RECENT CONCEPT AND CHANGES IN MANAGEMENT OF SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY: A REVIEW OF LITERATURES

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ABSTRACT

The management of oral cavity cancer is challenging in the light of recent updates and guidelines. Decision making should involve multidisciplinary team including surgical oncologist, radiation oncologist and medical oncologist. However, majority of the center in our country lack multidisciplinary team and the clinicians are solely responsible for decision making. Hence this review article might be helpful for clinician to make a rationale decision based on recent updates while managing oral cavity cancer.

Keywords: Cancer oral cavity, Guidelines, Malignancy

INTRODUCTION

Oral cancer is the sixth most common cancer worldwide.[1] India has always been projected as the country with highest incidence but there are reports from the Pakistan and Sri Lanka which shows they have higher incidence.[2] However, there are not many published data on incidence and prevalence of oral cancer in Nepal.

The etiology of oral malignancy is multifactorial. The most important etiological factors are tobacco use, excess consumption of alcohol and betel quid usages.[3] Based upon the global evidence of risk factors it can be categorized into established, strongly suggestive, possible and speculative.[2] Among them the established factors are smoking, Chewing tobacco, snuff dipping, alcohol misuse and betel and syphilis. Whereas strongly suggestive factor are Sunlight (for carcinoma of Lip) and radiation, similarly the viruses and immunodeficiency are thought to be possible causes.

The daily use of fruits and vegetables are associated with decreased incidence of oral cancer at least by quarter. It indicates lack of consumption of antioxidant in our diet may be predisposing factor for malignancy; however, it is yet to be established.[4]

METHOD FOR LITERATURE SEARCH AND REVIEW

A search for relevant publications was carried out. The online databases PubMed and google scholar were searched using the term "current management of oral cavity". Studies were limited to those written in English language, and including abstracts. On initial search, more than 1000 of articles relevant to the topic were identified, but on further review only articles published after 2000 except one article written by McGregor et al were included. We finally reviewed 15 articles which covered the recent changes and new concept in treatment of oral cavity cancer.

DISCUSSION

We have discussed the result highlighting in radiological assessment and new changes in 8thAJCC classification.

Radiological assessment

There are basically the two modalities to assess the extent of tumor in oral cavity i.e, MRI and CECT. Broadly, CECT is for bony assessment when the tumor is near the bony framework and the MRI is done for soft tissue, marrow extension and perineural spread in oral cavity.

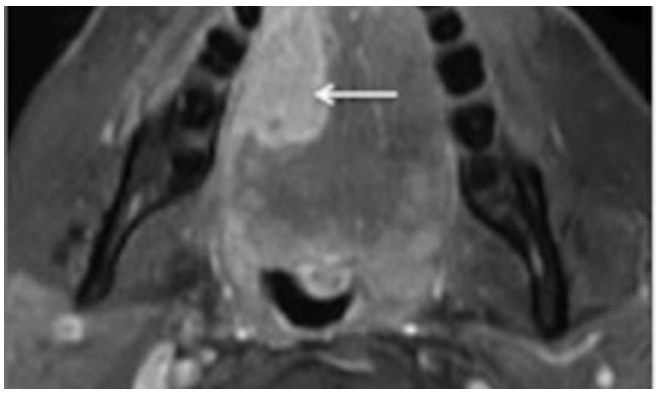

Figure I: T1W MRI image showing the intensely enhancing lesion at right lateral border of tongue(shown by arrow) in T1FS contrast enhanced.

For the tongue, floor of mouth lesion and hard palate, MRI is preferred with different sequences. Routinely, T1 and T2 sequence are done with and without fat suppression. T1W images are good for anatomy of the site whereas T2 images are for tissue characterization. STIR sequences[5] have similar signal like T2 images but it is better for study of denervation changes after perineural invasion by the cancer. An optimal MR imaging protocol is incomplete without post-gadolinium T1W sequences as the tumor frequently shows intense enhancement and is best displayed on this sequence (Figure I).The sign of perineural invasion in T1W images are replacement of high signal marrow fat by intermediate signal tumor and asymmetrical thickening of the nerve which can be further enhanced by administration of paramagnetic contrast.

