Overview

Oral Cavity Cancer in the Indian Subcontinent — Challenges and Opportunities

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Abstract

Oral cavity cancer (OCC) poses a global challenge that plagues both the Orient and the Occident, accounting for an estimated 350 000 new cases and 177 000 deaths in 2018. OCC is a major public health problem in the Indian subcontinent, where it ranks among the top three cancer types in both incidence and mortality. Major risk factors are the use of tobacco, betel quid and alcohol consumption. OCC is a heterogeneous group of multiple histologies that affects multiple subsites. The oral cavity includes the lips, buccal mucosa, teeth, gingiva, anterior two-thirds of the tongue, floor of the mouth and hard palate. OCC is defined as cancer of lips, mouth and tongue as defined by the International Classification of Diseases coding scheme. The epidemiology, aetio-pathogenesis and treatment philosophy are similar within this group. Although salivary gland malignancies, sarcomas, mucosal melanomas and lymphomas can also arise within the oral cavity, this review will focus on squamous cell cancer, which is the predominant histology in OCC. We review and contrast data from developing and developed countries. We also highlight the unique regional challenges that countries in the East face; citing India as an example, we elaborate on the opportunities and scope for improvement in the management of OCC.

Epidemiology

Worldwide, oral cavity cancer (OCC) has crude and age-standardised rates of 4.6 and 4 per 100 000 population, respectively. Geographic diversity is evident by the varying age-standardised rates for incidence and mortality across the globe (see Table 1). Oral cancer is one of the highly prevalent cancers and a leading cause of mortality in countries like India, the Taiwanese region, Sri Lanka, Pakistan and Bangladesh, accounting for nearly one-third of all cancers [1]. In India alone, an estimated 120 000 new patients with OCC were diagnosed in 2018, of which about 72 000 patients died. OCC is one of the three most common cancers in the country, with an age-standardised rate of 7.2 per 100 000 population compared with 3.8 in Asia [2]. The Taiwanese region also has one of the world's highest incidence rates of OCC. In 2014, 8270 new cases were diagnosed, with 2925 deaths in Taiwan, accounting for 8.0% of all new cancers diagnosed and 6.3% of all cancer deaths [3].

The gingivobuccal region is the commonly involved subsite in the South-East Asian subcontinent, whereas tongue and floor of mouth cancers are more common in the Western world [4]. Also, patients from the developing nations present a decade earlier than those from the Western world. Within India, the age adjusted rates for tongue cancer are highest in the north-east states and a few northern states, such as Uttar Pradesh, compared with the rest of the country [5,6]. Population-based cancer registries have also shown increased age adjusted rates of OCC in young males, especially in the western region followed by the north region [7]. These differences in incidence and pattern can be attributed to ageing of the population as well as some regional differences in the prevalence of specific risk factors. Although the West has seen a decline in the incidence of OCC over the last 25 years, which could be attributed to reductions in the consumption of tobacco and alcohol [8], India has witnessed an increase in incidence over the last two decades [3,7].

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Table 1
Regional differences in oral cavity cancer incidence and mortality (data from the International Agency for Research on Cancer)

Region	Incidence			Mortality		
	Number	Crude rate*	Age-standardised rate*	Number	Crude rate*	Age-standardised rate*
India	11 992	8.9	9.1	72 616	5.4	5.6
South-Central Asia	159 750	8.1	8.7	98 851	5.0	5.4
Asia	227 906	5	4.3	129 939	2.9	2.4
Europe	61 885	8.3	4.4	24 063	3.2	1.7
North America	27 112	7.5	4.3	5198	1.4	0.72
World	354 864	4.6	4.0	177 384	2.3	2.0

* Rates per 100 000.

The GLOBOCAN data may underestimate the true incidence, as rural populations are under-represented in these cancer registries. Data from the Million Death Study, which is more nationally representative, showed that the age-standardised mortality rate for head and neck malignancies was 22.1 compared with 8.2 according to the GLOBOCAN data [9].

The public health importance of OCC in India is multi-faceted. Most of the affected patients belong to the lower socioeconomic strata, who are at a higher exposure to risk factors such as the use of tobacco. Also, patients from rural areas in middle- and low-income countries have limited access to trained providers and health services [10]. This leads to delays in diagnosis and referral, which result in an advanced stage at presentation with reduced survival and greater costs to the patient [11,12].

Aetiology

The main risk factors related to OCC are tobacco and alcohol use, independent of the type of tobacco used or alcohol consumed, with a synergistic association. Other risk factors reported include oral hygiene, hot beverages, human papilloma virus, genetic and dietary factors [13,14].

