

## Review Article

# Oral cancer: Review of current management strategies

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### ABSTRACT

**Background.** India has one of the highest incidences of oral cancer and accounts for about 30% of all new cases annually. A high prevalence of smokeless tobacco use has led to an increasing incidence, which in combination with delayed presentation has made oral cancer a major health problem in India. Limited access to cancer care, relative lack of trained healthcare providers and financial resources are some of the challenges to the management of oral cancer in India despite improvements in diagnostic techniques and management strategies.

**Methods.** We reviewed the literature pertaining to the epidemiology, aetiopathogenesis, pre-malignancy, tumour progression, management of the primary site, mandible, neck lymph node metastases, reconstruction options and screening of oral cancer. The parameters evaluated were overall survival, disease-free survival, recurrence and loco-regional control.

**Results.** Nine studies on surgical intervention were reviewed. There were 23 studies on the management of chemotherapy and 30 trials analysing radiotherapy as an intervention.

**Conclusion.** India has one of the highest incidences of oral cancer and delayed stage presentation is common. Surgery remains the treatment of choice and adjuvant treatment is recommended in high-risk patients. Elective neck dissection is warranted in clinically lymph node-negative neck for patients with thick tumours, imaging-suspected lymph nodes and those who may not have a reliable follow-up. Functional outcomes and treatment-related morbidity needs to be considered, and reconstruction with free tissue transfer provides the best results.

Natl Med J India 2013;26:152–8

### INTRODUCTION

#### Epidemiology

Oral cancer is the eleventh most common cancer globally.<sup>1</sup> There is a wide geographical variation in the incidence of oral cancer, with approximately two-thirds of patients in the developing countries of Southeast Asia, Eastern Europe and Latin America.<sup>2</sup> In India, the gingival–buccal complex (alveolar ridge, gingival–

buccal sulcus, buccal mucosa) forms the most common subsite for cancer of the oral cavity, in contrast to cancer of the tongue that is more common in the western world.<sup>3</sup> India has one of the highest incidences of oral cancer (age-standardized rate of 9.8 per 10 000) making it the most common cancer among men (men:women ratio 2:1) and accounts for about 30% of all new cases annually.<sup>4</sup> A recent survey of cancer mortality in India shows cancer of the oral cavity as the leading cause of mortality in men and responsible for 22.9% of cancer-related deaths.<sup>5</sup>

There is a trend towards increasing incidence and delayed presentation of oral cancer (about 60% patients present at stage III or IV).<sup>6</sup> The Indian national cancer registry data show an increasing incidence as per age. However, the incidence among women is lower than among men. This can be related to differences in lifestyle and behavioural pattern between the two genders.<sup>7</sup>

The age group of 55–64 years has the highest incidence of oral cancer in the USA. In contrast, many patients were <40 years of age in high incidence countries such as India, Pakistan and Sri Lanka.<sup>8</sup> The incidence of oral cancer is higher in the lower socioeconomic strata of society due to the higher prevalence of risk factors such as use of tobacco. The age-standardized mortality rates (India, 5.2 per 100 000) have been stable despite improvements in diagnostic and management techniques.<sup>9</sup>

The overall 5-year survival rate for all stages of oral cancer is 60%. These rates are better for localized tumours (82.8%) as compared to tumours with regional (51.8%) or distant metastases (27.8%).<sup>1</sup>

### METHODS

A systematic review of the literature was done using Medline, the Cochrane database of systematic reviews and PubMed, focusing on management of oral cancer. This search included trials, meta-analyses, reviews, government publications, guidelines and journal articles published with the key words 'oral cancer' in the title and 'treatment' or 'management' in the title or abstract. The search identified 912 titles. The following restrictions were applied—human and English language, standardized criteria for diagnosis and/or management.

We reviewed studies pertaining to epidemiology, aetiopathogenesis, pre-malignancy, tumour progression, management of the primary site, mandible, neck lymph node metastases, reconstruction options and screening. The parameters evaluated were overall survival, disease-free survival, recurrence and locoregional control. A synopsis of controversies in oral cancer, evidence from published studies and future directions is given in Table I.

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Primary data from the regional and national cancer registry in India were included, as were studies pertaining to oral cavity cancer among the Indian population. Articles with a significant impact on the diagnosis and management of oral cancer and which led to a paradigm shift were also included in this review.