In the past, lot of importance was given for measuring the tumor thickness in MR. A tumor thickness of > 4 mm on histopathology has been associated with increased incidence of cervical nodal metastases.[6] Lam et al. found a higher concordance rate for tumor thickness using contrast-enhanced T1W images (83%) than with T2W images (56%) due to peritumoral inflammation seen as hyper-intensity with the latter.[7] However , now a days we are doing prophylactic neck dissection even in N0 neck (Node negative neck) therefore measuring the tumor thickness on MR to decide for the neck dissection does not have any difference. The decision of doing prophylactic neck dissection in all N0 neck has emerged after the research article by D'cruz et al.[8]

For Gingivobuccal and Retromolar lesion, Multidetector contrast enhanced CT scan (CECT) with puff technique is preferred. Gingivobuccal lesion is the cancer arising from the gingiva, alveolus, buccal mucosa and gingivobuccal sulcus. In cases of Squamous Cell Carcinoma of oral cavity, one should look at CECT focusing following things; a. Epicenter of tumor, soft tissue extension (paramandibular disease extension), b. Involvement of infratemporal fossa (ITF), c. Masticator space and Pterygomaxillary fissure (T4a and T4b), d. Bone erosion, and e. Nodal status.

The important thing to consider here is whether the tumor has involved high Infra Temporal fossa (ITF) because once the high ITF is involved, it is technically unresectable. Although the AJCC 6th edition mentioned masticator space involvement (T4b) as unresectable, the 7th and 8th edition reclassified this as very advanced disease. Hence, the high ITF is the only sub-site where we cannot obtain adequate margin for tumor clearance.

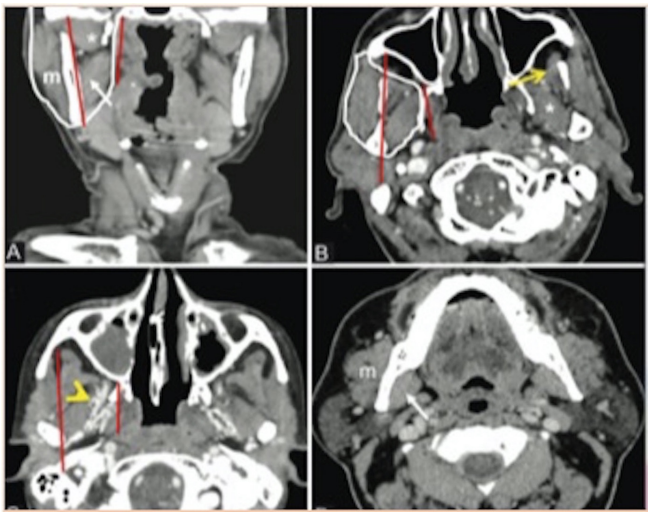

Figure II: CECT showing the difference between masticator space and ITF. A: long white arrow-medial pterygoid, B: yellow arrow temporalis muscle, C: yellow arrow head pterygoid venous plexus, D: long white arrow medial pterygoid

The masticator space is the area bounded by fascial layer from masseter muscle to medial pterygoid plates. It contains ramus of mandible, posterior part body of mandible, masseter muscle, temporalis, pterygoid muscle and inferior alveolar nerve as blanketed by white line in figure II (A & B). ITF is also one of the compartment of masticator space. It is the compartment covered by red line in the figure III (C). ITF is bounded anteriorly by posterior surface of maxilla, superiorly by greater wing of sphenoid, posteriorly by mastoid temporal bone, laterally by medial surface of ramus of mandible, medially from anterior to posterior by sphenoid pterygoid process, pterygomaxillary fissure and lateral wall of nasopharynx. Hence the masseter muscle is not component of ITF.

The ITF is divided into supra notch and infra-notch compartment by Sigmoid notch. It is the notch formed between coronoid process and condyle of mandible as shown in Figure III. Radiologically, if the tumor has reached lateral Pterygoid muscle which lies in high ITF it will be technically not resectable. However, tumor upto the medial Pterygoid muscle which forms the lower boundary of ITF is consider as low ITF and is resectable with adequate margin.

Figure III. The sigmoid notch of mandible

Eigth AJCC Staging - New Changes

Clinical and pathological TNM staging has been modified recently by AJCC from 2018.

