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ORIGINAL RESEARCH

Patterns of involvement of mandible in oral malignancies

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ABSTRACT

Background: Head and Neck Squamous cell carcinoma (HNSCC) including oral cancers which constitutes the most common upper aero digestive tract carcinomas. It accounts for 3% of all cancers in the developed countries like USA whereas in developing countries like India it accounts for 30% of all cancers. More than 90% of oral cancers are squamous cell carcinomas. Oral cancer is a major problem in the Indian subcontinent where it ranks among the top three types of cancer in the country. An age-adjusted rate of oral cancer in India is high that is, 20 per 100,000 population.**Materials and methods:** This study consisted of 80 randomly selected patients with histologically diagnosed SCC, who underwent mandibular resection as part of their treatment. Mandibular resection was deemed necessary either because of the clinical diagnosis of bone involvement or to achieve R-0 resection. All patients were treated at the Gujarat Cancer and Research Institute, Ahmedabad, India, from October 2010 to December 2012. Tumors were staged (clinical TNM stage groupings) according to the 2010 guidelines of the AJCC.**Results:** Eleven patients (13.75%) had grade I tumors, fifty-one patients (63.75%) had grade II tumors and eighteen patients (22.50%) had grade III tumors. After preliminary investigations patients were assigned into Clinical TNM stage groups as per AJCC staging system (seventh edition). One patient (1%) belonged to stage I, 13 (16%) patients belonged to stage II, 12 (15%) patients belonged to stage III and fifty-four patients (68%) belonged to stage IV.**Conclusion:** Significant contributing factors of oral squamous cell carcinoma infiltration into the mandible are the size/T-stage and location of the primary tumor. Larger tumors are more likely to infiltrate. Gingiva and retromolar trigone are the most favored locations that facilitate tumor infiltration into the mandible. Direct contact of the tumor on the attached mucosa usually provides a portal of entry of the tumor into the medullary space.

Key words:HNSCC, TNM Stage, AJCC

1. INTRODUCTION

Head and Neck Squamous cell carcinoma (HNSCC) including oral cancers which constitutes the most common upper aero digestive tract carcinomas. It accounts for 3% of all cancers in the developed countries like USA whereas in developing countries like India it accounts for 30% of all cancers [1, 2]. More than 90% of oral cancers are squamous cell carcinomas. An age-adjusted rate of oral cancer in India is high that is 20 per 100,000 population. Oral cancer is of significant public health importance to India. Firstly, it is diagnosed at later stages which result in low treatment outcomes and considerable costs to the patients who typically cannot afford this type of treatment. Secondly, rural areas in middle and low-income countries also have inadequate access to trained providers and limited health services. As a result, delay has also been largely associated with advanced stages of oral cancer. Earlier detection of oral cancer offers the best chance for long term survival and has the potential to improve treatment outcomes and make healthcare affordable. Thirdly, oral cancer affects those from the lower socioeconomic groups, that is, people from the lower socioeconomic strata of society due to a higher exposure to risk factors such as the use of tobacco. Lastly, even though clinical diagnosis occurs via examination of the oral cavity and tongue which is accessible by current diagnostic tools, most cases present to a healthcare facility at later stages of cancer subtypes, thereby reducing chances of survival due to delay in diagnosis. The oral cavity is defined as the

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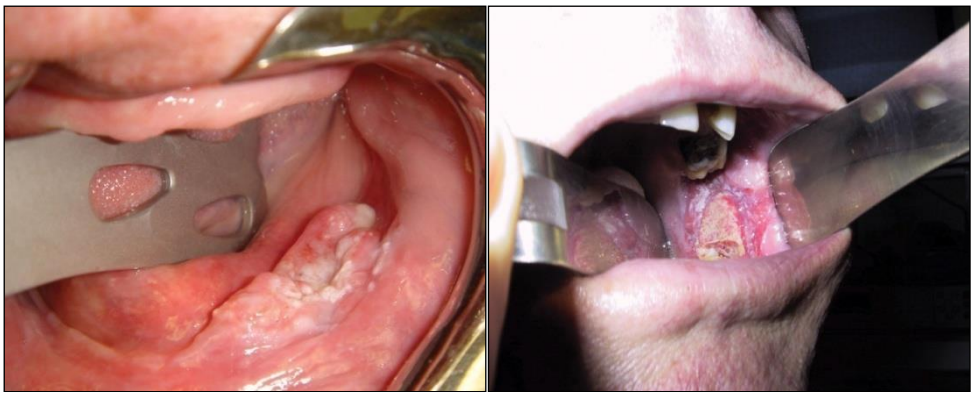
area between the vermilion border of the lips to the junction of the hard and soft palate superiorly, and to the line of the circumvalIate papillae of the tongue inferiorly. It is divided into the following regions: lip, buccal mucosa, lower and upper alveolar ridges, retromolar trigone, floor of mouth, hard palate, and anterior two thirds of the tongue. Oral SCC adjacent to the mandible can invade bone by direct extension, necessitating mandibular resection. Mandibular bone invasion alters the staging and treatment of oral SCC, wherein treatment involves resection of a part of the bone followed by reconstruction in some patients.

