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Management of oral cancer: current concepts and a review of the literature

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Abstract:

Oral cancer is an emergent health problem which is common in several regions of the world. The treatment of patients with oral cancer is mainly directed at controlling the primary tumor and regional neck metastases. Oral cancers are best managed by surgery first, regardless of disease stage. Surgical resection is the treatment of choice for early stage cancers whereas a combined treatment modality is used for advanced stage carcinoma where surgery followed by postoperative radiation therapy remains the standard treatment. Inoperable advanced cancers are frequently managed with a combination of radiotherapy and chemotherapy. The cure rates drop to nearly half with involvement of regional lymph nodes. Selective Neck Dissection (SND) (I-III) or Supraomohyoid Neck Dissection removes the nodes at highest risk for a primary tumour originating in the oral cavity. It is extensively accepted as the appropriate selective neck dissection for patients with oral cancer with N0 neck and a clinically negative neck. In a select group of patients with N+ disease, SND is also rapidly gaining similar support. However, in N+ patients comprehensive neck dissection with preservation of the spinal accessory nerve if possible is advocated. The philosophy of neck dissection is changing as surgeons realize that more extensive surgery does not always yield a better oncologic outcome.

Patients with human papillomavirus (HPV) associated head and neck squamous cell carcinoma have significantly better survival outcomes compared to those with traditional head and neck cancers, and this has led to treatment dose reduction in these patients.

The sentinel node (SN) biopsy as a diagnostic staging procedure is gaining popularity in the management of oral cancer. Sentinel lymph node biopsy is an alternative to elective neck dissection for the identification of occult cervical metastasis in patients with early (T1 or T2) oral cavity carcinoma.

General dental practitioners are an integral part of the multidisciplinary team for the management of oral cancers and should have knowledge of the care necessary for these patients.

Introduction

Oral cancer is an emergent health problem which is common in several regions of the world.¹ Squamous cell carcinoma of the oral cavity is the most common cancer of the head and neck region² and is a leading cause of morbidity and mortality worldwide.³ Oral squamous cell

carcinoma represents a malignant transformation of keratinocytes in stratified squamous epithelium⁴. It is the sixth most frequently seen cancer of all sites.⁵⁻⁸ It has been found to be more prevalent in males with a gender ratio (M: F) of 2.0.⁹ Various factors have been implicated in the aetiology of oral cancer and include smoking, separately and in conjunction with betel-quid chewing and alcohol consumption. Other factors such as poor oral hygiene, nutrition and certain occupational exposures have also been implicated in the aetiology of oral cancer.¹⁰ Among these cigarette smoking continues to play a key role in the development of oral cancer.^{11, 12} Published reports also suggest that human papillomavirus (HPV), particularly HPV type 16/18, may be a factor, especially among persons who do not smoke or abuse alcohol.^{3, 13} The treatment of patients with oral cancer is mainly directed at controlling the primary tumour and regional neck metastases.¹⁴

Choice of treatment

The treatment of oral cancer is primarily based on three modalities: surgical resection, radiation therapy, chemotherapy and a combination of these procedures.^{15, 16} Surgery is one of the most significant treatments in oral squamous cell carcinomas.¹⁷ Surgery and radiation therapy are considered as local therapies but they do not address the issue of distant metastasis, which can only be accomplished with chemotherapy.¹⁵ The best chance of treating oral cancer is with effective primary treatment. Initial radical therapy has the best success rate, as treatment of recurrent disease has a poor outcome.¹⁸ Various factors of paramount importance that influence the choice of initial treatment are related to the attributes and stage of the primary tumour (tumour factors), to the patient (patient factors), and to the providers of treatment (physician factors).^{19, 20} The goals to be achieved in the management of oral cancer are eradication of the cancer, preservation or restoration of form and function, reduction of the sequelae of treatment, and prevention of subsequent new primary tumors.²⁰