In Clinical and Pathological Staging, Depth of invasion (DOI) has be incorporated for carcinoma of tongue as follows:- DOI <= 5 mm T1, DOI >5-10mm T2, DOI >10mm T3 . This was after the research finding by Ardalan Ebrahimi et al which concluded the DOI is the significant independent predictor of disease specific survival (p value <0.01).[9]

The Clinical nodal staging in 8th AJCC has incorporated extra nodal extension (ENE) which may be detected while doing radiological evaluation but the final confirmation is through the histopathology report. Rest of the staging has remained same as that of 7th edition. The pathological nodal staging is slightly different than the clinical one on 8th edition. The nodes with extra nodal extension of size less than 3 cm will still be classified into N2a but if the node of size more than 3 cm with ENE will be classified into N3b.

Surgical approach

Most of the SCC of oral cavity are resectable if we have good reconstructive team. However tumor involving high ITF are not surgically salvageable which includes a) Lateral pterygoid or temporalis muscle involvement in CECT, b) Perineural invasion of V3 reaching upto skull base/foramen ovale or pterigopalatine fossa, c) Significant oropharyngeal involvement encasing the carotid, d) unresectable nodes and e) Tumor involving hyoid bone from tongue.

While selecting the surgical approach surgeon must aim for at-least clear margin (5-10 mm) microscopically and have to plan the incision addressing the neck nodes and bone (if required). At the same time he should be able to reconstruct the defect with available expertise. Regarding the margin, surgeon should be aware of the fact that the margin can shrink up to 30% while processing of the resected specimen in the lab. Similarly, surgeon should have good conceptualization of third dimension of margin which is also known as the base of tumor.

Per-oral approach:

This approach allows natural opening to remove the lesion from oral cavity and it is routinely practiced for small tumor like T1 and sometimes T2 especially of tongue. However, it has major limitation in patients with extensive submucosal fibrosis where mouth opening is restricted.

Mandibulotomy:

This approach is suitable for posteriorly based lesion in oral cavity and the patient having trismus. Mandibulotomy is generally combined with midline lip split incision . The osteotome is best done in-between the lateral incisor and canine where the dental roots are apart. The injury to mental foramen has to be avoided to preserve labial sensation. Marking of the plates and screw before commencing osteotomy is done to avoid malocclusion at the end of the surgery.

Visor approach:

This approach is very useful when we have to do bilateral neck dissection for the mid line lesions. It is basically done for advanced tongue lesion (T3 T4) which has also involved floor mouth and/or mylohyoid muscle. The tongue and floor of mouth are pulled into the neck by this approach hence it is also known as pull through approach. This allows surgeon to remove tongue, floor of mouth alongwith involved muscles with adequate margins all around. The defect at floor of mouth and the tongue has to be replaced either by free or regional flap.

Lower cheek flap:

This approach is best suited for lower gingivobuccal sulcus or buccal mucosa lesions which also need mandibular resection either marginal or segmental. It can be accomplished either by midline split or angle split incisions but the golden rule here for both incisions is to raise

the flap above the bucinnator muscle keeping good amount of fat in the flap if the skin is not involved. At the same time surgeon must not compromise the margins for the base of tumor arising from Lower gingibobucal sulcus or buccal mucosa while raising the flap.

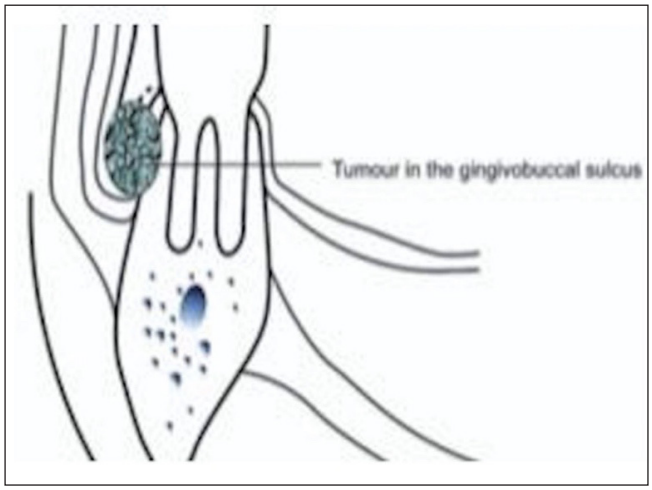

Figure IV. Tumor invasion via occlusal surface and alveolar process

There are generally two types of mandibulectomy practiced these days which are marginal mandibulectomy and segmental mandibulectomy. In order to understand the rationale of choosing these procedures one should understand the mechanism of tumor invasion into irradiated and non-irradiated mandible.

