Surgical management of oral squamous cell carcinoma infiltrating mandible

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1. Introduction

Recent trends in treatment of oral cancers that involve or abut the mandible are primarily focused on 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. 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. The concept of management of oral cancer was first developed in accordance with the description of Halstead’s radical mastectomy and Mile’s abdominoperitoneal resection. Polya and von Navratil (1902) first described lymphatic drainage of the buccal mucosa to the neck through lymphatic channels in the mandibular periosteum in their anatomic studies. With these procedures as a foundation, the ideal cancer operation, the so-called composite resection, was introduced by Crile in 1906. This surgery involved removal of the cervical lymph node-bearing regions (neck dissection) and intervening lymphatic channels (mandibulectomy) in continuity with the intraoral primary. However, these early efforts were plagued by high perioperative mortality, significant functional morbidity, and low cure rates. Remarkable developments in anesthesia, antibiotics and perioperative nutrition made advanced surgical techniques possible and thus the advent of the modern composite operation (Sugarbaker and Gilford 1946, Slaughter 1949, Ward and Robben 1951, Byars 1955). The introduction of the less radical pull-through operation by Kremen (1951) was effective for some oral cancers in which mandibular infiltration of tumor was inevident. Nevertheless, radical resections, such as segmental mandibulectomies and hemimandibulectomies, that resulted in loss of mandibular continuity and consequent functional and cosmetic deficit have been adopted by oncologic surgeons at that time. Besides Modlin and Johnson (1955) reported that sacrifice of a portion of the mandible is obligatory when the jaw was invaded. Even when the mandible was not involved they urged that the bone should be removed without hesitation and without considering function or esthetics.

The remarkable studies by Marchetta and Sako (1966), Marchetta et al (1971) and Carter et al (1983) demonstrated that periosteal invasion does not occur without actual tumor-bone abutment. They determined that carcinomatous infiltration of the mandible occurred by direct infiltration rather than by lymphatic spread. These findings permitted less radical operations that preserved mandibular continuity in lesions not involving bone without compromising local tumor control. Histologic studies by O'Brien et al (1986) and McGregor and MacDonald (1987, 1988, 1989, 1993) ensured the rationale for conservative operation.

As a result of extensive research on this matter, a variety of conservative mandibulectomy techniques have been announced. Consequently, marginal mandibulectomy is now a generally accepted technique with many favorable treatment results (Som and Nussbaum 1971, Flynn and Moore 1974, Mazzarella and Friedlander 1981, Beecroft et al 1982, Wald and Calcaterra 1983, Barttelbort et al 1987, Barttelbort and Ariyan 1993, Randall et al 1987, Shaha 1992, Esser and Krech 1992, Bremerich et al 1992, Krause et al 1992). However, it still seems difficult to plan the appropriate extent of a mandibulectomy, while avoiding residues or needless defect. In addition, there is not yet a definite diagnostic tool to verify the details of cancer involvement in the mandible. Oral cancer treatment is a matter of surgical intervention especially in cases of mandibular tumor invasion. Neither the irradiation therapy nor the chemotherapy seem that they yielded better treatment results than complete surgical eradication in case of the mandibular infiltration of oral squamous cell carcinoma (Wang 1981, Larson and Sanger 1995). Furthermore, postoperative irradiation usually causes severe consequences that compromise patients' return to their ordinary living.

Despite recent advances in reconstruction techniques, the functional and cosmetic ramifications are still significant, so more conservative surgical extirpation in respect to mandibular preservation can have significant functional and cosmetic implication for the oral cancer patients. However, failure to remove the mandible when carcinoma has invaded it allows progression of disease. Therefore, better understanding of the details of cancer involvement into mandible is necessary to yield better functional, esthetic and psychological results.

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 actually 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. Of equal importance is the need to identify those carcinomas that do not invade the mandible. 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. Sometimes, a more conservative operation may be recommended to preserve the function of the oral cavity. For these reasons, exact location of the tumor margin will help preserve function of the oral cavity and pharynx and reduce the chance of local recurrence. Clinical examination and radiographic studies to determine the extent of mandibular resection required are not usually precise. In light of the difficulty in predicting extent of mandibular involvement and the effort required for mandibular reconstruction, the oncologic surgeon needs an intraoperative means of predicting adequate resection.

The pattern of invasion and spread found in histologic studies provided the basis for this study. Cortical involvement may be grossly detectable on examination, however, no prediction as to the extent of cancellous involvement can be determined at time of resection. Once the tumor has access to the cancellous space, the spread of the tumor can be rapid and the extent of involvement difficult to determine. Swearingen et al (1966) characterized the radiologic appearance of carcinoma of the gingiva involving mandible into two types - ‘erosion’ and ‘invasion’. Erosion is described as U-shaped excavation of the medullary bone in shallower portion, or a punched-out or scalloped lesion usually along the superior margin of the alveolus. The cause of erosion is mainly the pressure of the gingival tumor, rather than the infiltration of tumor cells. Intraoral size of the tumor usually equals the measured size of the mandibular defect. The margins of the mandibular defect are smooth and the defect is lucent in radiographs. The term invasion should be applied only to actual infiltration of the tumor cells into the medullary bone. It is most often observed in rapidly growing tumors and small, diffuse patches of osseous degeneration in which spicules of bone are apparent in radiographs. Invasions are also characterized by poorly defined margin of the superior alveolar cortex. The more rapidly growing tumors produce an invasive mandibular defect which is generally much smaller than the intraoral lesions of the soft tissues. Erosive lesions may be adequately treated by radiation therapy or surgery. Local excision rather than hemimandibulectomy is usually adequate. Invasive lesions are not amenable to radiation therapy. Hemimandibulectomy is indicated for such lesions. Brown et al (1994) and Brown and Browne (1995), stated that early tumor infiltration shows an erosive pattern which changes to an invasive pattern as the disease progresses in the mandible. In addition, he described in the mixed group, an erosive pattern peripherally and an invasive pattern in the central and more deeply infiltrated areas of the mandible. As the lesion progresses, the erosive pattern is overtaken by the more widespread and aggressive invasive pattern of disease, and therefore cannot be detected. They concluded that it may be considered unwise to plan a marginal resection in the posterior edentulous mandible in the presence of invasion, as the height of mandible is reduced and the invasive pattern of disease is seen at a shallower depth. There are more options when planning anterior resections, as there is greater thickness of bone and the invasive pattern of disease develops at a greater depth. McGregor and MacDonald (1983, 1987, 1988, 1988, 1989, 1989, 1993, 1994, 1995) recommended throughout their histopathologic studies of squamous cell carcinoma infiltration into the mandible that in both marginal and segmental mandibulectomies, the anteroposterior margin of resection should contain the entire course of inferior alveolar neurovascular bundle. Larson and Sanger (1995) accepted and adopted McGregor and MacDonald's suggestion of conservative resection of the ramus of the mandible. Totsuka et al (1986, 1991), Tsue et al (1994), Byers (1995), Ahuja et al (1990) also mentioned the preoperative evaluation and determination of extent of mandibular resection. However, all the suggestions seemed inconclusive since there was no delineation of a 'universal' safety margin, thus leaving the extent of resection in both anteroposterior and craniocaudal dimensions to the discretion of each individual surgeon.

