Management of gingivobuccal complex cancer

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ABSTRACT

INTRODUCTION Squamous cell carcinoma of the oral cavity ranks as the 12th most common cancer in the world and the 8th most frequent in males. It accounts for up to one-third of all tobacco-related cancers in India. Cancer of the gingivobuccal complex is especially common in Indians due to their tobacco habits. This review focuses on the management of lower gingivobuccal complex cancers.

PATIENTS AND METHODS References for this review were identified by search of Medline and other bibliographic information available in the PubMed database. The search terms carcinoma oral cavity, and cancer oral cavity, buccal mucosa, gingiva, gingivobuccal complex, and alveolus cancer/carcinoma were used. References from relevant articles and abstracts from international conferences were also included. Only articles published in the English language were used.

RESULTS Treatment of gingivobuccal complex cancer is primarily surgical. Radical neck dissection, or its modification, is the standard treatment for the node-positive neck. Supraomohyoid neck dissection is the accepted treatment for the node-negative neck. Radiotherapy is usually not the preferred modality of treatment for early gingivobuccal complex cancer. It is used either as postoperative adjuvant treatment or as definitive treatment for advanced cancer with or without chemotherapy. Chemotherapy has been used as neo-adjuvant, adjuvant or palliative treatment. Advanced cancers are common and continue to pose a challenge to the multidisciplinary team.

CONCLUSIONS Gingivobuccal complex cancer remains a major public health problem despite being highly preventable and easily detectable. Advanced cancers constitute a major proportion of patients presenting for treatment. These patients are difficult to treat and have a poor outcome.

KEYWORDS

Buccal mucosa – Gingivobuccal complex – Squamous cell carcinoma – Management

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Squamous cell carcinoma of the oral cavity ranks as the 12th most common cancer in the world and 8th most frequent in males.^{1,2} There is not only a marked variation in the incidence and mortality from oral cancer between various countries but also between ethnic groups and regions of one country. This is primarily attributable to variations in the prevalence of major risk factors between populations. However, other dietary and genetic influences may also contribute.³

The lower gingivobuccal complex is comprised of buccal mucosa, gingivobuccal sulcus, lower gingiva and retromolar trigone. It is the most common site for oral cancer in the Indian subcontinent due to the habit of chewing tobacco (Fig. 1). This review will describe the management of lower gingivobuccal complex cancer, which has been aptly described as the 'Indian oral cancer'.

Patients and Methods

References for this review were identified by search of

Medline and other bibliographic information available in the PubMed database. The search terms carcinoma oral cavity, and cancer oral cavity, buccal mucosa, gingiva, gingivobuccal complex, and alveolus cancer/carcinoma were used. References from relevant articles and abstracts from international conferences were also included. Only articles published in the English language were used. As this review is opinion-based, it also reflects our large personal experience in management of gingivobuccal complex cancer.

Results and Discussion

Clinical evaluation

The goal of evaluating a patient with gingivobuccal complex cancer is to assess the extent of disease and to define the tumour type histologically. Patients usually present with a persistent ulcer or an exophytic growth in the gingivobuccal complex, loosening of teeth, ill-fitting dentures or trismus. Pain is a late feature. Patients with

Figure 1 Gingivobuccal complex cancer and tobacco-stained teeth due to chewing tobacco.

advanced disease present with orocutaneous fistula, severe trismus and lymph node metastasis. Many patients have associated premalignant lesions like leukoplakia and erythroplakia or premalignant condition like submucous fibrosis. An asymptomatic lesion, with a history of tobacco and/or alcohol consumption, should raise suspicion of oral cancer and biopsy should be done.

Examination assesses the extent of involvement of important structures such as mandible, floor of the mouth musculature and cervical nodes. The presence of trismus may suggest deep invasion. It is important to determine whether this trismus is due to associated submucous fibrosis or malignant disease.

The clinician should evaluate any medical and nutritional problems. Common problems in patients with cancer of the oral cavity are hepatic disease, pulmonary disease and malnutrition.