Recent trends in treatment of oral cancers involve preservation of the mandible because the mandible serves several important roles in functional, esthetic and psychological aspects of the human being. In terms of function and esthetics, the result achieved after resection of an oral squamous cell carcinoma and subsequent reconstruction depends on whether it was possible to maintain continuity of the arch of the mandible [3]. The desired result is achieved either by preserving continuity or by reconstructing the arch if it is necessary to sacrifice a segment of the bone. Of these two alternatives, preservation of the arch has the advantage of simplicity, and therefore would be preferable if it was compatible with effective tumor excision. With completion of clinical staging of disease, that is the assimilation of all information from clinical examination, imaging studies, and pathology; the patient should be prepared for surgery.



(A) **(B)**

A: Carcinoma of the floor of the mouth involving lower alveolus.
B: Carcinoma of the retro molar trigone.

A perplexing problem facing the head and neck surgeon is the assessment of the relationship of oral cancers to the mandible prior to definitive therapy. Of particular importance is the detection of those tumors that invade the mandibular periosteum or bone. Tumors invading the mandible tend to be more aggressive locally and are usually large and require partial or total mandibular excision. Determination of the extent of mandibular invasion by oral cancer is crucial for treatment planning. Treatment failures of oral squamous cell carcinoma usually results from local recurrence. To minimize recurrence, resection of the tumor must include a margin of normal tissue.

Presence of sub mucosal fibrosis further complicates the situation. Oral sub mucous fibrosis is a disease due to a chronic, insidious change in fibro-elasticity, characterized by burning sensation in the oral cavity, blanching, and stiffening of the oral mucosa and oro-pharynx leading to trismus and inability to open the mouth [4]. It is predominantly seen in Indians and other Asians. Once, the disease has developed, there is neither regression nor any effective treatment. Oral submucous fibrosis has a high rate of morbidity because it causes a progressive inability to open the mouth, resulting in difficulty in eating and consequent nutritional deficiencies. The prevalence of sub mucosal fibrosis in our population is about 3.39%. Oral sub mucous fibrosis also has a significant mortality rate because it is a premalignant condition and malignant transformation has been noticed in 3-7.6% of cases [5].

2. AIMS AND OBJECTIVES

1) To study the mandibular involvement with respect to sub-site of tumor within the oral cavity.
2) To study the accuracy of OPG and CT scans to predict the mandibular involvement and comparing with histopathological examination.
3) To study the relationship of tumor differentiation and neck node disease with mandibular invasion.
4) To identify the possible routes of entry of tumor into the mandible.
5) To study the influence of oral submucosal fibrosis on mandibular resections.

3. MATERIALS AND METHODS

This study consisted of 80 randomly selected patients with histologically diagnosed SCC, who underwent mandibular resection as part of their treatment. Mandibular resection was deemed necessary either because of the clinical diagnosis of bone involvement or to achieve R-0 resection.

All patients were treated at the Gujarat Cancer and Research Institute, Ahmedabad, India, from October