2. Aim of the study

The aim of this study is to compare discrepancies among clinical, radiographic and histopathologic entities of oral squamous cell carcinoma infiltration into the mandible by way of measuring the actual size and infiltrating depth of the tumor. The study also intends to establish a logical prospective diagnostic and operative scheme as to performing a more conservative mandibulectomy. If such a scheme can be outlined, we could gain the magic number regarding the extent of mandibular resection which maximizes oncologic safety, as well as functional and reconstructive advantages.

3. Material

From January 1993 till March 1998, 124 mandibles were partially removed as part of composite resection for primary oral squamous cell carcinomas in the department of Oral & Maxillofacial Surgery, University of Munich, Germany. Eighty-two of 124 mandibulectomies for which the clinical and radiological data were well preserved, were selected as the subjects of this study.
Most of the surgeries were conducted following the conservative concept in order to spare mandibular continuity whilst maintaining oncologic safety. The patient records regarding preoperative clinical examination, plain dental radiographs and orthopantomograms, computerized tomography (CT), and Tc-99m skeletal scintigraphy were reviewed. Twenty-three of 82 mandibles resected exhibited pathologic evidence of mandibular infiltration. Of these 23, 18 were segmental resections, 5 were marginal resections, and all of them were nonirradiated and had no evidence of distant metastasis at time of surgery. A series of 21 mandibles, 5 of 5 marginal and 16 of 18 segmental resections, which showed adequate storage conditions for retrospective study, were chosen to undergo histopathologic reexamination.

4. Methods

4.1. Clinical examination

Clinical factors such as primary site of tumor, size of tumor on the mucosal surface, depth of tumor, status of dentition, and the presence of preoperative treatment were assumed. Clinical judgment of mandibular infiltration and overall preoperative judgment was assumed in combination with radiologic judgment. The type of operations and tumor staging according to UICC TNM classification (UICC 1992) were recorded.

4.2. Radiologic examination

The osseous defects in orthopantomograms were traced on the '5 millimeter grid' (Fig. 1) to measure the size and depth of infiltration of tumor and to verify the radiographic type of tumor infiltration. The irregularity of the infiltrating margin was measured in each case and each margin was classified as erosive or invasive. The size of tumor was measured two-dimensionally, anteroposteriorly and craniocaudally. Radiologic judgment of mandibular infiltration by means of orthopantomogram, axial sections in computerized tomography and Tc-99m skeletal scintigraphy was assumed. The measurements on the orthopantomogram were adjusted to compensate for the magnification of the image, and the overall magnification ratio of 1.3 was calculated.

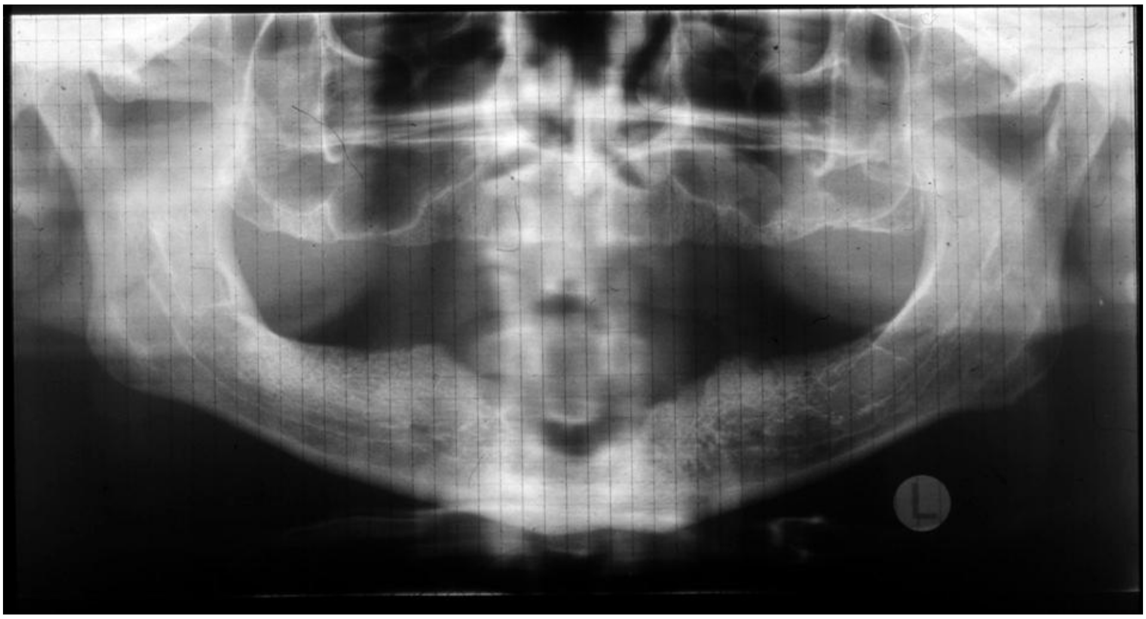


Fig. 1 - Orthopantomogram on the '5 millimeter grid'

4.3. Histologic examination

Five of 56 marginal resections and 18 of 26 segmental resections reported histopathologic evidence of tumor infiltration into the mandible. Of those, 5 marginal resections and 16 segmental resections which showed perfect storage state were selected to carry out histologic examination.