**RESULTS**

Our search yielded 484 articles. Abstracts were reviewed in detail and 84 articles were selected on the basis of their relevance. Five of these 84 titles were excluded from further study, as they were not national studies, included fewer than 20 cases, presented duplicate data, non-verifiable references, the oral subsite cancer data was not separate or predominantly screening and investigational studies. The highlights and clinical implications of these studies are discussed further.

We selected nine studies—seven randomized controlled trials, one prospective and one retrospective study—that analysed surgical intervention in the management of oral cancer. Six of these studied the surgical management of neck lymph nodes, of which four studies compared the timing of neck dissection (elective *v.* therapeutic; locoregional recurrence risk ratio of 0.6 with 95% CI favouring elective neck dissection). Two studies have compared different types of neck dissection (radical *v.* selective). There is no evidence from these studies regarding difference in overall survival (hazard ratio [HR] 1.0, 95% CI 0.4–1.8), disease-free survival (HR 0.57, 95% CI 0.2–1.1) and recurrence (risk ratio 1.21, 95% CI 0.6–2.3). One study compared surgical intervention to radiotherapy (RT) alone (HR 0.24, 95% CI, favouring surgery with adjuvant RT over RT alone). The management of the mandible was analysed in two studies and reconstruction following surgery (free tissue *v.* pedicled flaps) was analysed in two studies.

There were 23 trials that looked at chemotherapy intervention in the management of oral cancer, of which 11 trials had only oral cancer patients while the rest had a combination of oral and

oropharynx cases. Pooled data of the included trials of induction chemotherapy plus locoregional treatment versus locoregional treatment alone showed small improvement in overall survival (HR 0.92, 95% CI 0.84–1.0, *p*=0.06).

There were 30 trials that assessed the role of RT in the management of oral cancer. These show that altered fractionation RT is associated with improvement in overall survival and reduced locoregional recurrence (HR 0.86, 95% CI 0.76–0.98 on comparison with conventional regimen).

**DISCUSSION**

*Aetiology*

Tobacco is the single most important risk factor for oral cancer. In comparison to people who never smoked, the relative risk of oral cancer is 5.3 for people smoking <15 cigarettes per day, and 14.3 for people who smoked ≥25 cigarettes per day.<sup>10</sup> In India the use of smokeless tobacco is rampant in the form of betel quid (*pan*) that contains areca nut and lime with dried tobacco leaves; this form of tobacco has been shown to be highly carcinogenic.<sup>11</sup> Traditionally, the *pan* is placed in the gingival–buccal sulcus and often retained for prolonged durations, which is responsible for the high prevalence of gingivo-buccal cancer. Recently, there has been increasing popularity of dried tobacco and areca nut mixtures (*pan masala, gutkha, zarda, khainni*) especially among the youth, owing to their aggressive marketing in India.

Alcohol alone confers a 1.7-fold risk to men drinking 1–2 drinks per day as compared to non-drinkers. The consumption of 25, 50 and 100 g/day of pure alcohol was associated with a pooled relative risk of 1.75, 2.85 and 6.01, respectively, of oral and pharyngeal cancer.<sup>12</sup> Tobacco and alcohol share a synergistic relationship, with alcohol promoting the carcinogenic effects of tobacco leading to a multifold increase in the risk of oral cancer with combined alcohol and tobacco exposure. Heavy drinkers and smokers have 38 times the risk of oral cancer compared with abstainers.<sup>13</sup>

TABLE I. Current controversies in oral cancer

Domain	Issue	Comment
Tumour biology	Do molecular level changes (mutations, oncogenes) differ as per geography, ethnicity, carcinogen type and exposure?	A few studies have conflicting results with regard to differences. Larger and well-matched molecular epidemiology studies are required to validate differences, if any.
Chemoprevention	Is there a role of chemoprevention in malignant lesions?	Published literature lacks evidence for the role of chemoprevention. Further studies are required to demonstrate their efficacy and application in the clinical setting.
Screening	Is population-based screening for oral cancer recommended?	There is no strong evidence to include or exclude adjunctive diagnostic tests for population-based oral cancer screening. Further randomized controlled trials are recommended for practice implications.
Adjuvant treatment	Risk-stratification-based recommendations for adjuvant therapy	Published studies show a benefit in overall survival with adjuvant concomitant chemoradiation in high-risk patients. However, given the associated morbidity, further studies are required for stratifying patients requiring adjuvant radiation versus adjuvant chemoradiation.
Neo-adjuvant treatment	Does induction chemotherapy have a survival advantage or role in organ preservation?	Evidence is weak regarding improved survival; there may be a role in organ preservation. Strong evidence is required to set practice implications defining the role of induction chemotherapy.
Management of lymph nodes in the neck	Elective versus therapeutic neck dissection in clinically lymph node-negative neck in early stage oral cancers.	Published literature shows weak evidence favouring elective neck dissection. Larger trials with stringent follow-up, especially in the observation arm, are required to answer this question.
Functional outcomes	Surgery, the preferred treatment modality for oral cancer, has significant functional morbidity in terms of speech and swallow. Advances in chemotherapy and radiotherapy may have improved functional outcomes.	Studies are required to analyse the functional outcomes relative to the advances, combination and timing of various treatment modalities (surgery, chemotherapy and radiation).