Tumours in their early stage are well controlled equally by either surgery or radiotherapy when used as a single modality. However, radiotherapy is not preferred because of its long-term side effects, so surgery yields minimal aesthetic or functional debility in early stage carcinoma. However, combined treatment is used for advanced stage carcinoma where surgery followed by postoperative radiation therapy remains the standard treatment modality.²⁰

Oral cavity cancers embody an area of head and neck oncology with some inimitable management themes. The use of primary chemoradiation for oral cancer is limited despite a paradigm shift in the treatment of many head and neck cancers towards primary chemoradiation. The treatment option varies for small cancers of oral cavity which can be managed by surgery alone, while larger cancers are usually treated with primary surgery followed by chemoradiation.²¹ Oral cavity cancers are best managed by surgery first regardless of disease stage.¹⁵ In patients who have small oral cavity lesions (T1/T2 N0), surgical resection is the treatment of choice. For patients who have a true T1/T2N0 lesion, adjuvant radiation therapy is not required when surgical margins are negative and the patient has no risk factors for locoregional recurrence such as perineural invasion/lymphovascular invasion.²² Early stage oral squamous cell carcinoma is adequately treated by surgery alone,²¹ but only if the resection margins are negative. Usually, multimodality therapy is used for more advanced or difficult lesions.²³⁻²⁵ Tumours of the oral cavity frequently adjoin or overtly invade the mandible or the maxilla. In such patients, primary chemoradiation can result in exposed bone, osteoradionecrosis, pathologic fractures, and infected, necrotic fields. Therefore, the primary treatment of advanced oral cancers with close or overt bone involvement still usually involves surgery first, often with composite resection and more complicated reconstructions, followed by chemoradiation.²¹ Inoperable advanced cancers are typically managed with a combination of radiotherapy and chemotherapy.¹⁶

The dialectics for combined therapy is that surgery best addresses gross disease, whereas radiotherapy eradicates microscopic disease, for which surgery is less effective.²⁶ Radiotherapy is indicated when the primary tumour is large and in cases of positive surgical margins. In N0, neck radiotherapy is not required. However, radiotherapy is indicated in the presence of multiple node metastasis and extra-capsular spread.²⁷ When the surgical margins are positive, postoperative radiotherapy should be delivered as early as possible at full therapeutic dose.²⁸

Recent developments in molecular techniques have provided further evidence that surgical margins are frequently involved by tumour, even though such involvement is not always obvious on microscopic examination.²⁶ The prudent use of postoperative radiotherapy may provide the required margin of security in cases where adequacy of the surgical eradication of every cancer cell is dubious.²⁹

It has been observed that a significant number of patients develop recurrence at the primary site and in the neck even after adequate initial treatment. Hence, it is suggested that to reduce the recurrence varying combinations of treatment methods can be employed, utilizing all or as many modalities as possible at the time of initial treatment of primary tumour.³⁰ It has been seen that in patients with N3 metastases failure rates remain high in spite of the combined treatment.³¹ Early stage oral cancers also have a high local and regional failure rate despite their size and relative amenability to surgical

resection.³² Almost all local and regional recurrence occurs within 3 years, and early recurrence under 6 months has a poor prognosis. Locoregional recurrence is most likely incurable.¹⁸

Management of the neck

Treatment of regional lymphatic tissue is an essential part in the management of squamous cell carcinoma of the head and neck.³³ Neck dissection is frequently done as a part of management of the neck in oral cancer.²¹ The cure rates fall to nearly half with involvement of regional lymph nodes.³⁴⁻³⁶ The status of cervical metastases is therefore the single most important prognostic factor in the survival of patients with squamous cell carcinoma of the oral cavity.^{34,37,38} More than 50% of patients with oral squamous cell carcinoma have lymph node metastases³⁹ and the patterns of nodal spread in the neck are relatively predictable.³⁴ Neck levels I,II and III are at highest risk of nodal metastasis from primary squamous cell carcinoma of the oral cavity.⁴⁰ In patients clinically staged N0 the nodal level at risk are I-III, while in those clinically N+ the levels at risk are I-IV. The posterior triangle (level V) is rarely involved by metastases from these lesions.^{34,41}