All data from macroscopic findings during routine processing were carefully reviewed and recorded with a pathologist. Hematoxilin-Eosin stained sections were prepared from embedded paraffin wax blocks. Every section was examined and an assessment of the type of infiltration was made. Tumor size and distance between tumor margin and resection margin (surgical clearance) were measured anteroposteriorly and craniocaudally on the fixated specimen (Fig. 2).

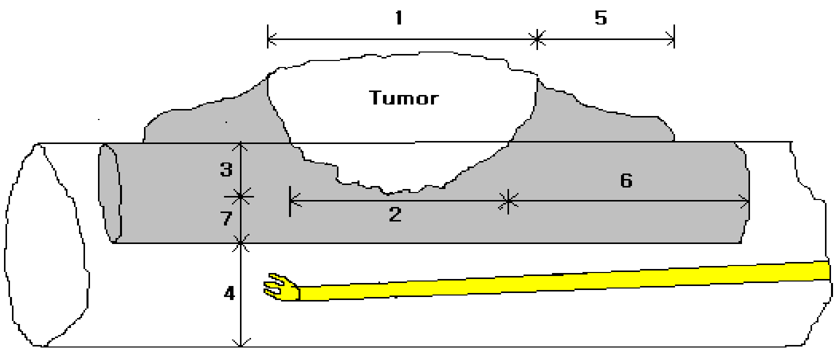


Fig. 2 - Measurements in histologic examination

1: Maximum tumor size on mucosa
2: Maximum tumor size in bone
3: Infiltrating depth in bone
4: Post-surgical mandibular height
5: Anteroposterior surgical clearance in mucosa
6: Anteroposterior surgical clearance in bone
7: Craniocaudal surgical clearance

4.4. Statistical analysis

Data from the clinical, radiologic and histologic examinations were recorded and sorted in the Microsoft Excel Version 7.0 computer program. Statistical comparison was made by the Spearman rank correlation coefficient (Daniel 1987) in the IBM compatible software package SAS (Statistical Analysis System).

Sensitivity (the responsiveness of radiographic examination tool to predict positive tumor infiltration in the mandible) was calculated as true positives / [true positives + false negative] and specificity (the responsiveness of radiographic examination tool to predict negative tumor infiltration in the mandible) was calculated as true negatives / [true negatives + false positives]. Positive predictive value was calculated as true positives / total positives and negative predictive value was calculated as true negatives / total negatives.

Overall test efficiency was calculated as [true positives + true negatives] / total tested.

5. Results

5.1. Preoperative staging and location of primary tumor

According to the specific distribution based on T stage, T2 was most prevalent (33 of 82, 40.2%) and T4 showed the highest frequency of histologic tumor infiltration into the mandible (11 of 16, 68.8%). The specific rate distribution had statistically significant correlation with the histologic bone involvement ($P < 0.05$).

The floor of the mouth was the most prevalent location (37 of 82, 45.1%) of primary tumors in our series, but the frequency of histologic bone involvement in the location specific rate distribution showed its peak on gingiva (5 of 9, 55.6%), retromolar trigone (7 of 18, 38.9%), tongue (5 of 17, 29.4%) and floor of mouth (4 of 37, 10.8%) respectively (Table 1). The location specific rate distribution showed statistically significant correlation with the histologic bone involvement ($P < 0.05$).

Presence or absence of cervical lymph node enlargement by stage exhibited no significant correlation with the histologic bone involvement ($P < 0.05$).

Table 1 - Preoperative staging and location of primary tumor

	T1			T2			T3			T4			Total
	N0	N1	N2	N0	N1	N2	N0	N1	N2	N0	N1	N2	
FOM	6	4	2	13(2)	2	4	0	1	1	1(1)	2	1(1)	37(4)
RMT	4(1)	1	1(1)	4(1)	1	1	1	1(1)	0	2(1)	1(1)	1(1)	18(7)
GIN	1	0	0	2(1)	1	1(1)	2(1)	0	0	0	1(1)	1(1)	9(5)
TON	3	1	1	1	1	1	2(1)	0	1	2(1)	3(2)	1(1)	17(5)
TSL	0	0	0	1	0	0	0	0	0	0	0	0	1
Total	14(1)	6	4(1)	21(4)	5	7(1)	5(2)	2(1)	2	5(3)	7(4)	4(4)	82(21)

FOM: Floor of mouth
RMT: Retromolar trigone
GIN: Gingiva
TON: Tongue
TSL: Tonsil
( ): number of histologic bone involvement
N2: N2a, N2b and N2c

5.2. Diagnostic reliability

Preoperative judgment concerning mandibular infiltration of oral squamous cell carcinoma is always based on the clinical assessment including palpation and direct inspection, radiologic evaluation such as orthopantomogram and/or standard radiography, computerized tomography and Tc-99m skeletal scintigraphy.

Diagnostic values were analyzed by means of sensitivity, specificity, positive predictive value, negative predictive value, and overall test efficiency (Table 2).

Orthopantomogram showed 88% of sensitivity and 98% of specificity in our series (n=82). It also proved that orthopantomogram had the highest predictive values and overall test efficiency. A comparison of proportional infiltrating depths (infiltrating depth of tumor / mandibular height) measured in orthopantomograms and pathologic specimens showed quite good accordance with each other in our series (Fig. 3).

Computerized tomography had as low a false positive [radiographically positive but histologically negative] value as orthopantomograms (2%), but it showed the highest false negative [radiographically negative but histologically positive] value (Fig. 4). Tc-99m skeletal scintigraphy was extremely sensitive (100%) but less specific (78%).

However, a combination of orthopantomogram and computerized tomography made good complementary cooperation and provided a better diagnosis (Fig. 5).

All three diagnostic modalities showed significant correlation with the histologic bone involvement in the specific rate distributions ($P < 0.05$).