Human papillomavirus (HPV) is widely accepted as a causal factor for cancer arising in the lymphoepithelium of the oropharynx; its presence in lesions of oral cavity is less common; and its contribution to oral cancer development is uncertain.<sup>14</sup> Koppikar *et al.* studied the impact of HPV in head and neck cancer patients in India; this study showed 31% HPV incidence rate in head and neck cancer patients. The majority of these were oral cavity cancers.<sup>15</sup> However, other studies do not substantiate such a high rate of HPV in oral cancer.

Malnutrition, vitamin deficiency, poor dental and oral hygiene are additional predisposing factors for oral cancer;<sup>16,17</sup> a role of *Candida* spp. has also been documented.<sup>18</sup>

#### *Molecular pathogenesis*

Advances in molecular biology provide an insight into the process of malignant transformation and tumour progression. The basic but oversimplified concept of cancer is upregulation of oncogenes and/or downregulation of tumour-suppressor genes. Molecular markers assessed in oral cancer development include p53 protein expression, and changes in chromosome 3p or 9p.<sup>19</sup> A study applying oncogenetic tree models to comparative genomic hybridization revealed the most frequent gains on chromosome 8q and 9q and most frequent losses on 3p and 8p.<sup>20</sup> The concept of field cancerization was proposed to explain the development of multiple primary tumours and local recurrence.<sup>21</sup> A biological progression model was postulated for 'field cancerization' with monoclonal origin as the base and subsequent genetic alterations leading to an expanding clone that turns into a large genetically altered field. Ultimately, clonal divergence leads to the formation of one or more tumours within a contiguous field of preneoplastic cells.<sup>22</sup>

The incidence of oral cancer is significantly higher in the Indian population compared with that in the USA and Canada (age-standardized rate 9.8 v. 2.4). The gingival-buccal complex (alveolar ridge, gingival-buccal sulcus, buccal mucosa) forms the most common subsite for oral cavity cancer in India, in contrast to the tongue and floor of the mouth, which are more common sites in the West.<sup>23</sup> This difference can be correlated to the tobacco consumption habits; in India smokeless tobacco exposure is common as compared to the smoked version in the West. Population characteristics of oral cancer also differ between India and the West, with higher preponderance among men, younger age group and advanced stage at presentation among Indians. The advanced stage at presentation often warrants radiation or palliative chemotherapy for surgically unresectable tumours. This correlates with high treatment mortality and adverse outcomes in patients from the developing world. Higher prevalence of smokeless tobacco is associated with higher rates of second primary tumours compared with the West.<sup>24</sup> Studies pertaining to tumour biology have noted changes at the molecular level that differ as per carcinogen exposure pattern and ethnicity. In the West, p53 mutations are common (53%) as compared to those in the East (7%), while tumours in India and Southeast Asia have *ras* oncogene involvement, which is not common in the West.<sup>25</sup> Another comparative study looking at presentation, management and outcomes of patients with oral cancer from a developing nation to a developed nation found similar outcomes after controlling for site, stage and treatment.<sup>24</sup> A comparison of treatment outcomes and prognostic factors in patients with buccal carcinoma from the North American continent to the Indian subcontinent found no difference in the biological behaviour of tumour or age-adjusted, cause-specific survival among the two geographical regions.<sup>23</sup> However, these data need to be viewed with caution, as the

comparison was among groups in different time-frames. Management protocols do not differ by geography.

Efforts to understand the oral cancer genome are aimed at obtaining genomic and proteomic profiles and using this information in its diagnosis and management. Researchers at our institution have spearheaded the oral cancer genome database with the current update including 374 genes<sup>26</sup> and a user-friendly interface.