The tumours of the tongue have the highest incidence of neck metastasis followed in descending order by the floor of mouth, lower gingiva, buccal mucosa, upper gingiva, hard palate and lips.^{27,34} The incidence of pathologically proven metastasis in the clinically N0 neck follows a similar pattern. Tumors of the upper gingiva, hard palate and lips have such a low rate of occult metastasis that elective treatment of the neck is not necessary. Surgical management of the neck in patients with oral cancer should be based upon the known risk factors for neck metastasis (tumour location, size, and thickness) and the knowledge of patterns of nodal metastasis from these lesions^{34,41}. A rational approach to surgery can be developed based on this information. In clinically N0 patient SND (I-III) or a SOHND (Supra Omohyoid Neck Dissection) is adequate whereas in N+ patients comprehensive neck dissection with preservation of the spinal accessory nerve if possible is advocated.³⁴

The concept of neck dissection was introduced in 1906 by Crile, the pioneer in the field with the idea to optimize surgical treatment for patients with cervical lymphatic spread of head and neck cancer. Various nerve, vein, and muscle preserving techniques have subsequently been developed, the most recent being selective neck dissection.⁴² In the management of lymph node disease, the most profound alteration probably in philosophy over the past decade relates to the selectivity with which lymph node groups at risk are being removed.⁴³

In Selective Neck Dissection (I-III) or supraomohyoid neck dissection removal of nodal regions I, II and III is done.^{44,45} The procedure involves removal of the nodes at highest risk for a primary tumour originating in the oral cavity.²⁹ SOHND or SND (I-III) is the standard staging procedure.⁴⁶ It is extensively accepted as the appropriate selective neck dissection for patients with oral cancer with N0 neck and a clinically negative neck.^{44,47,48}

This procedure is recommended for patients with oral cancer who are at risk of harbouring occult nodal disease. Tumours originating in this region, particularly the subsites of the oral tongue and the floor of mouth have a high tendency to metastasize early, regardless of their size and differentiation. Unless the treatment of choice for the primary lesion is radiotherapy, elective neck dissection with removal of levels I through III (level IV for tongue cancer) is the minimal recommended treatment for oral squamous cell carcinoma associated with N₀ nodal disease.⁴⁵ With its tremendous outcomes supraomohyoid neck dissection has assumed increasing importance as a staging lymphadenectomy in patients with N₀ oral and oropharyngeal squamous cell carcinoma, as well as a potentially curative procedure in selected patients with limited metastatic disease in the neck.⁴⁸ Recently, various pathological studies of lymph node metastases suggest that it is also logical to use SND in some patients with clinically obvious cervical lymph node metastasis. The application of postoperative radiation therapy further diminishes the rate of regional failure in patients following SND when indicated. SND is now the preferred surgical management in elective treatment of cervical lymph nodes. In a select group of patients with N+ disease, SND is also rapidly gaining similar support.⁴⁹ SND (I-III) in patients with pathologically positive nodes in neck is inadequate therapy for regional control without post-operative radiation therapy. However, in patients with pathologically positive nodes in the neck, SND (I-III) with postoperative radiation therapy can achieve regional control comparable to that of comprehensive neck dissection and postoperative radiation therapy.⁵⁰ Furthermore, SND plus adjuvant radiotherapy is highly efficacious, having minor morbidity for selected oral cancer patients with a pN+ neck with or without microscopic extra capsular spread (ECS).