Mode of spread

Knowledge of the mode of spread of gingivobuccal complex cancer is important for developing a rational therapeutic approach. Local spread to adjacent structures may lead to invasion of the underlying soft tissue, muscles, bone and neurovascular structures. Gingivobuccal complex cancer extends along surface mucosa and the submucosal soft

tissue to approach the buccal or labial gingiva. From this point onwards, the tumour does not extend directly through the intact periosteum and cortical bone towards the cancellous part because the periosteum acts as a significant protective barrier. Instead, the tumour advances along the attached gingiva towards the alveolus. Subsequently, the mandible is involved by infiltration through the dental sockets or the dental pores (in edentulous patients) on the alveolar ridge.⁴ These cells proceed along the root of the tooth into the cancellous part of the mandible and then along the mandibular canal. This understanding has led to the development of mandible-sparing, surgical resections. Cervical lymph nodes are the most commonly involved metastatic site. The neck has been divided into five nodal levels for planning treatment of gingivobuccal complex cancer (Table 1). The gingivobuccal complex has a predictable lymphatic drainage. The first echelon lymph nodes are in the supraomohyoid triangle of neck (levels I, II, III). Spread to lymph nodes in posterior triangle in the absence of metastasis at other levels is rare.⁵⁻⁷ Skip metastasis from gingivobuccal complex carcinomas are rare. Distant metastasis at the time of initial diagnosis is exceedingly rare and occurs to lung and bones.

Investigations

BIOPSY

Biopsy of the lesion is mandatory before treatment. Often, this can be done under local anaesthesia. The biopsy should be deep and encompass a portion of the tumour as well as adjacent normal appearing mucosa. Superficial biopsies are inconclusive and yield negative results. In suspected verrucous carcinomas, where basement membrane is intact, a deep biopsy is mandatory to reach a diagnosis.

IMAGING

Investigative work-up depends on the extent of the disease. Patients with early lesions do not need an extensive evaluation. An orthopantomogram or oblique radiograph of the mandible is a cost-effective initial investigation to assess mandibular involvement. The accuracy of clinical examination, peroperative periosteal stripping and imaging

Table 1 Nodal levels in the neck

Level I	Submental and submandibular triangle lymph nodes
Level II	Upper deep jugular lymph nodes (skull base to carotid bifurcation)
Level III	Mid deep jugular lymph nodes (carotid bifurcation to omohyoid muscle inferiorly)
Level IV	Lower jugular lymph nodes (omohyoid muscle to clavicle)
Level V	Posterior triangle lymph nodes

techniques have been compared.^{8,9} Clinical examination alone was not shown to be accurate, but periosteal stripping

at the time of resection was extremely accurate. No single imaging technique will accurately predict mandibular

Table 2 UICC/AJCC TNM Clinical Classification and Staging of Carcinoma Oral Cavity (6th edn, 2002)¹¹

T – Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4a (lip)	Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
T4a (oral cavity)	Tumour invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b (lip and oral cavity)	Tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery

(Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4)

N – Regional lymph nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension.

(Midline nodes are considered ipsilateral nodes)

M – Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

invasion; however, a combination of orthopantomogram and bone scintigraphy is recommended in early invasion. Magnetic resonance imaging (MRI) is more sensitive than computerised tomography (CT) for mandibular invasion. CT scanning gives additional information regarding the extent of mandibular involvement, malignant infiltration and cervical nodal disease. MRI can be used to determine soft tissue and perineural involvement. However, all patients do not need CT scan or MRI. These are especially indicated in patients with large lesions having trismus and lesions abutting the mandible where marginal mandibulectomy is being planned. It is also used to evaluate patients with a clinically negative neck or those with large nodes for presence of carotid involvement. Ultrasound guided fine needle aspiration cytology (FNAC)¹⁰ has the highest accuracy in diagnosing cervical nodal metastasis in the clinically negative neck compared to ultrasonography, CT scan and MRI. However, none of the imaging methods can determine occult metastatic nodal disease.

In view of the risk of multifocal changes, endoscopic evaluation (panendoscopy) of the upper aerodigestive tract is recommended to evaluate the presence of second primaries. Direct laryngoscopy, bronchoscopy, oesophagoscopy and examination under general anaesthesia may be done for accurate assessment of the disease and the upper aerodigestive tract.