#### *Potentially malignant oral disorder*

A pre-malignant lesion is a misnomer. The current nomenclature of potentially malignant disorders is based on the WHO (WHO, 2005) workshop, as reported by van der Waal.<sup>27</sup> The term potentially malignant oral disorder replaces the older terminology of pre-malignant lesions or potentially malignant conditions of the oral cavity. These disorders predominantly comprise leukoplakia, erythroplakia and lichenoid lesions. Leukoplakia/erythroplakia lack clear histological definitions and are diagnosed by excluding other white or red lesions. Clinically, leukoplakia can be subdivided into homogeneous and non-homogeneous types, which may further be speckled or nodular. The annual malignant transformation rate of all types of leukoplakia together averages around 1%.<sup>27</sup> Malignant transformation of leukoplakia is more common in non-smokers than smokers. Erythroplakia has a higher chance of malignant transformation than leukoplakia. For a uniform reporting of oral leukoplakia, a classification and staging system has been proposed in which the size and histopathological features are considered.<sup>27</sup> The current literature seems to accept oral lichen planus as a potentially malignant disorder, although its malignant potential (<1%) is lower than that of leukoplakia.<sup>27</sup> Oral submucous fibrosis (OSMF), associated with the use of areca nut and betel quid or substitute, is a potentially malignant disorder, which is more common in the Indian subcontinent.<sup>28</sup> This condition is characterized by fibrosis and atrophy of the mucosa predisposing to the development of squamous cell carcinoma (SCC) in the presence of carcinogens. In India, OSMF occurs five times more often among men than among women, and predominantly affects the lower socioeconomic classes. Studies have documented a rapid increase in the incidence of OSMF in India.<sup>29,30</sup> The role of antioxidants in the management of leukoplakia lacks evidence. Surgical excision is the current treatment recommendation for all high-risk leukoplakia (idiopathic, size >2 cm, non-homogeneous, tongue, floor of the mouth lesion, presence of epithelial dysplasia) lesions.<sup>27</sup>

#### *Mandible and tumour spread*

The older concept of mandibular involvement in oral cancer through adjacent lymphatics, which required *en bloc*<sup>31</sup> mandible resection along with the primary in the periosteum was challenged by Marchetta *et al.* They showed that tumours involve the mandible by first invading the periosteum.<sup>31</sup> When the periosteum is free of direct tumour invasion, a mandible-sparing surgery can be considered. A study by McGregor and MacDonald on 46 non-irradiated cases (36 edentulous, 10 partially dentate) showed tumour entry through the occlusal surface of the edentulous mandible.<sup>32</sup> Brown *et al.* prospectively studied the pattern of tumour involvement and spread in the mandible, and showed that tumour entry in the mandible was direct at the point of tumour abutment to the mandible.<sup>33</sup> They concluded that larger or deeply invading tumours in the soft tissue are more likely to invade the mandible and lead to an aggressive form of tumour spread, reducing the option of conservative (rim) resection.<sup>33</sup> Carter *et al.*

described two main histological patterns of mandibular invasion by oral SCC—the invasive type (osteoclastic independent) or the erosive type (pushing or osteoclastic-dependent).<sup>34</sup>

#### *Diagnosis and evaluation*

A detailed history and physical examination are critical for the comprehensive evaluation of patients with oral cancer. In the early stages, oral cancer may have few symptoms which are often ignored. The most common presentation is a patch or a non-healing ulcer; any such lesion particularly with a history of tobacco and alcohol consumption and which is persistent for over 6 weeks warrants a thorough investigation. Trismus, especially of recent onset, is an indication of infratemporal fossa involvement, a sign of relative inoperability. Physical examination should allow for accurate mapping of the extent of contiguous involvement of surrounding structures such as the bone, deep musculature of the tongue, floor of the mouth, patient's functional ability, search for synchronous second primary, fixity to surrounding skin and soft tissue and regional lymph node status. Pathological diagnosis should be confirmed with tissue biopsy from the most representative non-necrotic area of the lesion. A fine-needle aspiration (FNA) should be done (ultrasound-guided FNA improves the accuracy and specificity) of suspected regional cervical metastases. Imaging is mandatory for locally advanced disease; CT scan has been shown to be better in demonstrating mandibular cortical involvement and the status of cervical lymph nodes.<sup>35</sup> MRI is preferred to assess the extent of involvement of soft tissue, skull base, infratemporal fossa, RT planning and medullary bone involvement. Hence, CT scan is preferred in buccal mucosa cancer while MRI is favoured for tongue cancer.