Efforts are being made to replace Modified Radical Neck Dissection (MRND) with SND for early node positivity.⁵¹ It is conceivable that in the near future SND combined with adjuncts such as radiotherapy or chemotherapy will become the standard treatment for advanced nodal disease.²⁷ Metastasis to level V lymph nodes is a rare occurrence in carcinoma of the upper aerodigestive tract. Owing to the low prevalence of level V metastasis in N₀ and N+ disease with metastases, SND is adequate management in these cases. The low likelihood of metastases at level V, even in N+ disease, should be kept in mind when performing lymphadenectomy for squamous cell carcinoma of the upper aerodigestive tract.⁴¹

The indications for elective cervical lymphadenectomy of the contralateral neck includes patients with primary lesions involving the floor of mouth, ventral surface or midline involvement of the tongue, for whom ipsilateral neck dissection is planned, and when there are no definitive indications for postoperative radiotherapy. Furthermore, contralateral therapeutic neck dissection is indicated for patients with clinically N_{2c} disease.⁴⁵ The neck should always be treated in patients who have larger T3 and T4 cancers because of the high incidence of nodal metastasis.²¹

Currently, Radical Neck Dissection (RND) and modified RND (MRND) are the major players for the surgical management of advanced nodal disease.²⁷ The accrued knowledge suggests radical neck dissection is the standard by which all cervical lymphadenectomy procedures are judged.⁵² The current indications for classical RND are (a) patients with N3 neck disease not allowing the preservation of the spinal accessory nerve, (b) multiple positive lymph nodes involving the spinal accessory nerve and /or the internal jugular vein, and (c) extensive residual or recurrent neck disease after radiotherapy and grossly extranodal spread.⁴⁹ The major indication for the classical radical neck dissection remains the presence of multiple lymph node metastasis in patients with oral cancer involving the spinal accessory nerve and internal jugular vein; however, in these cases the probability of long term survival is low and the indication for surgery needs to be reviewed. These patients may benefit from surgery followed by chemoradiotherapy.⁵³

One of the most important prognostic factors in head and neck squamous cell carcinoma is neck metastases.^{34,35, 37,52,54-56} On account of this widely demonstrated fact the management of neck disease in head and neck cancer has been considered one of the most important aspects of treatment. In principle, the indication of neck dissection in oral cancer is a problem of risk-benefit evaluation between the probability of neck metastases, the probability of complications associated with neck dissection and the possible prognostic influence of late diagnosis of metastasis during follow-up.³⁹

The philosophy of neck dissection is evolving quickly with regard to the selectivity of the removal of lymph nodes which are at risk of metastasis.⁵⁷ The doctrine of neck dissection is changing as surgeons comprehend that more extensive surgery does not yield a better oncologic outcome. The RND has been essentially replaced by SND and MRND with appropriate use of postoperative radiation therapy thus marking a turning point in the treatment of oral cancer.⁴⁹ Such developments are in the best interest of maximizing cure of these patients while also maintaining the patient's function and quality of life. It is anticipated that further development of novel treatment strategies will occur in the future.⁵⁸ Eventually the decision to treat the neck and the modality used depend on the patient's preference, physician and institution experience, the risk of a second primary cancer in the future, and the modality used to treat the primary cancer.³⁸

It seems that in the near future SND can be replaced by even more selective neck dissection, such as superselective neck dissection. This involves the compartmental removal of fibrofatty tissue contents within the defined boundaries of two or fewer contiguous neck levels. It is indicated mostly for elective treatment of the clinically N₀ neck⁵⁹ but can be done for salvage treatment of persistent lymph node disease after chemoradiotherapy.⁶⁰

Furthermore, if comparable results can be attained with a more selective neck dissection, then this will considerably improve the quality of life of patients with oral cancer.⁵⁷

De-escalation treatment protocols for human papilloma virus-associated HNSCC squamous cell carcinoma

Human papillomavirus associated head and neck squamous cell carcinomas (HNSCC), mainly oropharyngeal squamous cell carcinomas (OPSCC), are characterized by a significant survival advantage over their HPV-negative counterparts. Even though the reasons behind this are still not fully elucidated, it is usually accepted that these tumours have a greater response to ionizing radiation that might explain their favourable outcomes.⁶¹

Furthermore, Lill C et al⁶² observed a considerable better response to concomitant radiochemotherapy or radioimmunotherapy (or even radiation alone) in HPV-positive patients compared to the HPV-negative group. Overall, patients with HPV-positive OPC usually have a better prognosis than patients with traditional, HPV-negative, head and neck cancer.⁶³ Since patients with HPV-associated head and neck squamous cell carcinoma have significantly better survival outcomes compared to those with traditional HNC, this has led the philosophy of treatment dose reduction in these patients.⁶⁴

Is radiation dose reduction the right answer for HPV-positive head and neck cancer?