Staging

The UICC/AJCC TNM staging system¹¹ is currently followed (Table 2).

Treatment

Depending on the specific site in the gingivobuccal complex (alveolus, gingivobuccal sulcus or buccal mucosa alone), the extent of the primary tumour and the status of lymph nodes, the treatment of these cancers may be by surgery or radiation therapy used alone or in combination, with or without chemotherapy.

Early lesions (T1, T2) can be effectively treated with either surgery or radiation as a single modality. Certain factors influence this decision. For example, in the presence of associated submucous fibrosis, surgery is preferable to radiation therapy. Lesions located in lower gingivobuccal sulcus or involving mandible are usually not treated with radiation because of proximity to bone and chances of osteo-radionecrosis. Advanced lesions require a combined modality treatment.¹

Surgery

Treatment of gingivobuccal complex cancer is primarily surgical. The aim of surgical treatment is to excise the entire primary lesion with clear margins (1–2 cm) three-dimensionally, and also effectively treat the regional lymph

nodes. This ablative surgery is followed by primary reconstruction to provide rapid healing, restore function and appearance and thereby improve patient's quality of life. These lesions are resected either by an upper or lower cheek flap with a lip split, visor flap or per-orally, depending upon the size and location of the primary.

TREATMENT OF THE PRIMARY

These cancers often abut or involve the mandible. Most of these cancers are not amenable to per-oral resection owing to inadequate access, which may jeopardise the oncological resection. Per-oral resection is possible in small lesions (usually, 2 cm or less), situated anteriorly, with no or minimal mandibular involvement, and with good mouth opening.¹² Radical ablative surgery is followed by reconstructive surgery. Surgical defects may be reconstructed by primary closure, skin graft, locoregional flaps or free tissue transfer from different sites.

The decision to resect the mandible as part of the management of oral cancer should be taken on the evidence of clinical examination, periosteal stripping and at least two imaging techniques that complement each other in terms of specificity and sensitivity.⁸ Lesions that directly invade the bone should undergo a segmental or hemi-mandibulectomy. Resection of the posterior part of the body or ramus of mandible leaves very little aesthetic deformity, but there is always functional compromise with segmental resection of any part of mandible. Resection of anterior arch of mandible results in significant functional and cosmetic deformity and immediate reconstruction should be done by an osteomyocutaneous flap or composite free tissue transfer. If immediate reconstruction is not feasible or desirable, the mandibular stirrups should be immobilised by internal, external or interdental fixation. Heavy reconstruction plates may also be used in this situation.

Mandibular sparing techniques like marginal mandibulectomy have gained popularity for lesions with no, or minimal, cortical mandibular invasion. Marginal mandibulectomy has been used for a long time in cancer of the floor of the mouth and can also be used for cancers of gingivobuccal complex. Mandibular continuity is maintained and a much better cosmetic and functional end result is achieved with marginal mandibulectomy. At least, a 1-cm thick segment of bone must be left inferiorly after a marginal mandibulectomy. Marginal mandibulectomy is contraindicated in patients with gross clinical and radiological involvement of mandible, invasion of mandibular canal by cancer and in deeply infiltrating lesions of gingivobuccal sulcus where there is paramandibular infiltration, as the margin of resection may pass through infiltrated paramandibular tissue.^{13,14} It is also contraindicated in previously irradiated mandible. Reduced vertical height of the bone in an edentulous mandible is a relative contraindication for

Table 3 Types of modified radical neck dissection (MRND)

Type 1	Preservation of spinal accessory nerve
Type 2	Preservation of spinal accessory nerve and internal jugular vein
Type 3	Preservation of spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle

In all types, all 5 levels of cervical nodes are removed.

marginal mandibulectomy. Marginal mandibulectomy is also usually not done in lesions of the retromolar trigone as clearance of pterygoid region is possible only if ascending ramus of the mandible is resected. However, some studies have also reported satisfactory results of marginal mandibulectomy in lesions of the retromolar trigone.^{15,16} Results of marginal mandibulectomy for gingivobuccal complex carcinoma show an overall local recurrence-free survival rate of 79% and 70% at 2 and 5 years, respectively.¹⁷ Other studies have also demonstrated the oncological safety of marginal mandibulectomy in carefully selected patients with oral cancers.^{15–16,18}