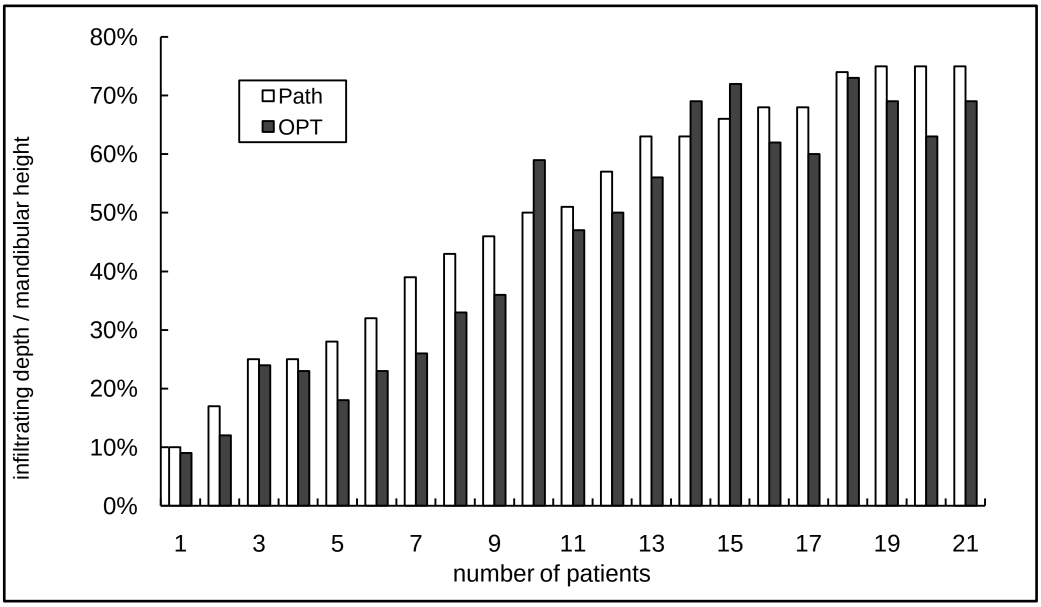
Table 2 - Diagnostic values of radiographic examination tools

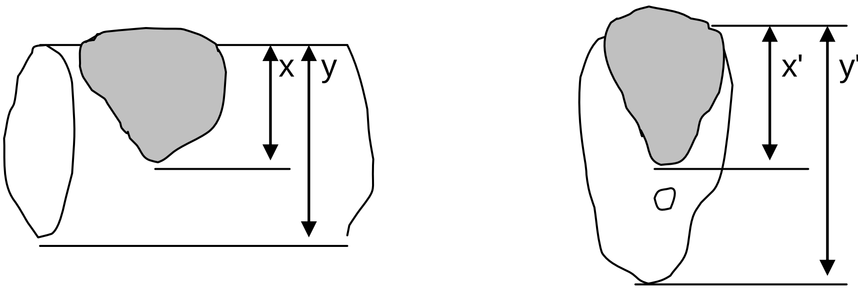
	Sensitivity	Specificity	PPV	NPV	OTE
OPT	88%	98%	96%	94%	83%
CT	72%	98%	96%	85%	76%
Sc	100%	78%	62%	100%	71%

OPT: Orthopantomogram CT: Computerized tomography

Sc: Tc-99m skeletal scintigraphy PPV: Positive predictive value

NPV: Negative predictive value OTE: Overall test efficiency





OPT: x / y Path: x' / y'