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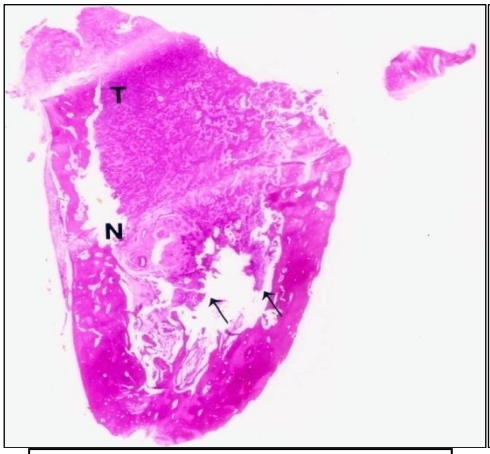
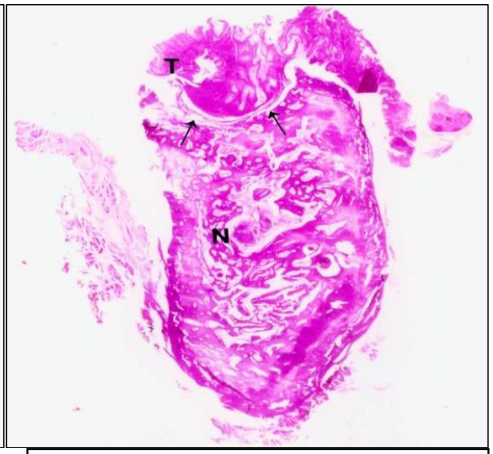
2010 to December 2012. Tumors were staged (clinical TNM stage groupings) according to the 2010 guidelines of the AJCC [6]. Lesions were divided into sub sites like floor of mouth, lower alveolus, and retromolar trigone. Those lesions which encompassed more than one site due to size were classified by the center of the lesion. Clinical assessment of mandibular invasion is performed by bimanually assessing the mobility of the tumor mass in relation to the mandible. Clinical examination also included measurement of sub mucosal fibrosis by way of mouth opening in centimeters. For dentulous patients it was between the incisors and for edentulous patients it was measured between the jaws.

All patients received a preoperative OPG. Radiographs exhibiting bone defects suspected from the tumor were classified into two types of bone invasion: erosion and infiltrative. Erosive bone invasion was characterized by loss of cortical continuity with a U-shaped or scalloped excavation of cancellous bone. The resultant radiolucent defect has a well-defined, smooth margin. Infiltrative bone invasion was demonstrated by loss of cortical continuity where there is a gradual transition between bone destruction and uninvolved cancellous bone. The resultant radiolucent defect has an ill-defined, 32 irregular margins. CT scans were done in doubtful cases and in patients with trismus. Patients underwent surgery by experienced surgical oncologists or under their guidance. Surgery consisted of wide excision of the tumor with a margin of at least 1.0- 1.5 cm, with comprehensive neck dissection and reconstruction. The resected tumors were fixed in formalin and sent for histopathology. Two to four cut slices of 5 microns thickness were made through the tumor at the center of bone invasion as determined by gross inspection of the resected specimen. Cut slices of the specimen were then decalcified and processed for paraffin sectioning followed by staining with hematoxylin and eosin.

The histologic slides were examined for bone invasion and were classified into two types: erosion and infiltration. In erosive bone invasion, the tumor advances as a compact, broad front into bone, such that the tumor-bone interface is well defined. There is loss of cortical continuity with inflamed fibro-connective tissue between the advancing tumor and receding cancellous bone. With infiltrative bone invasion, the tumor adopts a diffuse, irregular, infiltrating pattern, such that the tumor-bone interface is ill defined. There is loss of cortical continuity with inflamed fibro-connective tissue between the infiltrating tumor and cancellous bone, often with islands of unresorbed bone left behind the advancing tumor. The histologic findings of mandibular bone involvement were then compared with the radiographic findings, along with tumor location, stage, and grade.



Invasive pattern of involvement
T: tumor, N: inferior alveolar nerve,
Arrows: tumor within the body of mandible



Erosive pattern of mandibular involvement
T: Tumor, N: inferior alveolar nerve,
Arrows: erosion of the mandible

4. RESULTS AND OBSERVATIONS

AGE DISTRIBUTION

The patients ranged in age from 20 to 75 years with a mean of 47.5 years. There were 16 female and 64 male patients.

GRADES AND CLINICAL STAGE CATEGORIES

Eleven patients (13.75%) had grade I tumors, fifty-one patients (63.75%) had grade II tumors and eighteen patients (22.50%) had grade III tumors. After preliminary investigations patients were assigned into Clinical TNM stage groups as per AJCC staging system (seventh edition). This grouping guided us for the extent of resections. The following pie chart represents the stage groups of the study patients. One patient (1%) belonged to stage I, 13 (16%) patients belonged to stage II, 12 (15%) patients belonged to stage III and fifty-four patients (68%) belonged to stage IV.