TREATMENT OF NECK

The management of neck for gingivobuccal complex cancers depends on whether the neck is clinically node-negative or node-positive. In patients with clinically positive lymph nodes (N1, N2, N3), radical neck dissection (RND) has been the gold standard. However, there is mounting evidence that RND should not be the only therapeutic option for the clinically positive neck.^{5,19,20} In patients with clinical N1 disease and selected N2 disease, a modified radical neck dissection may be done for better cosmetic and functional results.^{19–21} Preservation of the spinal accessory nerve, internal jugular vein (IJV) and sternocleidomastoid muscle is done in the form of a modified radical neck dissection (MRND; Table 3). RND, however, is still appropriate for patients with massive lymphadenopathy (N3 disease), multiple positive nodes involving the spinal accessory nerve and/or the IJV, residual or recurrent neck disease after radiotherapy and gross extranodal spread. A supraomohyoid neck dissection (SOHND, clearance of level I, II and III nodes) plus postoperative radiation therapy has been advocated by a few authors^{22–27} for N1, level I disease. There are still no prospective, randomised trials comparing SOHND with RND/MRND in clinically positive neck and it is unlikely that studies large enough to answer this question will be carried out in the future.²⁷ Nodal spread can occur to both sides of neck especially in lesions close to mid-line.²⁸

In patients with bilateral nodal metastasis, a bilateral neck dissection with preservation of IJV on at least one side (the less affected side) is indicated. An alternative to this is to do a staged RND, the IJV resection is done on both the sides with an interval of 4 weeks between them.

Occult nodal metastatic disease is present in 5–26% of gingivobuccal complex cancers depending on the T-status and grade.^{29–32} Management of the clinically negative is thus an important issue.³³ Patients with T1/T2 cancers (low risk, < 20% risk of nodal metastasis) do not require elective neck treatment.³³ SOHND should be performed in patients with T3/T4 primary (high risk, > 20% risk of nodal metastasis), if entering the neck to resect the primary, short-necked individuals who require a bulky flap for oral reconstruction (to create space in neck) and patients who are unreliable for follow-up.^{27,34} Patients who are found to have pathologically positive neck nodes after SOHND should receive additional treatment. If detected positive intra-operatively (on frozen section), then SOHND should be changed to RND or MRND. Patients with positive lymph nodes, diagnosed on histopathology following SOHND, should either undergo RND/MRND or postoperative radiotherapy (Fig. 2).^{24,26,35–39} Patients with a single positive, level I node only, without extracapsular spread, may not need additional treatment.^{37,38}

A randomised trial comparing SOHND with comprehensive neck dissection in patients with clinically negative nodes found no difference in the regional control and overall survival rates between the two groups.⁴⁰ However, SOHND alone is inadequate treatment for patients with pathologically confirmed or clinically positive nodes. Patients undergoing MRND need adjuvant radiation therapy to the

Figure 2 Algorithm for management of clinically negative neck.

*Treat if entering neck to remove primary or patient unreliable for follow-up. MRND, modified radical neck dissection; RND, radical neck dissection; SOHND, supraomohyoid neck dissection.

neck if N2 disease is present.^{5,41} Adjuvant radiation provides good regional control. The role of ultrasound-guided FNAC of the N0 neck in the decision for elective neck dissection has been reported.⁴² However, its application to gingivobuccal complex cancers in particular is uncertain. Recently, lymphatic mapping with sentinel lymph node biopsy has been used in N0 oral cancer patients but further refinement of technique and larger studies are needed before this can be recommended as standard treatment.^{43,44}