Fig. 3 - Comparison of proportional infiltrating depth

OPT: Orthopantomogram Path: Pathologic specimen

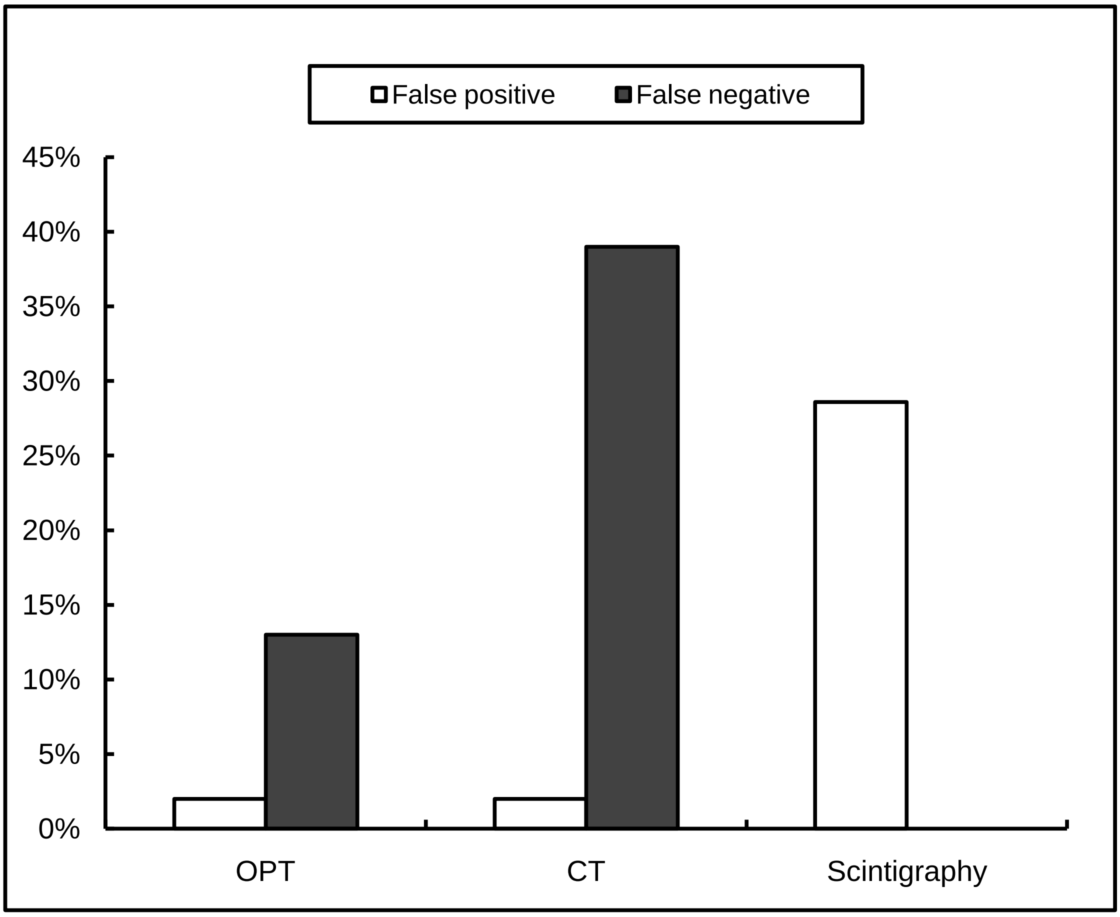


Fig. 4 - False diagnostic values of radiographic examination tools

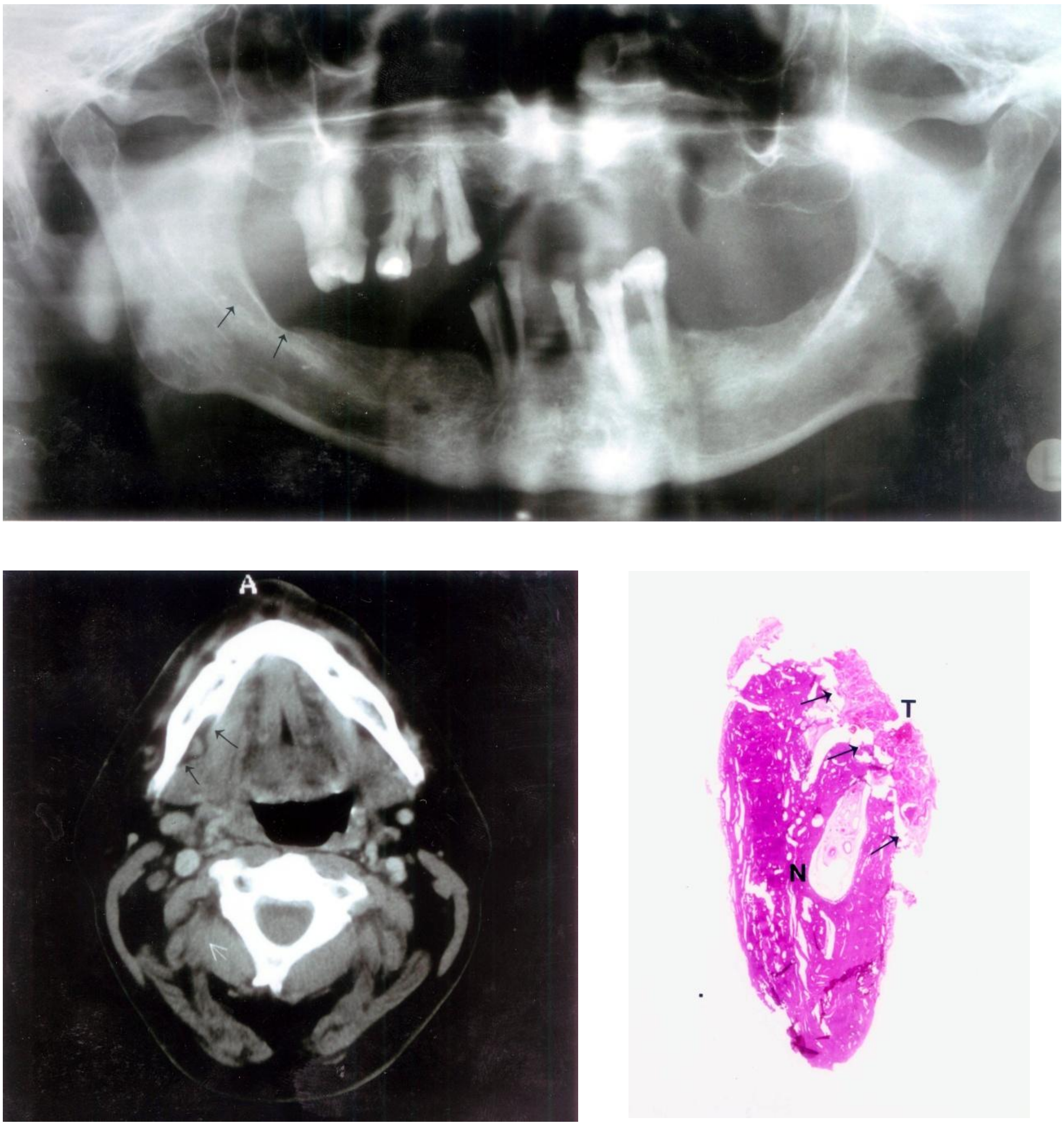


Fig. 5 - Combination of orthopantomogram and computerized tomography compared with surgical specimen - computerized tomography was an excellent supplement in screening the lingually deviated tumor infiltration.

5.3. Type of infiltration of oral squamous cell carcinoma into the mandible

Two different types of tumor infiltration into the mandible were observed. The erosive type, which exhibited histologically well demarcated smooth borders with an interfacing connective tissue band, showed 'punched-out' lesions in orthopantomogram (Fig. 6). Invasive type, characterized by a diffuse and aggressive pattern of infiltration into deeper portions, showed irregular margins in orthopantomogram (Fig. 7). In the case of tooth presence on the site of tumor infiltration, tumor spread through the periodontal space was observed (Fig. 8).

Twelve infiltrations were designated erosive type, 8 of which were located on the anterior portion of the mandible between mental foramina. In contrast, 5 of 9 invasive type infiltrations were found on the posterior mandible (Table 3).

Tumor infiltration in the inferior alveolar nerve was observed in 3 cases. Among them, 2 were erosive and 1 was invasive type. Two of 3 nerve infiltrations were found on the posterior mandible as usual, but 1 showed that the infiltration was facilitated by the tumor abutting the mental foramen and spread beyond the greater diameter of the tumor onto the resection margin (Fig. 9).