In early stage lesions amenable to transoral excision with a clinically node-negative (confirmed by imaging) neck, ultrasound with or without FNA is the initial investigation of choice for the neck.<sup>36</sup> Ultrasound is also preferred for close observation and follow-up of the neck in patients who are lymph node negative. The role of newer imaging modalities such as PET-CT scan in pretreatment assessment lacks evidence. However, it is useful in assessing post-treatment residual/recurrent disease.

#### *Staging*

The stage of cancers of the oral cavity is based on the size of the primary tumour along with involvement of surrounding structures, cervical lymph node status and distant metastases (2009 American Joint Committee for Cancer revised cancer stage groupings for oral cavity SCC).<sup>37</sup>

#### *Treatment considerations*

The locoregional control of the primary tumour is the key to a successful outcome. Early stage tumours (I/II) are managed with a single treatment modality such as surgery or RT.

Surgery is often the treatment of choice as transoral resection is possible with complete removal of the tumour and adequate margin control. It is cost-effective, well tolerated, repeatable, and of a relatively shorter duration (opposed to 6–8-weeks of RT). Surgically, tumours are excised with a normal margin of 1 cm in all dimensions from the primary tumour. A margin <5 mm is considered compromised. Histopathology may demonstrate tumour involvement of the margins and is associated with adverse prognosis.<sup>38,39</sup> Robertson *et al.* compared surgery followed by RT with RT alone in patients with oral and oropharyngeal cancer.<sup>40</sup> The trial was terminated prematurely due to a high death rate in the RT only arm. Interim analyses of this trial (35 patients after 23

months) showed a HR for total mortality of 0.24 favouring the surgical treatment group.<sup>40</sup>

Chemotherapy by itself is not definitive in the management of head and neck cancer. A Cochrane systematic review on oral cancer analysed 89 trials related to chemotherapy in the management of oral cavity and oropharyngeal cancer.<sup>41</sup> Eleven of these trials had only oral cancer patients. Pooled data of the included 25 trials of induction chemotherapy plus locoregional treatment versus locoregional treatment alone showed no significant benefit for overall survival (HR 0.92, 95% CI 0.84–1.0,  $p=0.06$ ). The implications for practice based on this meta-analysis are as follows:

1. Induction chemotherapy is not associated with statistically significant improvement in overall survival compared to locoregional treatment alone.
2. There is evidence that concomitant adjuvant chemoradiotherapy improves overall survival compared to these treatments given sequentially.
3. In patients with unresectable tumours, there is evidence that concomitant chemoradiotherapy leads to improvement in overall survival of 10%–20%.

Well-differentiated keratinizing SCC often have less reliable response to RT and chemotherapy; furthermore the maxilla, mandible and dental structures interfere with RT. In early stage lesions, RT is suitable only for superficial lesions measuring <3 cm, away from bony structures and accessible for brachytherapy. RT intervention in treatment of oral cancer has been analysed by a Cochrane systematic review on oral cancer.<sup>42</sup> This meta-analysis included 30 trials involving 6535 participants. These analyses conclude that altered fractionation RT is associated with overall improved survival and locoregional control in patients with oral cavity and oropharynx cancer. The benefit may be greater with hyperfractionated regimens rather than accelerated regimens.

Combined treatment modality is required for the management of advanced stage (III/IV) tumours. For locally advanced and operable tumours, surgery followed by adjuvant treatment is the preferred treatment modality.<sup>43</sup> Recommendations for adjuvant RT include multiple pathologically positive lymph nodes in the neck, perineural invasion, angiolymphatic invasion, high-grade histopathology and advanced T (III or IV) stage (RTOG 73-03).<sup>44</sup> Adjuvant concomitant chemoradiation is recommended when surgical pathology shows extracapsular spread in the cervical nodes and positive or close margins ( $\leq 5$  mm) at the primary site (EORTC 22931, RTOG 95-01).<sup>45,46</sup> In adjuvant RT the dose and volume for primary and uninvolved cervical nodes are 55–60 Gy/28–30 fractions over 6 weeks using reducing fields, for residual disease and positive margins a 4–10 Gy boost and for uninvolved cervical nodes 45–50 Gy.