Tobacco, smoked or smokeless, has been consistently shown to increase the risk of developing OCC. The risk of developing OCC is three times higher in smokers compared with non-smokers. In addition to promoting poor oral hygiene, smoke contains carcinogens such as nitrosamines, benzo-pyrenes and aromatic amines, which promote the formation of free radicals and DNA adducts, leading to carcinogenesis [15].

Tobacco smoking trends show geographic variation (see Figure 1); while the smoking prevalence rates have substantially decreased in several countries in North America, western and northern Europe, about 60% of the world's current smokers live in three Asian countries alone: China (317 million smokers), India (122 million smokers) and Indonesia (115 million smokers). In Canada and the USA smoking rates reduced from >55% in men in the 1950s and >35% in women in the 1970s and 1980s to <20% in men and <15% in women in 2012. In the UK, smoking rates decreased from >80% in men in 1950 and about 40% in women in the 1970s to 20% in both sexes in 2012 [16].
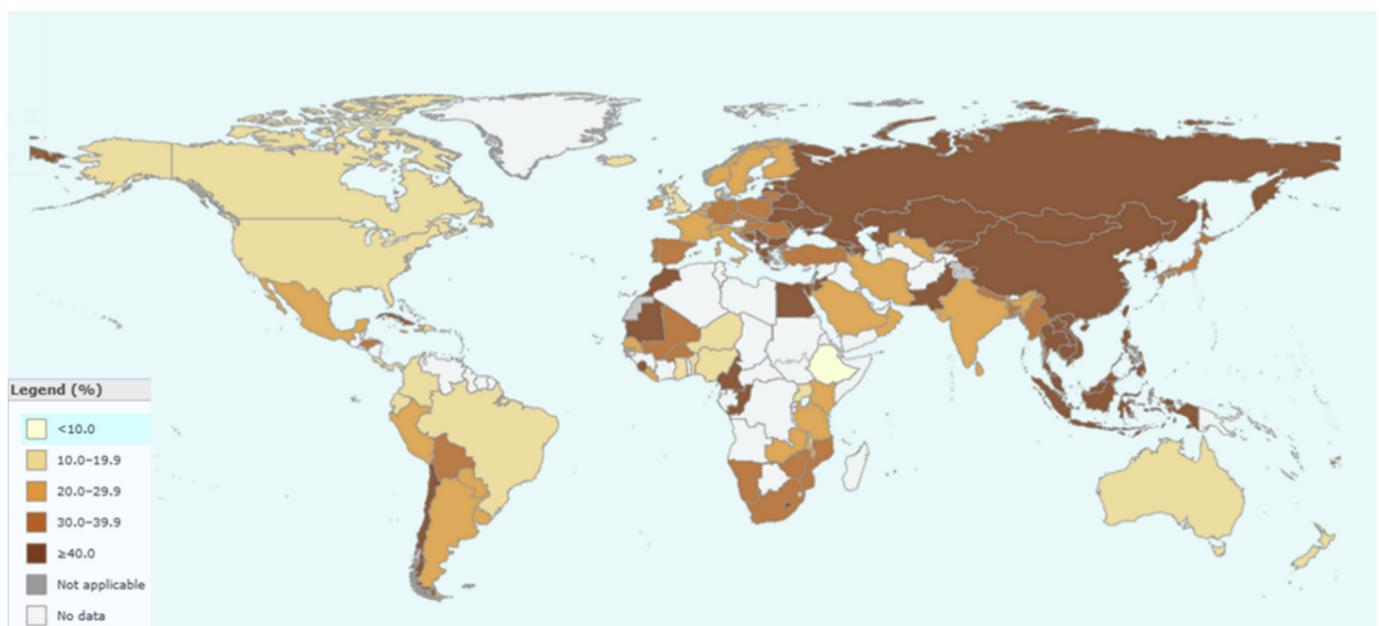

Fig 1. Global age-standardised prevalence of tobacco smoking (source: World Health Organization).

In India, the last two decades have witnessed an increase in the absolute number of male smokers aged 15—69 years from 79 million in 1998 to 108 million in 2015 [17]. Cigarettes are replacing bidis, especially among younger men and even among illiterate men. Also, smoking has marginally risen among younger women, who have seen more rapid income growth and are the subject of tobacco industry promotion.