The possibility of de-escalating treatment intensity provides an opportunity to reduce morbidity from standard treatment protocols. At present, three main de-escalation treatment policies are being investigated: (1) Exploring cetuximab as an alternative to cisplatin when given concurrently with radiation; (2) Reduction of radiation dose when given in combination with chemotherapy as primary treatment (guided by induction chemotherapy response) and (3) Reduction of adjuvant chemotherapy or radiotherapy dose following primary treatment with surgery (guided by histopathological features in the resected specimen).⁶⁵

Modifications in treatment protocols aimed at de-escalation are currently being evaluated. These tumours are more responsive to treatment with a favorable patient outcome and good prognosis.⁶⁶

Role of sentinel lymph node biopsy in management of oral cancer

The sentinel node (SN) biopsy as a diagnostic staging procedure is gaining popularity in the management of oral cancer. Sentinel lymph node biopsy is an alternative to elective neck dissection for the identification of occult cervical metastasis in patients with early (T1 or T2) oral cavity carcinoma in centers where experience for this procedure is available.⁶⁷ The principal endeavour of sentinel node biopsy is to precisely identify lymph node metastases without the requirement for lymph node dissection, thus curtailing morbidity from potentially redundant surgery and facilitating the treatment of patients with or without nodal disease. The standard SLNB procedure involves a peri-tumoural injection of a ^{99m}Tc-labelled colloid tracer, with drainage mapping by lymphoscintigraphy and the injection of a blue dye into the primary tumour intra-operatively. Radioactivity

is detected with a gamma camera, and/or blue lymph nodes are harvested during a surgical procedure. Using step-serial sectioning, immunohistochemistry and histopathology, it is possible to detect micrometastases and isolated tumour cells with higher sensitivity compared to traditional histology. SLNB-positive patients subsequently undergo neck dissection while SLNB-negative patients are observed.^{68,69} It has been suggested that for accurate biopsy, the three hottest sentinel nodes should be sampled for histology and it is also important to be aware that sentinel nodal size is an inaccurate predictor of nodal metastases.⁷⁰

Role of the general dentist in the management of oral cancer

General dental practitioners (GDPs) have a major part to play in the early diagnosis, referral and management of patients with oral cancer. They not only play a key role in arresting the mortality rate due to oral cancer, but also educate their patients. GDPs should immediately refer a patient with a suspicious lesion to a specialist.

Before the start of the radiotherapy treatment, proper clinical and oral radiographic examination of the patient is required. The patient is assessed for any caries and root canal treatment which may be necessary. Prosthodontic requirements are managed. The patient should be instructed to maintain proper oral hygiene and mouthrinses with chlorhexidine (alcohol-free) together with the use of soft toothbrush and interdental hygiene aids are advised. In patients where the mouth is too painful for cleaning and a mouthwash cannot be tolerated, the oral tissues should be swabbed with polygon oral swabs. Daily application with 1.1% sodium fluoride in a custom tray should also be advised. Supragingival prophylaxis or scaling and root planing should be done if required. The maximum mouth opening (inter-arch or inter-incisal distance) should be measured before radiotherapy is started, and the patient and/or clinician should measure this distance frequently thereafter to ensure it is maintained.⁷¹

The general consensus is that teeth with a poor prognosis must be extracted before radiotherapy. This includes teeth that present with advanced carious lesions with questionable pulpal status or pulpal involvement, extensive periapical lesions, moderate or advanced periodontal disease (extensive attachment loss) especially teeth with advanced bone loss and mobility or furcation involvement, and impacted or incompletely erupted teeth, particularly third molars. The extractions should be done 10 to 14 days before radiotherapy. Before doing extractions a complete blood count of the patient is necessary.^{72,73}

