method⁽⁸²⁾. Ramanjaneyalu and PrabhakarRao (1980) advocated 2 cc placentrax injection at weekly interval for 10 weeks. They have found it to be superior to Cortisone. They have even found two cortisone resistant cases responded well to placentrax.⁸³

Furthermore Katharia et al., (1992) also carried out a study on 22 OSMF patients and injection of 2ml Placental extract (Inj. Placentrex) was given locally in the predetermined areas, once a week up to a total duration of one month. Effects were monitored in reducing the severity of the disease.⁸⁴

Physiotherapy

Cox and Zoellner (2009) advocated five times daily physiotherapy by inter-positioning tongue spatulas between teeth and adding a new spatula every 5–10 days for 4 months and observed improved oral opening.⁸⁵

Surgical management

Management of stage III and IV patients is challenging in terms of restoring inter-incisal distance. A wide range of treatments such as medicinal management, surgical therapy, and physiotherapy have been discussed in literature but with varying results.^{1,9,86} Surgical treatment is indicated in patients with severe trismus and/or biopsy results revealing any dysplastic or neoplastic changes. Surgical modalities that have been

used include the following: Simple excision of the fibrous bands, excision of bands with myotomy with or without coronoideectomy, coverage of the raw area with skin grafts, fresh amnion, collagen membrane, buccal pad of fat, local flaps or vascularized free flaps, followed by active post-operative jaw physiotherapy with anti-oxidants and proper nutrition and regular follow-ups to ensure maintenance of oral opening and early detection of malignant changes if any.⁵⁴

Use of lasers for band excision also has been documented. The most common lasers used in primary incision were the ErYCCG laser⁸⁷, KTP 532⁸⁸, and the diode lasers.⁸⁹

Interpositional Grafts (Flaps)

Use of interpositional grafts in areas of band excision have been the most widespread methods of surgical intervention in OSF. Common intraoral flaps are Tongue flaps, Palatal island flaps and Buccal fat pad; on the other hand Nasolabial flap and Temporalis fascia flap are most commonly used as extra oral flaps.⁷

Tongue flap- The use of a tongue flap is rather surprising in the treatment of OSMF. Apart from the short-term morbidity of the donor site in terms of speech and mastication, post-operative fibrosis and constriction of tongue mass can have deleterious effects on the lifestyle of the patient. The single longest follow up of surgically treated cases was published by Mehrotra et al.¹ The authors used the tongue flap procedure for interpositional graft stabilization in 60 OSF patients over a 7-year period. The authors reported good maintenance of oral opening and graft health extending through the follow up period.¹ The bilateral tongue flaps cause severe dysphasia, disarticulation and carry the risk of post-operative aspiration. Also they provide limited amount of donor site tissue as their reach is inadequate. The stability of tongue flap and dehiscence are the common post-operative complications of uncontrolled tongue movement apart from this; reported involvement of the tongue is 38 % which precludes its use for reconstruction.⁶⁶

Palatal island flap- The palatal flap based on the greater palatine artery was used by Golhar et al⁹⁰ in 33 patients of their series of 100 cases. This technique, accompanied with bilateral Temporalis myotomy and coronoideectomy, was a highly effective surgical procedure.⁶¹ However, use of island palatal flap has limitation such as its

involvement of donor site fibrosis and second molar tooth extraction required for flap to cover without tension.^{24,68}

Buccal Fat Pad- The buccal fat pad is a mass of specialized fatty tissue which is distinct from subcutaneous fat. It is termed **syssarcosis**; it enhances intermuscular motion. It consists of a main body and five extensions: buccal, pterygopalatine, pterygomandibular, superficial and deep temporal. The body is centrally positioned and is located above the parotid duct and extends along the anterior border of masseter muscle. It courses medially to rest on the periosteum of the posterior maxilla and overlies the uppermost fibres of buccinator muscle. The buccal extension lies superficially within the cheek. The superficial and deep temporal extensions reside in the temporal region.⁹¹ Yeh described the application of pedicled buccal fat pad after incision of fibrous bands and suggested that this was a very logical, convenient, and reliable technique for treatment of oral submucous fibrosis.⁹²