Betel quid and smokeless tobacco chewing play a major role in oral carcinogenesis [18]. In South and Central Asia, the use of smokeless tobacco is highly prevalent and its use is more common than smoking. Some reports suggest that in India, 57% of all men and 11% of women between 15 and 49 years of age use some form of tobacco and 32.9% of men and 18.4% of women are smokeless tobacco users [16]. The term 'smokeless tobacco' refers to the consumption of unburned tobacco, in the form of chewing, spitting, dipping and snuff. There are more than 30 types of smokeless tobacco, which are different dry mixtures of lime, areca nut flakes and powdered tobacco. In one study, the mean age of starting this habit was found to be less than 25 years in both sexes [11,19]. Chronic betel nut chewing can induce premalignant lesions, such as oral submucosal fibrosis; they contain alkaloids and other substances that are hypothesised to contribute to carcinogenesis by the generation of reactive oxygen species, the formation of DNA adducts and causing DNA strand breaks [20,21].

Alcohol can act as a local and a systemic risk factor by increasing the permeability of the oral mucosa, dissolving lipid components of the epithelium, causing epithelial atrophy and interference in DNA synthesis and repair; it has geno-toxicity and mutagenic effects and also affects the liver's ability to clear toxic or potentially carcinogenic compounds [22]. A prospective study from Kerala showed that both current and past drinkers were associated with a significantly increased risk of developing OCC [23]. A significant dose—response relationship between intake frequencies, duration and risk was also observed [24]. Alcohol acts synergistically with smoking and raises the risk of developing OCC 10- to 15-fold.

Management

A work-up includes a thorough physical examination to determine clinical stage, a biopsy from a representative area to establish the diagnosis, histological subtype, grade, other histological prognostic factors and an appropriate imaging modality. Computed tomography is the preferred investigation in OCC as it provides good delineation of local extent, bone involvement and extracapsular nodal spread [25]. Magnetic resonance imaging is preferred for tongue and floor of mouth lesions, as it provides complementary information on superior soft tissue characterisation and peri-neural invasion. Positron emission tomography-computed tomography is optional for evaluating distant metastases in advanced disease, particularly with large (N2/N3) and lower level neck nodes and in a recurrent setting. Ultrasonography with or without guided fine needle aspiration suffers from low sensitivity, but is a cost-effective investigation to evaluate the neck for metastatic nodes [26].

Treatment and Outcomes of Oral Cavity Cancer in India

Treatment Overview

The management of OCC depends not only on the location, size and stage of the primary tumour, but is also influenced by comorbidities, nutritional status and the patient's preference to therapy [27,28].

Early Stage Oral Cavity Cancer

Single-modality treatment with surgery or radiation therapy is the standard of care for patients with early stage OCC. Superficial carcinomas of the oral cavity can be treated with equivalent cure rates with either radiation therapy (external or brachytherapy) or surgical excision. Surgery is often preferred for the management of early cancers of the oral cavity, as treatment is shorter. Margin status is one of the most important variables associated with survival in OCC. Close and positive margins were found to be significantly associated with increased local and regional recurrence [29,30]. Many studies have identified that adverse features including peri-neural and lymphovascular invasion, differentiation and pattern of invasion influence the recurrence pattern and must be considered while deciding on the optimal adjuvant therapy [31—34].

About two-thirds of patients with early stage OCC present with a clinically negative neck and about 20—30% will have microscopically evident nodal metastasis on histological examination after elective neck dissection. Nodal metastasis is the single most important prognostic factor in OCC; survival rates are halved compared with tumours without neck metastases. Squamous cell carcinoma of the oral tongue and the floor of the mouth are known to be more likely to metastasise to the neck and patients are offered elective nodal dissection, even for early stage tumours. A randomised prospective trial from India established that elective neck dissection resulted in higher rates of overall and disease-free survival than observation [35].

Advanced Stage Oral Cavity Cancer

Surgery remains the mainstay of treatment for resectable, advanced stage disease. Postoperative adjuvant treatment is indicated in patients with a high risk of locoregional recurrence. This includes patients with large primary tumours (pT3 or pT4), bulky nodal disease (pN2 or pN3), metastases to lower neck nodal levels, positive surgical margins, lymphovascular invasion, peri-neural invasion and extracapsular spread. Concurrent chemotherapy is offered in patients with positive margins and extra-nodal extension.

A large proportion of patients present late with locally advanced and unresectable tumours. Unresectable disease is treated with either definitive radical chemoirradiation, neoadjuvant chemotherapy followed by definitive local

therapy, palliative chemotherapy or palliative radiation therapy.