Radiation therapy

Radiation therapy and surgery have equal success in controlling early lesions of the oral cavity. Radiation is given either as external beam, brachytherapy or a combination of both. For gingivobuccal complex cancers, radiotherapy is usually not the preferred modality of treatment for early cancers (T1, T2) due to the close proximity of the tumour to bone and risk of radionecrosis. Radiotherapy is used for treatment of early lesions of buccal mucosa and gingivobuccal sulcus where the patient is not medically fit or is unwilling for surgery. It is also used as an adjuvant treatment for the primary tumour in patients with histologically positive margins on resection and has been shown to decrease the local recurrence rate.⁴⁵

In patients with advanced lesions (T3, T4), a combination of surgery and radiation therapy provides a better chance of cure than either modality alone. The 3-year survival for stages III and IV disease treated with radiation therapy or surgery alone is 41% and 15%, respectively. These rates increase to 60% and 35%, respectively, when surgery is combined with postoperative radiation therapy.³⁰ In a randomised trial, Mishra *et al.*⁴⁶ have reported a significant improvement in disease-free survival in patients with T3/T4 carcinoma of the buccal mucosa. Postoperative radiation therapy is indicated in all patients with T3, T4 primary, patients with positive or close surgical margins, pathologically positive lymph nodes after SOHND and two or more positive lymph nodes after RND/MRND and lymph nodes showing extracapsular spread.⁴¹ There is emerging evidence for the use of adjuvant concurrent chemoradiotherapy in patients of head and neck cancers with poor prognostic factors.⁴¹

Definitive radiation or concurrent chemoradiotherapy is used in advanced (stage III/IV) disease, if the disease is inoperable or the patient is unfit or unwilling for surgery. Concurrent chemoradiotherapy has evolved as the standard of care for such locally advanced head and neck cancers. The toxicity of concurrent chemoradiotherapy is more than radiation therapy alone and requires aggressive supportive measures. However, evidence for use of concurrent chemoradiotherapy for oral cavity subsite is sparse.⁴¹

In clinically node-negative neck cancer, elective neck irradiation is done if the primary is being treated with radiation therapy.

Chemotherapy

There has been a paradigm shift in the use of chemotherapy for management of head and neck cancer. Conventionally, chemotherapy has been used as palliative treatment for unresectable advanced/metastatic oral cancer. However, over the last few decades with the development of several highly active cytotoxic agents (cisplatin, taxanes and infusion 5-fluorouracil) and their combinations, there has been an expanding role for chemotherapy as induction and adjuvant therapy for squamous cell cancer of the head and neck. The highly effective combination of concurrent chemotherapy and radiation and the development of the sequential treatment approach have further improved results of treatment.^{47–52} Though there is lack of site-specific data pertaining to gingivobuccal complex cancer, we can perhaps build management strategies similar to other head and neck sites.

A meta-analysis of randomised trials of chemotherapy in head and neck cancers has shown that induction chemotherapy using platinum and 5-fluorouracil combinations has an absolute survival benefit of 5% at 5 years, compared to 8% with concomitant chemoradiotherapy.⁵² Even though induction chemotherapy may not impact significantly on survival, there may be other benefits to using it in locally advanced oral cancer.^{53–55}

Targeted therapy

Promising data are emerging from efforts to modulate specific molecular targets that control tumour growth in head and neck cancer. Epidermal growth factor receptor, which is overexpressed in more than 80% of cases, represents one such target that is important in pathogenesis of squamous cell cancer of the head and neck. A Phase III randomised trial has shown a survival benefit with the addition of cetuximab to radiation therapy compared to radiation therapy alone for patients with locally advanced squamous cell cancer of the head and neck.⁵⁶ Further combinations of cetuximab with chemotherapy and radiation therapy are being actively explored.⁵⁷ Other agents currently of clinical interest are tyrosine kinase inhibitors like gefitinib and erlotinib. They have been used as single agent or in combination with chemotherapy, radiation therapy or other biological agents like bevacizumab in treatment of recurrent or metastatic disease.⁵⁷

Conclusions

Gingivobuccal complex cancer remains a major public health problem in the Asian subcontinent. Despite being highly preventable and easily detectable, advanced oral cancers constitute a major proportion of patients presenting for treatment. These patients are difficult to treat and have a poor outcome. With the increasing use of smokeless

tobacco, it is likely that gingivobuccal complex cancers will occur more frequently in the Western world.

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