The numerous advantages of employing buccal fat pad include ease of accessibility through the very incision used for creating surgical defect, thereby obviating the necessity of an alternative donor site and its ensuing morbidity. The buccal fat pad as a donor tissue is not involved in the pathological process unlike other donor tissues such as the tongue or palate. It also improves the physiological functions of cheek by regaining its suppleness and elasticity post surgically.⁹² Buccal fat pad serves as a good substitute, because it provides excellent function without deteriorating the esthetics and the results obtained were sustained long term. Thus Lai DR et al considered this as the quickest and most efficient form of therapy for OSMF patients with severe trismus to ensure long-term improvement in mouth opening.⁹

Nasolabial Flap- The nasolabial flap proved to be the most popular procedure used in the surgical treatment of OSMF. Apart from the easy accessibility, the availability of a healthy vascular pedicle based on the inferior nasal vessels and the possibility of using this flap to cover almost all regions in the oral cavity make it a well justified choice for the treatment of OSMF.⁷ The nasolabial flap is typically classified as an axial pattern flap based on angular artery. It can be based superiorly or inferiorly. Most of the studies using the nasolabial

flap reported post-operative oral openings of over 35 mm at the end of the follow up periods which ranged from 1 to 36 months. In the single largest study using nasolabial flaps David Tauro⁹³ reported satisfactory oral opening of 40 mm postoperatively in his series of 85 cases. The common complications following this flap have been scars in the facial region, decrease or accentuation of the nasolabial fold and development of hair on the flap tissue in the intraoral region and also it cannot be extended adequately to cover the raw area.⁹⁴

Temporalis Fascia Flap- The flap seems to be the least popular amongst all facial flaps preferred. Janjua et al⁹⁵ carried out this technique on five patients and reported good results. The procedure involved detachment of the masseter muscle insertion in the zygomatic arch and temporalis attachment to the coronoid process before the flap was raised. The flap was then covered with a split skin graft. All five cases reported satisfactory uptake and maintained vascular supply.⁹⁵

Distant Flaps - Interestingly use of free flaps for surgical management of OSMF has been reported only from the Chinese subcontinent with no reports available from other regions of the world. Five studies using a split technique of a radial forearm free flap from a single donor site and a single study using a similar split flap harvested from anterolateral thigh based on the lateral dorsal circumflex artery have been described. All the studies reported common complications of aberrant microvascular stenosis in the anastomoses and need for debulking at a later stage.^{93,96}

Use of Grafts- Split skin grafts (SSG), collagen membranes and artificial dermis, human placenta and amnion have been the common materials preferred in the grafting of mucosal defects in the surgical management of OSMF.^{95,97,98} The use of SSG, and allogenic materials is purely supportive and protective in the post-operative healing period. The use of commercially available dermis and collagen seems to be gaining popularity due to the ready availability and the decreased incidence of morbidity in donor sites when harvesting SSG.^{97,98}

Fibrin glue is a biological tissue adhesive based on the final stage of coagulation wherein Thrombin acting on fibrinogen converts it into fibrin. Thus, it has two components, fibrinogen and thrombin obtained from patient's own blood. Use of the fibrin glue is simple,

safe, cost effective, and rapid technique. Its use to cover the raw areas after excision of fibrous bands is being tried at various institutes.⁵⁴

Absorbable Atelocollagen Membrane is available as a sterile, pliable surgical porous scaffold agent made of highly purified type I atelocollagen derived from porcine skin. It is being used for coverage of the raw areas in non-healing and burn wounds. Its advantages include, bleeding control and stabilization of the blood clot, acceleration of the wound healing process, provides matrix for tissue ingrowth, can be cut to fit any size wound, soft and conformable to wound site, maintains integrity in moist state, leaves wound free of fiber. Its use in OSMF is being tried in many institutes and long term results are awaited.⁵⁴

Oral sub mucous fibrosis is one of the most unsatisfactorily treated diseases and definitely established as a pre-malignant oral condition so there is an urgent need to initiate public health education measures to educate people about these debilitating oral pre-malignant condition before it is too late. Dentists can play a significant part in educating patients about the dangers of betel quid chewing and in the early diagnosis of such high-risk premalignant lesions and cancer. Regular oral checkups for pre-cancer and cancer should be conducted frequently during periodic oral examinations. Treatment must be combined with discontinuation of betel quid / tobacco chewing active jaw physiotherapy to correctly control early and advanced phases of OSMF.

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