Outcomes

The treatment of early oral cavity squamous cell carcinoma (OCSCC) has not changed substantially in the past several decades. However, differences in outcomes between the West and East could be attributed to the challenges unique to developing countries compared with developed countries (see Table 2). Data from the Commission on Cancer's National Cancer Data Base showed 5-year survival rates of 69.7% in early stage OCC [36]. Outcomes were significantly different based on the primary modality used: 3-year overall survival rate by treatment was 72.6% for surgery alone, 36.0% for radiotherapy alone and 56.1% for combined treatment [37].

Five-year absolute survival in patients with OCC according to the Mumbai registry prior to 2000 were 62.5%, 18% and 1.1%, respectively, for localised, regional and metastatic disease; the figures according to the Chennai registry were 54.9%, 30% and 10%, respectively [43]. Modern series from large hospital registries have shown 3-year local control, locoregional control and disease-free survival of 74%, 65% and 60%, respectively, in patients undergoing surgery followed by radiation therapy. Also, patients with carcinoma of the gingivobuccal sulcus, palate and lip had significantly better locoregional control (68% versus 57%) and disease-free survival (64% versus 52%) when compared with patients with squamous carcinoma of the tongue and floor of the mouth [44]. Another study of 850 patients with OCC treated at a tertiary care centre showed 5-year overall survival of 70.4%; survival of early and locally advanced stages were 75.1% and 68.4%, respectively [40].

Depth of invasion is another important predictor of nodal metastases; however, investigators across the globe have proposed varying cut-offs [35,45,46], making the decision to offer adjuvant therapy solely on depth of invasion a difficult and controversial one. Administration of chemotherapy concurrently with postoperative radiotherapy improves locoregional control and survival in head and neck cancer patients with extracapsular spread and/or positive surgical margins [47]. However, in a large phase III study from India, intensification of therapy with concurrent chemotherapy and altered fractionation did not improve outcomes in all resected locally advanced OCC [48]. The group to benefit most were T3/T4 tumours with advanced nodal disease with extra-nodal extension.

Locally advanced primaries (T4b disease) have a poor prognosis and are generally considered unresectable. Radical radiation therapy alone or in combination with chemotherapy results in poor control rates, with locoregional control and disease-free survival rates of 30% [44]. However, in carefully selected patients with T4a/T4b disease in whom clear margins are achievable, excellent 3-year local control of 49.6%/41.1% and disease-free survival of 65.3%/42% were seen [49].

Table 2
Selected survival outcomes in oral cavity cancer from large institutions in the East and cancer registries in the West

Region	Dataset	Outcome
Taiwanese region [38]	698 patients Single institution data Buccal mucosa: 46.5% Tongue: 25%	5-year overall survival: 61% 5-year local regional control: 46%
China [39]	3362 patients Single institution data Tongue: 57%	5-year overall survival: 52% 1960–1969: 47.8% 1970–1979: 47.6% 1980–1989: 51.1% 1990–1999: 52.2% 2000–2009: 55.6%
India [40]	850 patients Single institution data Buccal mucosa: 65% Tongue: 28%	5-year overall survival: 70.4% (early stage: 75.1%; locally advanced: 68.4%)
Netherlands [41]	13 108 patients Cancer registry data Tongue: 33% Floor of mouth: 28%	5-year overall survival: 52% 5-year relative survival: 59% 1991–1995: 57% 2006–2010: 62%
Europe [42]	46 206 patients Cancer registry data	5-year relative survival 1999–2001: 45.6% 2002–2004: 45.5% 2005–2007: 48.1%
USA [36,37]	58 295 patients (early stage: 6830 patients) Cancer registry data Tongue: 49% Buccal mucosa 5%	5-year overall survival: 70% (early stage) 3-year overall survival: 61.5%

In technically unresectable OCC patients, who have a dismal median survival of 2–12 months, neoadjuvant chemotherapy could decrease the tumour extent and result in successful resection and ultimately improved outcomes. Most studies in the East and West have failed to show an improved outcome with the addition of neoadjuvant chemotherapy in resectable OCC [50,51]. However, in a study of more than 700 patients with unresectable OCC, administration of neoadjuvant chemotherapy resulted in subsequent surgery in 43% of patients. The median estimated overall survival in patients undergoing surgery was 19.6 months (95% confidence interval 9.59–25.21 months) and 8.16 months (95% confidence interval 7.57–8.76) in patients who underwent non-surgical treatment ($P = 0.0001$) [52].