According to Mc Gregor et al[10] patterns of invasion of squamous cell carcinoma to the non irradiated dentulous mandible is mainly via alveolar process at the occlusal surface (Figure IV). There is no direct invasion of periosteum over the mandible. Similarly, in edentulous mandible also the invasion is from the remaining alveolar process of the mandible. This finding confirms that the rationale of adopting conservative mandibulectomy in non-irradiated mandible. In irradiated mandible, tumor entry were found to be variable than in the non-irradiated mandible. They have multiple foci of tumor invasion to the bone. This information advocate not to perform any conservative mandibulectomy in previously irradiated mandible.

Marginal mandibulectomy is generally practiced in tumor of gingivbuccal sulcus which has abutted the mandible or has minimal alveolar process invasion provided there is no previous history of radiation. We have to preserve at least 1 cm of height of mandible in order to prevent fracture later on during mastication.

Segmental mandibulectomy is always preferred in irradiated mandible, edentulous mandible (where 1cm vertical height of mandible is not possible to maintain after marginal mandibulectomy), the paramandibular disease and gross bony erosion. The paramandibular disease is the condition when huge gingivobuccal sulcus tumor has involved the periosteum of mandible along its height which is suspected clinically by fixed soft tissue over the mandible when palpated from outside.

Neck dissection

Clearance of neck is one of the important aspect of treating the squamous cell carcinoma of oral cavity. It is not only the clearance of suspicious or positive neck nodes but it also has important role in final staging of the malignancy. This final histopathological staging helps surgeon to decide for further adjuvant treatment like Radiotherapy or Radiochemotherapy also provide information about the prognosis.

The controversies regarding elective neck dissection in N0 neck in oral cavity cancer was ended by the finding of study by D' Cruz et al8. In their randomized control trial of 500 patients with T1 and T2 SCC of Oral cavity, 245 underwent elective neck dissection at the time of first surgery and 255 therapeutic only when the neck nodes were detected during follow up. At the end of follow up of 3 years, the overall survival was 80% in elective and 67.5% in therapeutic group (p=0.01). Similarly, the disease specific survival was 69.5% in elective & 45.9% in therapeutic group (p= 0.001). Hence, D' Cruz et al concluded that elective Selective Neck Dissection of level I to III has higher rates of overall and disease specific survival and should be performed in all N0 SCC of oral cavity.

The management of clinically N+ nodes is dictated by the positive status of node at the level IIA. The Multivariate analysis of Gauri et al study revealed level IIA positivity as an independent predictive factor for metastases to both IIB and V level.[11] They also concluded that the positive nodes at level IIA and level III were statistically significant factors predicting metastases to level V. Hence once level IIA is positive either by FNAC or Frozen section surgeons have to convert SND (I-III) to MRND Type3.

According to American Society of Clinical Oncology (ASCO) 2019[15] recommendation

(Rec 1.2a), surgery for N0 T1,T2 oral cavity SCC should include level I- III with yield of lymph node equal to 18. Similarly, Recommendation 1.2b states surgery for cN+ neck should include I-IV with dissection, level V may be offered in patients with multistational disease.

The final histopathological specimen reporting is endorsed by United Kingdom National Multidisciplinary Guidelines.[12] The information which need to be mentioned from primary lesion are site, histological type, differentiation, growth pattern, maximum diameter, DOI, lymphatic, vascular & perineural invasion, invasion of bone and cartilage, distance of carcinoma from resected margin. Similarly, information needed from lymph nodes are number and site of positive lymph nodes, maximum size of positive lymph node and extracapsular invasion by the tumor in the lymphnodes.

Role of Adjuvant treatments:

Adjuvant treatment modalities after primary surgery are Adjuvant Radiotherapy and Adjuvant Chemoradiotherapy. The decision for adjuvant treatment should be based on the overall prognosis and the stage of the cancer.