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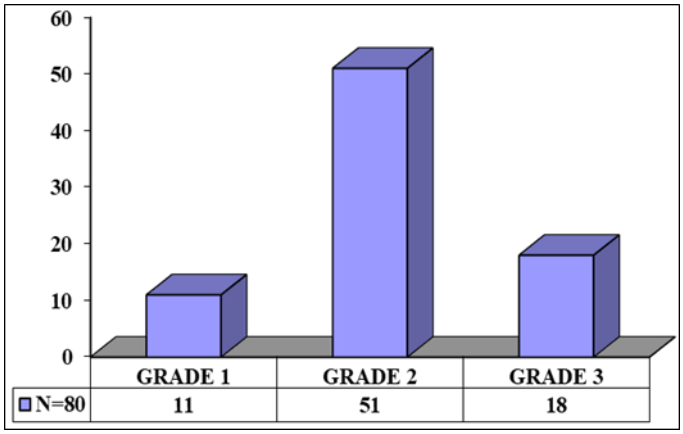
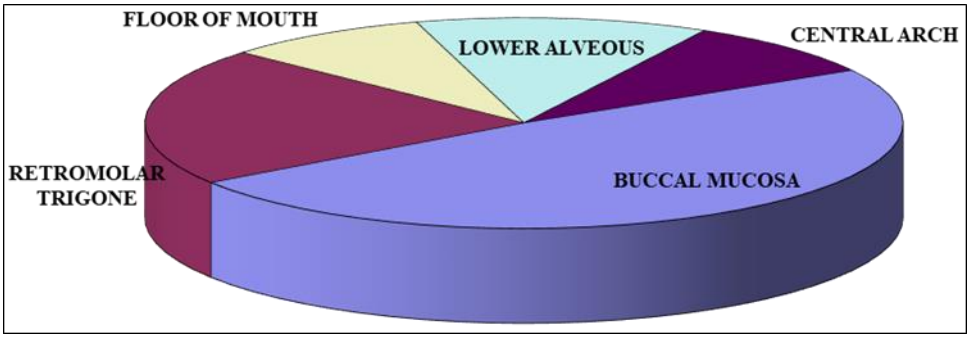


Subsite

Thirty-nine (48%) patients had cancers of buccal mucosa only, 17 (21%) had lesions in the retromolar trigone, 10 (13%) patients had lower alveolar carcinomas, 7 (9%) patients had carcinoma of floor of the mouth and central arch carcinomas were seen in 7 (9%) patients.

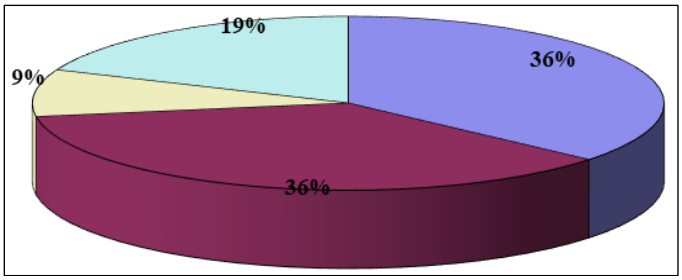


MANDIBULAR INVOLVEMENT OF IMAGING

Orthopantomography (OPG) was done for all the patients for preoperative assessment of thestatus of their mandible and if involved to decide the extent of the mandibular resection. Thirty-four patients (43%) had normal OPG, 29 (36%) individuals had erosive pattern of involvement and 17 (21%) patients had their mandible infiltrated by the tumor.

TYPE OF MANDIBULAR RESECTION

Fifteen (19%) patients underwent marginal mandibular resection, 29 (36%) patients underwent distal mandibulectomy, 29 (36%) patients underwent hemi-mandibulectomy and 7 (9%) patients underwent central arch resection.



PATHOLOGICAL ASSESSMENT

The specimens of mandible were examined for the type of involvement. They were diagnosed as normal (47%), erosive (19%) and infiltrative (9%) and mixed type (26%) of involvement. The routes of involvement were occlusal in 36%, contiguous in 26% and combined routes in 38% of involved mandibles. The above observations are depicted in the following graphs.