The challenges and obstacles to improving outcomes of squamous cell carcinoma in Asian countries are multifaceted. A few of these are examined below, with a focus on India.

Challenges in India

Delay in Seeking Treatment

Factors such as illiteracy, perceived social stigma, economic loss and lack of general awareness are major deterrents for patients in seeking timely medical attention. However, a lack of trained care givers and public health infrastructure to provide patients with affordable care closer to home, such that additional economic strain could be minimised, plays an equally important part in the delay.

Many studies have highlighted the delay in presentation from the origin of symptoms. One study observed that about one-third of patients presented more than 3 months after the onset of symptoms and close to half the patients (44%) had cancer-specific primary treatment after more than 90 days from the onset of cancer symptoms, with a median time of 154 days from the onset of cancer symptoms to primary treatment initiation [53].

Large population-based studies [54] have shown that patients who were treated after 120 days had a higher risk of death when compared with those treated within 30 days and that shortening the time interval from diagnosis to treatment may improve the survival of OCC patients. Another study from Taiwan reported an association of diagnosis to treatment interval longer than 30 days with potentially lower survival [55]. A study from the Tata Memorial Centre, Mumbai reported primary, secondary and tertiary delays of 2.75 months, 1.94 months and 1.4 months, respectively. Primary delay was defined as the time duration from the onset of symptoms to seeking a primary care physician; secondary delay was the time to referral to a tertiary care centre; tertiary delay was the time duration from seeking medical advice at a tertiary care centre to the start of definitive treatment. Another study [56] found that sociodemographic factors, such as illiteracy, older age group, female gender, low socioeconomic status, rural residence, lack of awareness and psychosocial factors, such

as absence of fear, and use of alternative therapy were significant factors responsible for delay.

Despite advances in imaging and clinical treatment modalities, delay in seeking medical attention remains a major impediment to improve outcomes and needs to be borne in mind when planning and implementing cancer control programs.

Cost Implications

According to an estimate, economic welfare loss due to a diagnosis of OCC in India equals $5000 million, which is equivalent to 0.09% of the gross domestic product [57].

Despite the existence of voluntary and social health insurance schemes, the Indian healthcare system is currently characterised by a high frequency of out-of-pocket payments. With only 15% of the country's entire population covered by some form of health insurance and high rates of privatisation since the 1960s, much of these payments are subsequently channelled into the private sector, which plays a significant part in the provision of health services for outpatient visits (78%) and hospital stays (60%) [58].

However, the care in many of these situations is dictated by affordability and local availability of resources. For example, most centres in India do not have access to radiotherapy facilities, with an average 2–5 million people per radiotherapy machine compared with less than 250 000 people per machine in many high-income countries. The inability to provide affordable care affects the financial situation of the patients and their subsequent generations, as health-related poverty sets the family down the social scale.

The diagnosis of cancer and its treatment can result in socioeconomic impairment. A recently published, national representative household survey examining the overall prevalence and economic burden of cancer in India found that the out-of-pocket spending on cancer treatment is among the highest for any ailment. Patients seek cancer treatment from private hospitals more often than from public hospitals. Richer and urban households rely more on private hospitals, whereas poor households mainly depend on public healthcare facilities. The average out-of-pocket expenditure on inpatient care in private facilities is about three times that on public facilities. Cancer treatment causes substantial financial shocks and affects the usual living standard of households; one in every three cancer patients' households spends about a half of their per capita annual household expenditure on cancer care. Forty per cent of cancer hospitalisation was found to be financed through borrowing, sale of assets and contributions from friends and relatives [59]. Almost all rural households with cancer patients resort to distress means of healthcare financing.

Yet another consequence of cancer treatment is the loss of employment and income. The absence of state-sponsored support and prolonged unemployment can further lead to impoverishment, poverty and social isolation, which is especially deleterious in young individuals with large dependent families. In a cross-sectional survey among head and neck cancer survivors studying the rates of return to work and associated factors, it was found that 65.6%

returned to work at 6 months after treatment and 81.2% returned at a median of 19 months [60]. These rates and temporal trend are comparable with the Western world; they also highlight the improvement in post-treatment quality of life, made possible with modern techniques and technology. However, it may also show the economic pressure that forces patients to return to work to support their family.