#### *Management of the mandible*

When the tumour closely approximates the mandible, marginal versus segmental mandibulectomy needs to be considered. Marginal mandibulectomy is contraindicated in cases that have been previously irradiated, as bony involvement is multifocal in these cases along with compromised vascularity. Marginal mandibulectomy can be horizontal (buccal tumours) or vertical (tongue, floor of the mouth).<sup>47</sup> Brown *et al.* studied patterns of tumour spread into the mandible, and found that tumour entry is at the point of tumour abutment to the mandible, which is usually below the occlusion ridge or gingival crest and this should be considered when planning marginal mandible resection.<sup>33</sup>

Haribhakti studied cadaveric mandibles for anatomical details, which include cortex-medullary thickness and the inferior alveolar nerve canal.<sup>48</sup> This study showed that the posterior segment of ramus can be spared in appropriate cases of segmental mandibulectomy. Also, marginal mandible resection that includes the entire medullary core and alveolar nerve results in inadequate bone stock.

A paramedian step-fashioned mandibulotomy provides optimal surgical access for larger and posteriorly located lesions.<sup>47</sup>

#### *Management of the neck*

Spread of tumour to the regional lymph nodes in the neck (cervical nodes) is an early and consistent event in the natural history of oral cancer.<sup>49</sup> The extent of cervical involvement is reflected in staging and has prognostic implications.<sup>50</sup> Cervical lymph nodal stage at presentation and extracapsular tumour spread are independently associated with poor prognosis.<sup>51</sup> Hence, management of the cervical nodes at risk of metastasis may be done along with treatment of the primary tumour site.

Classical radical neck dissection is outdated, associated with significant morbidity and now done only when the neck structures (sternocleidomastoid, internal jugular vessels and XI cranial nerve) are involved. Modifications of this procedure to preserve associated structures have reduced morbidity without compromising regional control or survival.<sup>52</sup> Thus, the trend has shifted from classical neck dissection to modified neck dissection. The Brazilian Head and Neck Cancer Study Group (BHNCSSG 1998) compared modified neck dissection with accessory nerve preservation to supraomohyoid (SOH) neck dissection for achieving a compartmental excision of level I to III nodes in T2 to T4 primary lesions of the oral cavity in 148 patients with clinically negative nodes. Intraoperative frozen section showed involved lymph nodes in three patients from the SOH group—these cases underwent modified classical neck dissection instead.<sup>53</sup> Bier studied 104 patients with oral cavity cancer having clinically negative or positive but mobile cervical nodes. Patients were randomized to radical neck dissection or selective neck dissection (preserving the sternocleidomastoid, internal jugular vessels and XI cranial nerve).<sup>54</sup> There is no evidence from these two trials of a difference in disease recurrence, disease-free survival or overall survival between radical or more selective neck dissection procedures.

A Cochrane systematic review<sup>55</sup> analysed four trials looking at the timing of neck dissection (elective v. therapeutic). All participants had clinically negative nodes at the time of entry to the study till its completion. Two trials found no difference in disease-free and overall survival between elective radical and therapeutic neck dissection.<sup>56,57</sup> In the trial by Kligerman *et al.*, where elective was a less extensive (SOH) surgery, there was a difference in overall and disease-free survival favouring elective SOH neck dissection.<sup>58</sup> All four studies had some evidence that elective neck dissection is associated with reduced locoregional recurrence rates. This Cochrane review summarized that there was weak evidence for elective neck dissection in clinically negative nodes associated with reduced locoregional recurrence and that there was no strong evidence of a difference in disease-free or overall survival. Fasnola *et al.* did a meta-analysis of these four trials, and found that elective neck dissection had reduced disease-specific death risk as compared to observation.<sup>59</sup> The limitations of this meta-analysis have been discussed previously.<sup>60</sup> Currently, there are two ongoing randomized controlled trials, one at our institute (NCT00193765) and the other in the UK (NCT

00571883) which will hopefully answer the question of elective or therapeutic neck dissection in N0 neck.