TNM STAGE GROUPS

	TNM Stages	
	Clinical	**Pathological**
Stage I	1	2

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Stage II	13	20
Stage III	12	5
Stage IV	54	53

MANDIBULAR INVOLVEMENT

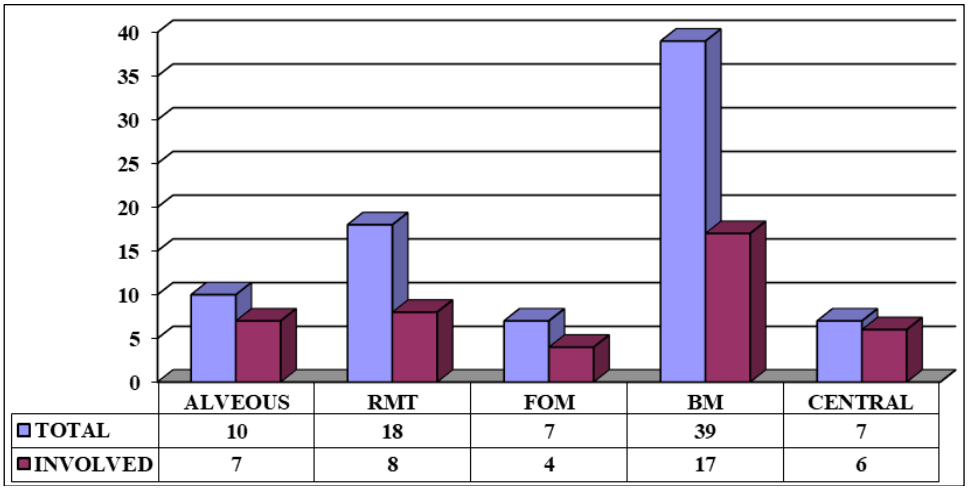
	Mandibular Involvment	
	Clinical	**Pathological**
Normal	35	37
Erosive	29	15
Infiltrative	17	6
Mixed		22

ROUTES OF INVOLVEMENT OF MANDIBLE

Routes	**Number of Specimen**
Occlusal	11
Contiguous	15
Mixed	7

SUBSITE-SPECIFIC INVOLVEMENT OF MANDIBLE

The data was also analyzed as to which sub-site of oral cavity cancer had higher propensity for involving the mandible. Highest chances for subsite-specific involvement of mandible were for lesions of lower alveolus and central arch regions and intermediate for lesions involving floor of the mouth and retromolar trigone region and least for the lesions involving the buccal mucosa.



SENSITIVITY AND SPECIFICITY OF ORTHOPANTOMOGRAPHY

Data obtained from the observations was systematically analyzed with and golden understanding that pathologic report was the ultimate report. OPG was found to have sensitivity of 97.8% and specificity of 94.6% with a positive predictive value of 95.8%. We evaluated the sensitivity and specificity of computerized tomography (CT SCANS) and found that it was comparable with OPG with sensitivity and specificity of 98.0% and 95.0%Respectively. We were able to do 3-D reconstruction and it helped us to plan soft tissue resections.

5. DISCUSSION

Carcinoma of the mandibular region is an important, distinct entity associated with special problems relating to diagnosis, evaluation of extension, planning of treatment, surgical techniques, treatment results, and prognosis. Assessment of mandibular bone involvement has therefore, been regarded as a central diagnostic and therapeutic issue. The present study confirms to some extent along with other studies, the general belief and expectation that larger tumors have a greater tendency to invade bone than smaller tumors. This is clear bydirectly comparing stage I and IV disease. Marchetta *et al*.[7] demostrated that bone invasion occurs in tumors directly resting against the mandible, tumors were considered as invading the bone when clinical signs of tumor fixation to bone or irregularities of bony contours when detected on clinical examination or imaging.

Brown *et al*.[8] found a higher incidence of bone invasion by SCC of the alveolus (78%) and retro molar trigone (75%) regions when compared to the

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pure buccal mucosal and floor of mouth (27%) tumors. This study has shown a similar tendency towards mandibular bone invasion by those tumors which are near bone, however majority of tumors of alveolus and central arch had bone invasion. This can be explained by the study design whereby a requirement of inclusion was mandibular resection as part of treatment, which was often the result of a large tumor. No conclusions were drawn on the influence of histological grade on tumor pattern (erosion versus infiltration) or extent of bone invasion. Previous studies also failed to show any correlation between the two. It has been suggested, however, that a dedifferentiated (poorly differentiated) tumor behaves in a more aggressive manner and is more likely to invade bone. The ability of the OPG to detect mandibular bone invasion by oral SCC in this study was good with an accuracy of 96.4% [8,9]. It is said that OPG lacks sensitivity, which is the inability to detect the early stages of bone invasion, has allowed for a high incidence of false negative interpretation. The reported values for false negative interpretations of the OPG range from 14% to 46% 62. In this study OPG failed to detect a mandibular bone involvement in one patient with central arch involvement that was histopathologically diagnosed as mixed type of bone invasion, however on the contrary 2 patients which had mandible involved as per the OPG were found to have normal mandibles and the erosion was merely due to the pressure from bulky tumor which was compressing on to the mandible. O'Brien *et al*.[10] examined the sensitivity of the OPG in detecting mandibular bone invasion when the tumor was restricted to the periosteum and mandibular cortex and found a false negative rate of 44%.