Subsuming multiple earlier schemes, the National Health Protection Scheme ('Ayushman Bharat Yojna') was launched in India in September 2018 to impart holistic healthcare in primary, secondary and tertiary care systems. The poorest and the vulnerable would be able to take cashless benefits from any empanelled public or private hospital across the country. It would provide a defined benefit cover of about $1430 per family per year to nearly 40% of the population, leading to increased access to healthcare, timely treatments, improvements in health outcomes, improvement in productivity and ultimately improvement in quality of life.

Early Detection and Screening

In India, 60–80% of patients present with advanced disease as compared with 40% in developed countries. This is despite the fact that the oral cavity is accessible for visual inspection and there are well-defined clinical diagnostic features between OCC and premalignant lesions such as leukoplakia, erythroplakia, oral sub-mucosal fibrosis (OSMF), lichen planus and actinic keratosis. Early detection could therefore potentially improve the cure rate and also lower the cost and morbidity associated with treatment. An ideal screening test must be easily applicable, acceptable to the population, cost-effective, detect early disease and have a high sensitivity and positive predictive value. Cost-effective oral cancer screening and awareness initiatives have been introduced and studied in certain high-risk populations in India with varied success.

A conventional oral examination is one of the easiest, cheapest and most effective methods of OCC screening. In a cluster-randomised controlled trial from Kerala evaluating the effectiveness of visual screening, Sankaranarayanan *et al.* [61,62] showed a 24% reduction in oral cancer mortality in a high-risk population after four rounds of screening; there was also a 38% reduction in oral cancer incidence and an 81% reduction in oral cancer mortality in this group [61,62]. Performing a cost-effectiveness analysis, they found that although the screening cost $6 per individual, the incremental cost per life-year saved was $835 for all individuals eligible for screening and $156 for high-risk individuals [33]. Mouth self-examination could potentially further reduce the cost of the screening and increase awareness in high-risk communities in India.

Several other screening methods that have been evaluated include exfoliative brush cytology and light-based detection systems such as chemoluminescence and tissue fluorescence imaging. However, other than visual inspection, no other screening method seems to be applicable and cost-effective in the general population.

National Policy

In 2003 the World Health Assembly adopted an international treaty, the World Health Organization Framework Convention on Tobacco Control. To implement this, six effective evidence-based measures were identified for reducing tobacco use and were promoted under the acronym MPOWER. Nearly 121 countries, comprising 63% of the world's population, have now introduced at least one MPOWER measure at the highest level of achievement (see Table 3) [63]. High-income countries have successfully implemented tobacco control policies by integrating cessation support by healthcare providers with communication technologies such as quit lines, appropriate text messaging, social networking and telephone applications.

The government of India launched the National Cancer Control Programme in 1975 in response to the increasing incidence of cancer. The National Cancer Registry Programme, to identify the magnitude of the burden of cancer in India, was developed under this programme. Data from this registry have enabled government policymakers to recognise the effect of cancer on the nation's health, resulting in the formation of 27 regional cancer centres in India [64,65].

The Cigarettes and Other Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act, 2003 (COTPA) is the principal comprehensive law governing tobacco control in India. Some of the provisions of the act ensure the prohibition of smoking of tobacco in public places, advertisement of tobacco products and sale of tobacco products to person below the age of 18 years. India also became a member of the World Health Organization Framework Convention on Tobacco Control in 2005. Apart from government initiatives, advocacy by civil society and efforts of non-government organisations also need to be promoted to tackle the growing burden of cancer.

Table 3
Percentage of countries covered by tobacco control policies at World Health Organization-recommended levels, 2012

Geographical region	M Monitoring	P Smoke-free policies	O Cessation programmes	W Warnings		E Advertising bans	R Taxation
				Health warnings	Mass media		
Asia	27	24	17	19	27	13	13
Europe	64	20	12	2	19	5	54
Americas	20	38	17	34	17	9	6

Source: World Health Organization Global Tobacco Control Report [63] and [16].

Conclusion

The widespread practice of tobacco use among the Indian population over many decades has led to a high incidence of OCC in this part of the world. Local cultural practices, illiteracy, poor socioeconomic status and a general lack of awareness have fanned the problem to an endemic proportion. Surgery, radiation therapy and chemotherapy are integral in the multimodality management of OCC. Technical and technological advances have improved the treatment outcomes in both early and advanced stages of OCC. Effective implementation of screening techniques to aid the early detection and treatment of oral pre-malignant and malignant disease are warranted. Strict enforcement of state laws to curb tobacco usage, provision of public health infrastructure for patients to seek and undergo timely treatment and an unwavering stance from policymakers and stakeholders would eventually lead to the eradication of this preventable cancer burden.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.05.013.

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