Wiess *et al.* proposed that an incidence of >20% occult node metastases warrants elective neck treatment.<sup>61</sup> In SCC of the tongue<sup>62</sup> and gingival-buccal complex,<sup>63</sup> tumour depth is an important parameter. Lesions with depth  $\leq 4$  mm are associated with occult neck lymph node metastases and elective neck dissection is warranted in these cases. A malignant lesion of the tongue <2 mm deep has less chance of neck metastases and hence the neck can be managed expectantly. Management of the neck in patients with lip cancer can often be expectant as cervical lymph node metastases occurs in only 10% of cases.<sup>64</sup> In clinically negative cervical nodes, elective neck dissection is warranted in patients who may not have a reliable follow-up.

#### *Second primary tumours*

Patients with smoking-related oral cancers are at high-risk for second primary tumours. The overall incidence of second primary tumours in patients treated for oral cavity tumours is 3%–7% per year.<sup>65</sup> Cancerous lesions detected simultaneously or within 6 months of a primary tumour are termed as synchronous lesions while those detected >6 months later are referred as metachronous. Most of the second primary tumours are metachronous (80%) with 50% of them presenting within the first 2 years of primary treatment, and are often located in the upper aerodigestive tract.

#### *Recurrent tumours*

The recurrence rate for oral cancer after treatment is 26%–41%.<sup>63,66</sup> These recurrences need to be assessed to ascertain whether these are potentially curable or not. The management largely depends on the initial staging, location and extent of the recurrence and primary treatment modality. Initial RT is usually provided in maximum lifetime tolerance of the tissue; this curtails the possibility of giving it again in patients with recurrence. Often surgery and RT (if permissible) are undertaken for those deemed potentially curable. Salvage surgery is challenging owing to fibrosis and altered anatomy. Surgical salvage cure rate is low (15%–21%).<sup>67,68</sup> Considering these factors it is imperative that the primary treatment modality should be optimal and carefully selected.

Palliative chemotherapy or symptomatic therapy is considered for incurable recurrences. If chemotherapy is used in the earlier treatment, the recurrent tumour is often resistant to those agents. Cetuximab in combination with platinum-based chemotherapy and fluorouracil improves overall survival when given as first-line treatment in recurrent or metastatic head and neck SCC.<sup>69</sup>

#### *Reconstruction*

Surgical resection of oral cavity tumours often leads to complex defects involving soft tissue and bone. Microvascular free tissue transfer has become the standard of care and provides optimal reconstruction with a consistent success rate of >95%.<sup>70</sup> The radial forearm fasciocutaneous free flap provides versatile, sensate and pliable skin paddle for tailored reconstruction of the tongue, buccal mucosa and floor of the mouth defect without additional bulk. When additional soft tissue bulk is required as in a total glossectomy defect, an anterolateral thigh flap may be harvested. The osteocutaneous fibula free flap is preferred in large segmental mandibular and maxilla defects.<sup>71</sup> The pectoralis major flap is one of the most reliable and widely used pedicle flaps in reconstruction of oral cavity defects. It can be used with a cutaneous island or as a myofascial flap; it is versatile and has multiple modifications customized to defects.<sup>72</sup> Functional advantage of free flap over

pedicle flap has been demonstrated with regards to improved speech.<sup>73</sup> Other indirect measures of functional outcomes such as G-tube dependence have also demonstrated superiority of free flap over pedicle flaps.<sup>74</sup>

### Screening

The Cochrane systematic review of screening programmes for detection and prevention of oral cancer concludes that there is evidence for visual examination in population-based screening programmes of high-risk individuals for oral cancer, leading to reduced mortality. This review did not find strong evidence for use of technologies such as brush biopsy, toluidine blue or fluorescence imaging in the primary care environment.<sup>75</sup>

### CONCLUSION

India has one of the highest incidences of oral cancer and delayed stage presentation is common. Currently there is insufficient data to suggest a role of diagnostic tests for early detection of oral cancers. These tumours have a well-defined tumour progression model characterized by potentially malignant disorders. Some studies have shown differences in tumour biology between Indian and western patients. However, treatment outcomes do not differ. There is a need for age- and stage-matched larger studies to validate the differences. Surgery remains the treatment of choice and adjuvant treatment is recommended in high-risk patients. Elective neck dissection is warranted in clinically negative cervical lymph nodes with thick tumours, imaging-suspected nodes and for those which may not have a reliable follow-up. Functional outcomes and treatment-related morbidity needs to be considered and reconstruction with free tissue transfer provides the best results.

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## Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attraction of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

*The National Medical Journal of India* wishes to recognize the efforts of these doctors. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his or her education and training and highlight the achievements as well as disappointments. A photograph should accompany the obituary.

—Editor