Table 3 - Type of infiltration

type of infiltration		operation		site of infiltration		IAN infiltration
erosive	12	marginal	4	anterior	2	0
				posterior	2	0
		segmental	8	anterior	6	1
				posterior	2	1
invasive	9	marginal	1	anterior	0	0
				posterior	1	0
		segmental	8	anterior	4	0
				posterior	4	1

IAN: Inferior alveolar nerve

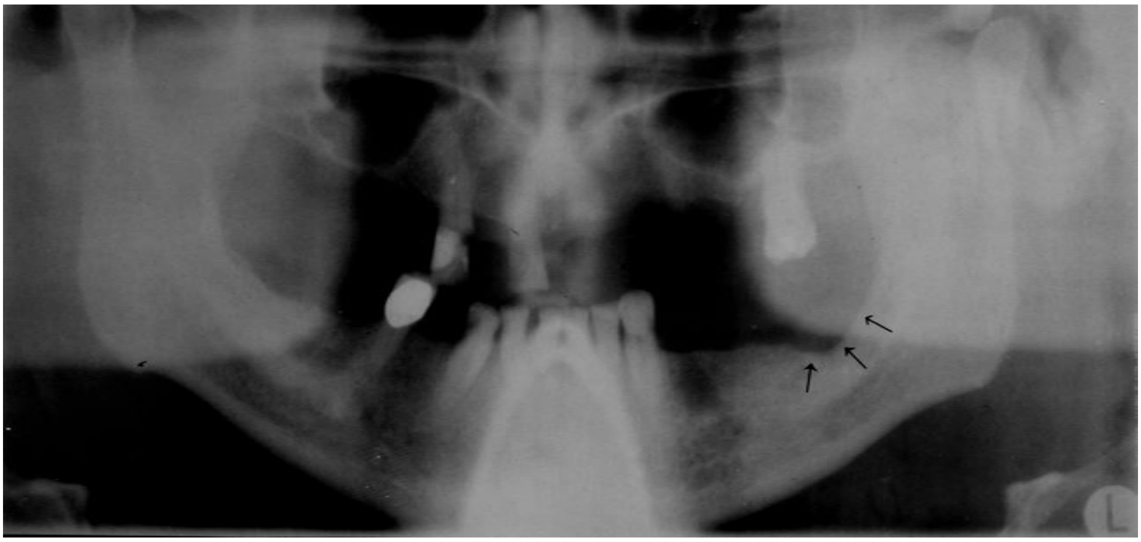
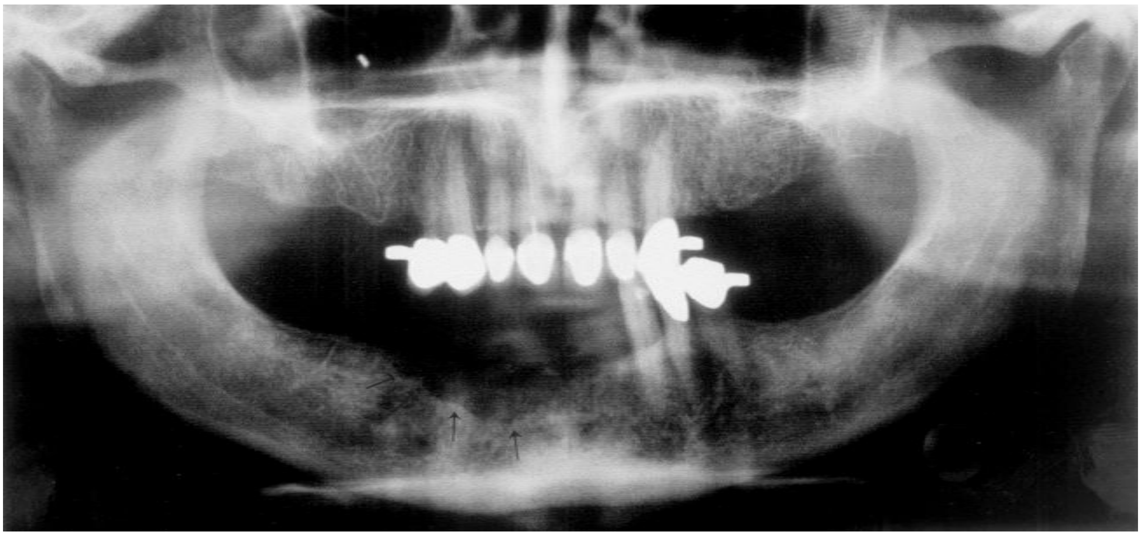


Fig. 6 - Erosive type - T: Tumor, N: Inferior alveolar nerve



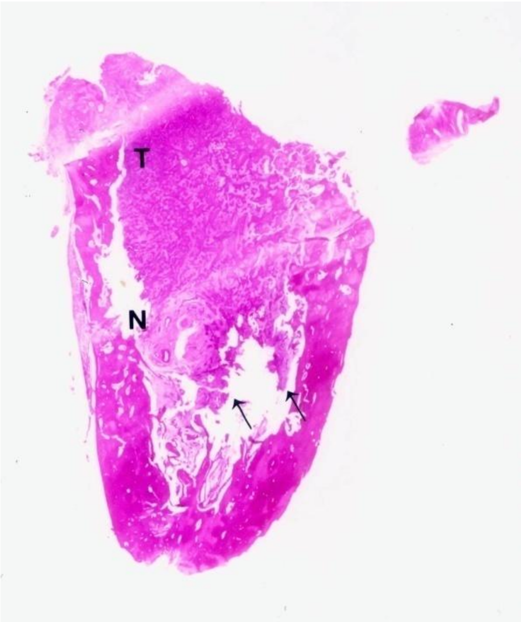


Fig. 7 - Invasive type - T: Tumor, N: Inferior alveolar nerve

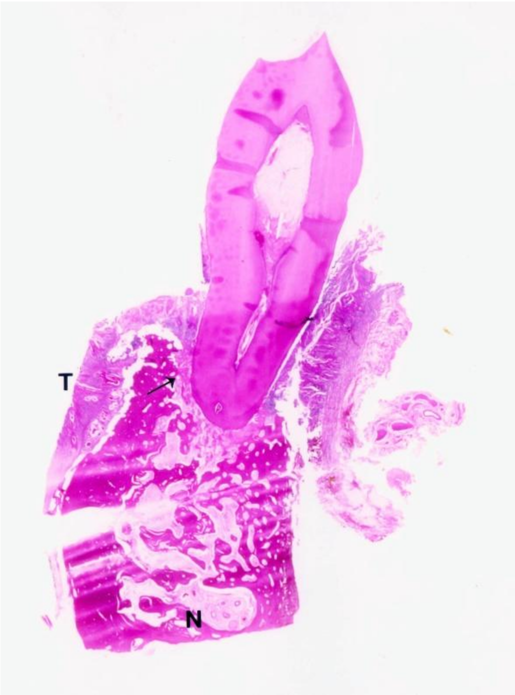


Fig. 8 - Tumor infiltration through the periodontal space

Fig. 9 - Inferior alveolar nerve related tumor spread (arrows) - Sagittal section of the specimen along the course of inferior alveolar canal. Primary tumor was reflected for convenience of coronal preparation.