There is robust evidence to advocate for adjuvant CTRT when there is positive or close margin or extra capsular spread of cancer in the lymph-nodes by the article by Bernier and copper et al.[13] In their study of 459 high risk patients who had two or more regional lymph nodes involved, extra-capsular spread of disease, or microscopically involved mucosal margins of resection of oral cavity, at the end of follow up of 45.9 months the rate of local and regional control was significantly higher in the adjuvant CTRT group than in the group given RT alone (hazard ratio for local or regional recurrence, 0.61; 95 percent confidence interval, 0.41 to 0.91; P = 0.01). Similarly estimated two-year rate of local and regional control was 82 percent in the Adjuvant CTRT group, as compared with 72 percent in the adjuvant RT group. Lastly, Disease-free survival was significantly longer in the combined-therapy group than in the radiotherapy group. ASCO 2019[15] has also advocated for Adjuvant chemoradiotherapy using intravenous bolus cisplatin 100 mg/m2 every 3 weeks to patients with oral cavity cancer and extranodal extension in any positive node, regardless of the extent of extranodal extension and the number or size of involved nodes.

Adjuvant Radiotherpy after primary surgery is generally practiced whenever the cancer is stage 3 or stage 4 or pN2 or pN3 disease. However, in small volume neck positive disease the role of adjuvant radiotherapy is still controversial. ASCO 2019 does not recommend (Recommendation 2.1a)[15] adjuvant neck radiotherapy to patients with pathologically node-negative pN0 or a single pathologically positive node (pN1) without extranodal extension after high-quality neck dissection, unless there are indications from the primary tumor characteristics. It should be administered in patients with pN1 who did not undergo high quality neck dissection (Recommendation 2.1b).

CONCLUSION

With the advancing technology and better understanding of pathophysiology, there has been constant change in the medical practice. Ongoing high quality research work worldwide is also bringing many new concepts in the cancer management. This article reviewed on the newer concepts in the management of oral cavity squamous cell carcinoma.

REFERENCES

1. Shah JP, Gil Z. Current concepts in management of oral cancer–surgery. Oraloncology. 2009;45(4-5):394-401.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral oncology. 2009;45(4-5):309-16.
3. World Health Organization, IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer. Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines. IARC; 2004.
4. Petridou E, Zavras AI, Lefatzis D, et al. The role of diet and specific micronutrients in the etiology of oral carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2002;94(11):2981-8.
5. Arya S, Chaukar D, Pai P. Imaging in oral cancers. The Indian journal of radiology & imaging. 2012;22(3):195.
6. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph node involvement in squamous cell carcinoma of the oral cavity: a meta analysis of reported studies. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2009;115(7):1489-97.
7. Lam P, Au-Yeung KM, Cheng PW, et al. Correlating MRI and histologic tumor thickness in the assessment of oral

tongue cancer. American Journal of Roentgenology. 2004;182(3):803-8.

8. D'Cruz AK, Vaish R, Kapre N, et al. Elective versus therapeutic neck dissection in node-negative oral cancer. New England Journal of Medicine. 2015;373(6):521-9.
9. Ebrahimi A, Gil Z, Amit M, et al. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. JAMA Otolaryngology–Head & Neck Surgery. 2014;140(12):1138-48.
10. McGregor AD, MacDonald DG. Routes of entry of squamous cell carcinoma to the mandible. Head & neck surgery. 1988;10(5):294-301.
11. McGregor AD, MacDonald DG. Routes of entry of squamous cell carcinoma to the mandible. Head & neck surgery. 1988;10(5):294-301.
12. Pantvaidya GH, Pal P, Vaidya AD, Pai PS, D'Cruz AK. Prospective study of 583 neck dissections in oral cancers: Implications for clinical practice. Head & neck. 2014;36(10):1503-7.
13. Helliwell TR, Giles TE. Pathological aspects of the assessment of head and neck cancers: United Kingdom National Multidisciplinary Guidelines. The Journal of Laryngology & Otology. 2016;130(S2):S59-65.
14. Jassem j, Ang KK, Lefèbvre JL. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the eortc (# 22931),2005.
15. Koyfman SA, Ismaila N, Crook D, et al. Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO clinical practice guideline. Journal of Clinical Oncology. 2019 10;37(20):1753.