During the treatment regular monitoring and management of the oral effects of cancer treatment on a weekly basis should be done. The patients are advised to keep a high level of oral hygiene. Tooth extractions or any surgery is avoided during the treatment. Patients should be made aware of oral mucositis that is a common and debilitating complication of cancer treatment. For the prevention of mucositis, patients should be told to maintain proper oral hygiene

and avoid smoking, alcohol, poorly fitting prostheses and should ensure adequate nutritional and hydration support. Various treatments have been identified as providing some benefit, albeit weak, to prevent or reduce the severity of mucositis. These include aloe vera, amifostine, granulocyte-colony stimulating factor, intravenous glutamine, honey, keratinocyte growth factor, laser, polymixin/ tobramycin/amphotericin antibiotic pastilles/ paste and sucralfate. For pain control of mucositis patient-controlled analgesia with morphine, 2% morphine mouthwash or 0.5% doxepin mouthwash can be used. Patients may also initially develop the symptoms of xerostomia within a couple of weeks of starting radiotherapy and the dry mouth may not recover until after the treatment has stopped. In general, this can be helped by frequent sips of cold water/milk or other sugar-free nonacidic cool drinks. The use of saliva substitutes may be helpful to patients complaining of a dry mouth and offers symptomatic relief for patients with insufficient salivary function.^{71,72} During the treatment the prevention of trismus, rather than its treatment, is a desirable objective. Patients can be advised on mandibular exercises or the use of the Thera Bite jaw motion rehabilitation system. Patients after radiotherapy are more susceptible to oral candidiasis. The treatment includes anti-fungal drugs totally or partially absorbed by the gastrointestinal tract (e.g. ketoconazole).⁷²

After the treatment has finished, xerostomia is likely to continue to be a problem and trismus may become progressively worse. The treatment approaches previously discussed need to be re-emphasized and continued. For the prevention of radiation caries and plaque control patients should be advised fluoride products (for example, Duraphat), sodium fluoride (0.05%) alcohol-free mouthrinse, self-applications of 1% sodium fluoride gel in custom-made applicator trays and chlorhexidine (alcohol-free) rinses. Extraction of teeth is not recommended for at least 6-12 months post radiotherapy.⁷²

Osteoradionecrosis (ORN) is an impending long-term and arguably the most serious side effect of radiotherapy. The definition of osteoradionecrosis is an area of exposed devitalized irradiated bone that fails to heal over a period of three to six months in the absence of local neoplastic disease. Efforts must be made to avoid osteoradionecrosis by pre-radiotherapy dental assessment. Careful oral health maintenance, timely dental treatment and dealing promptly with oral trauma are all essential in preventing ORN. Early diagnosis of ORN becomes important for the GDP. Hyperbaric oxygen (HBO) appears to reduce the risk of ORN. HBO is used before surgery for up to as many 20 daily treatments. Surgery (removal of necrotic tissue) is then followed by 10 daily postoperative HBO treatments to maximize healing. More recently in the treatment of ORN a synergic effect has been observed between pentoxifylline (PTX) and tocopherol (vitamin E). The suggested daily dose is 800 mg/day and vitamin E 1000 IU/day (five days a week), but more clinical trials are required to validate this treatment. Regular oral health monitoring is imperative with three monthly recalls initially until it has been determined that the patient is maintaining their oral care at a satisfactory level, and then recall can be extended. The GDP has a continuing role in the tertiary prevention, regular follow-ups and for any patient with a suspicion of recurrence or a new primary malignancy an urgent referral is required.^{72,74}

The idea behind all the strategies in the treatment of patients with oral cancer is control of the disease. However, with increasing recognition of the extensive morbidity of radical surgery, emphasis is being placed on surgical conservatism if it does not negatively affect disease control and if it offers improved post treatment function and cosmesis.⁷⁵ Cure of the cancer patient with the least possible morbidity should be the goal of the surgery.⁷⁶ A multidisciplinary approach is important to ensure the highest quality of patient care and GDPs are an integral part of this multidisciplinary team.

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