T: Tumor reflected N: Inferior alveolar nerve

5.4. Size of tumor

The size of the tumor measured in the bone was usually smaller than the size of the tumor measured on the mucosa and never exceeded the limit on the mucosa both in erosive and invasive groups (Fig. 10 & 11). The tumor size on the mucosa was greater in the invasive group than in the erosive group, on average (41.44 mm vs. 32.83 mm). The invasive group also showed greater tumor size in bone than the erosive group (33.33 mm vs. 26.17 mm in average).

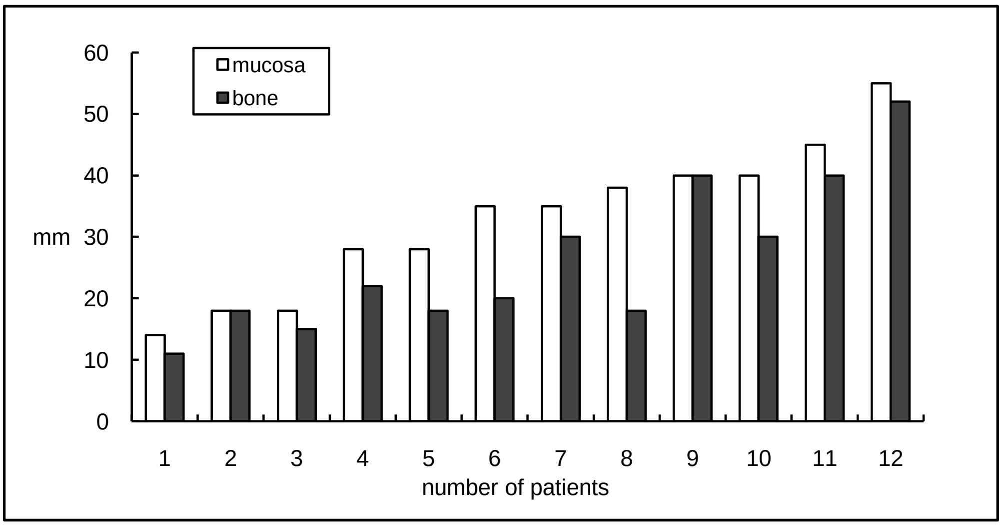


Fig. 10 - Size of tumor - erosive type

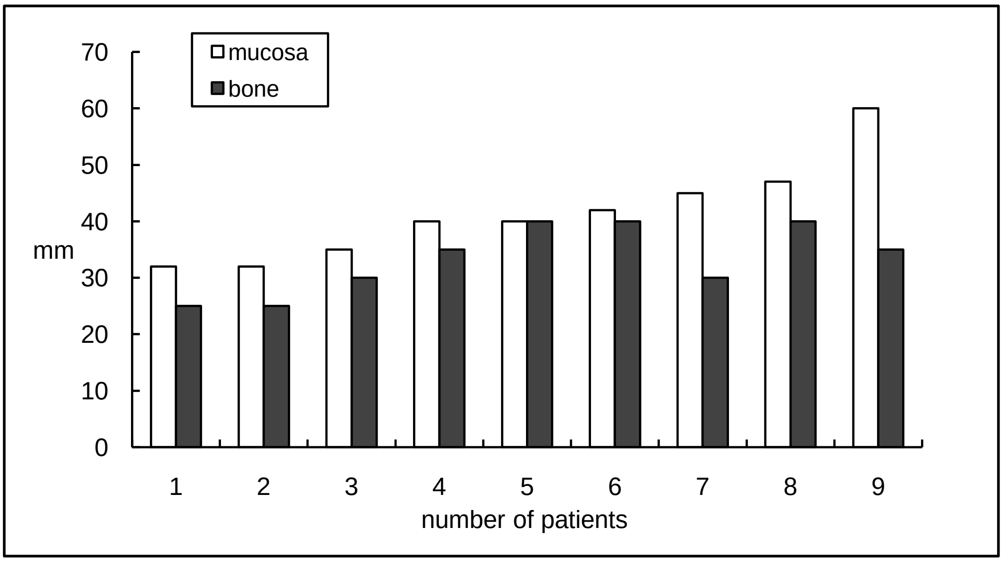


Fig. 11 - Size of tumor - invasive type

5.5. Infiltrating depth of tumor in the mandible

The infiltrating depth of the tumor was deeper in the invasive group, with a mean difference of 5.08 mm. There was no significant difference between anterior (average 9.92 mm) and posterior (average 10.33 mm) mandibular infiltrations (Fig. 12 & 13).

Three nerve related tumor spreads were observed. There was no preference between erosive and invasive groups, and the average infiltrating depth of tumor in the mandible in the case of nerve infiltration was 12 mm. In cases with deeper infiltration, the site of tumor infiltration was confined to the anterior mandible, thus no further nerve related spread was observed in the anterior mandible except in the one case abutting the mental foramen.