Brown and Browne [11] and Carter *et al*.[12] suggested that the erosive and infiltrative patterns of mandibular bone invasion by SCC are not separate entities, but rather different phases of the same process. Brown and Browne found that approximately 25% of their cases exhibited a mixed pattern of bone invasion. The present study does alsosupports this theory, which found two distinct patterns of bone invasion, erosion and infiltration as previously described, mixed patterns of invasion were also identified. The OPG is a useful adjuvant to the clinical examination. This study confirms that the OPG is a useful initial assessment of mandibular bone invasion by oral SCC. The OPGs lack of sensitivity however, allows for a relatively high incidence of false negative interpretations. This is reflected in the OPG's inability to detect the early stages of bone invasion where the tumor is limited to the mandibular cortex, which in this study were found to be mostly of the erosive pattern. The high false positive rates associated with these basic investigative modalities advocates the use of more sophisticated diagnostic tools like bone scans, CT scan, etc. and careful correlation of the observations. CT may provide information regarding staging of the primary site and lymph nodes. However, the diagnostic accuracy of CT in detecting mandibular invasion is variable. Brown *et al*.[11] (false-positive rate = 28%) and Curran *et al*.[13] (specificity = 57%; positive predictive value = 73%) acquired their images using 4-to 5-mm thick sections and did not routinely evaluate the mandible with bone algorithms. Shaha[14] (diagnostic accuracy = 68%) and Bahadur [15] (false-negative rate = 28%) did not describe their CT techniques.

Byars [16] described that upper surface of the mandible, mental foramen and lower border of the mandible were common portals which permitted oral squamous cell carcinomas to infiltrate the mandible. The occlusal ridge was the most favored portal of entry suggested by McGregor and MacDonald [17], and subsequent perineural spread was well described in their study. They emphasized that tumor spread in relation to the inferior alveolar nerve was confined to the intraosseous part of the mandibular canal and no skip lesion was found in their series. Spread in spaces between the cancellous bony trabeculae was also confined within the medulla to the limit of tumor through the occlusal surface. These studies supported the findings in our series that the favored route of squamous cell carcinoma entry into the mandible was direct contact of tumor with the attached mucosa, for example gingiva and retromolar trigone.

6. CONCLUSION

Significant contributing factors of oral squamous cell carcinoma infiltration into the mandible are the size/T-stage and location of the primary tumor. Larger tumors are more likely to infiltrate. Gingiva and retromolar trigone are the most favored locations that facilitate tumor infiltration into the mandible. Direct contact of the tumor on the attached mucosa usually provides a portal of entry of the tumor into the medullary space. Periodontal space in the dentate mandible is another possible portal of entry. Erosive-type infiltration is mostly seen in the shallower depth in the early phase of infiltration and is then followed by invasive-type infiltration in the deeper portion of the mandible. Infiltrating tumors usually do not exceed the limit of the primary tumor on the mucosa, but it becomes unpredictable when inferior alveolar nerve related spread is initiated. Five to 10 mm of surgical clearance is applicable to any surgical interventions regarding mandible infiltrating oral squamous cell carcinoma. However, thorough pre- and intra-operative attention should be put on the nerve related spread. Extended resection of the mandible is inevitable when nerve involvement is evident. A combination of orthopantomogram, computerized tomography and Tc-99m skeletal scintigraphy provide a good assessment of tumor infiltration in the mandible. Distance measurement in orthopantomogram is reliable in localizing the tumor and in planning the surgical margin. Magnetic resonance image tomography could be a substitute for computerized tomography in patients with metallic

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dental prosthesis. The operating scheme is based on the biologic behavior of oral squamous cell carcinoma within the mandible, and it is applied prospectively. Although the correlation between tumor grading and tumor infiltration into the mandible has not been investigated in this study, histological grading of tumor could be theoretically a contributing factor as well. Therefore, a further investigation concerning tumor grading and mandibular bone infiltration should be followed.

In cases of segmental mandibular resections immediate mandibular reconstruction gives the best possible outcome with respect to cosmesis and overall quality of life.

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