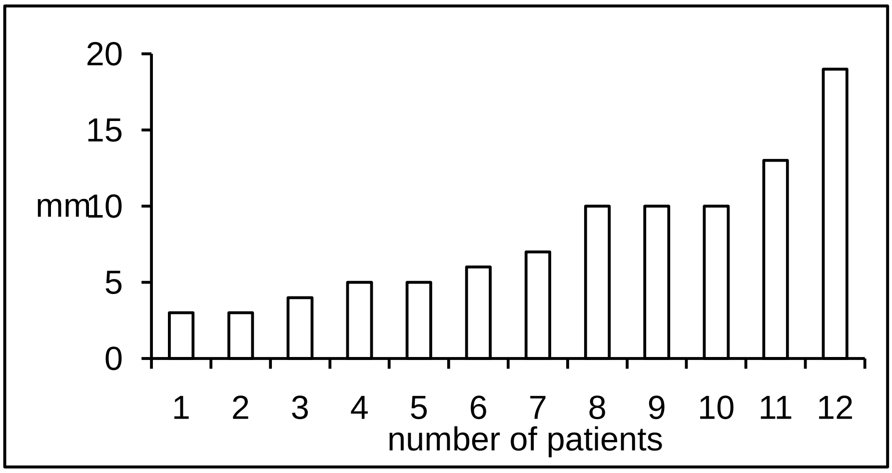


Fig. 12 - Infiltrating depth of tumor in the mandible - erosive type

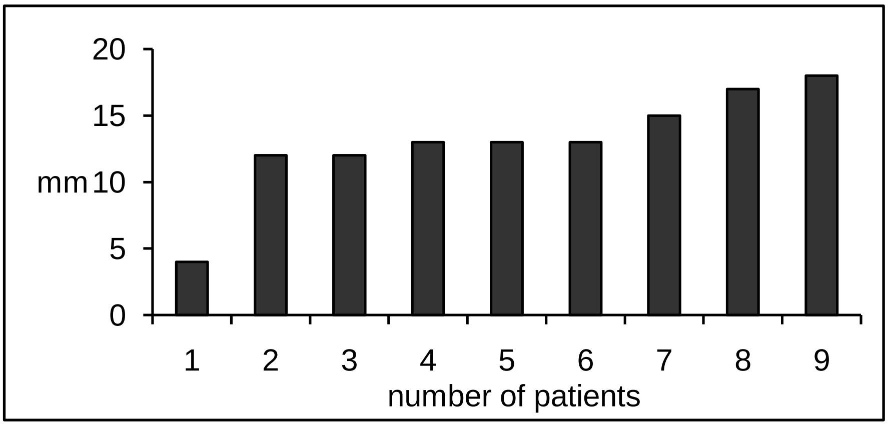


Fig. 13 - Infiltrating depth of tumor in the mandible - invasive type

5.6. Distance between tumor margin and resection margin (Surgical clearance)

5.6.1. Anteroposterior surgical clearance

Anteroposterior surgical clearance measured on the fixated specimen was greater in the bone than that of the mucosa (20.7 mm vs. 7.1 mm in average), although the measured tumor size was usually greater in the mucosa. Discrepancy in anteroposterior surgical clearance in the bone was significant between segmental and marginal resection groups (22.9 mm vs. 13.8 mm in average). Otherwise, anteroposterior surgical clearances in mucosa between two operation groups showed no remarkable difference (7.2 mm vs. 7.0 mm in average) (Fig. 14 & 15).

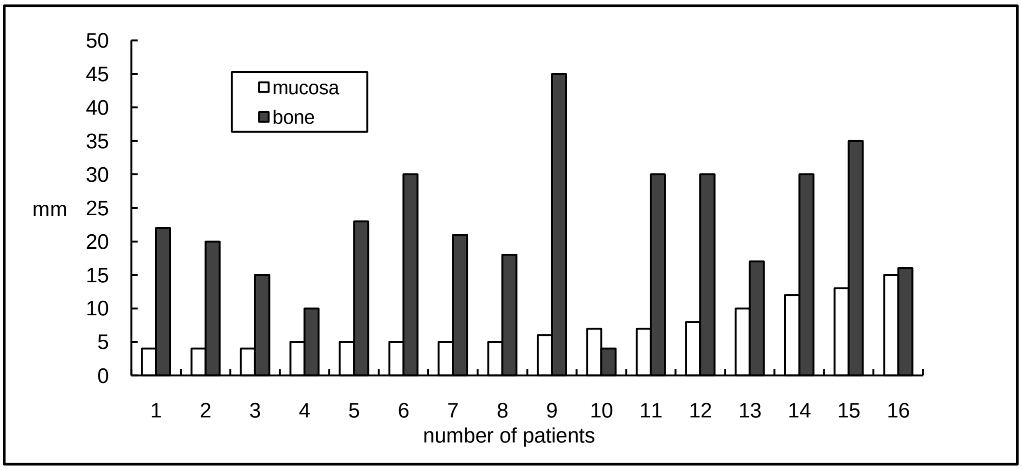


Fig. 14 - Anteroposterior surgical clearance - marginal resection group

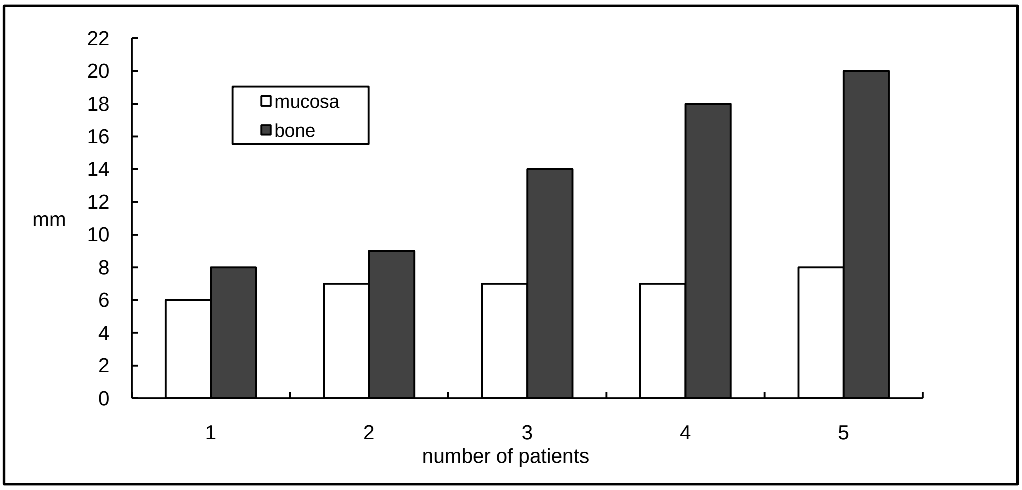


Fig. 15 - Anteroposterior surgical clearance - segmental resection group

5.6.2. Craniocaudal surgical clearance and post-surgical mandibular height in marginal resection group

In case of marginal resection, craniocaudal surgical clearance was smaller than anteroposterior surgical clearance (6.6 mm vs. 13.8 mm in average). It was also remarkably smaller than anteroposterior surgical clearance in segmental resection group (6.6 mm vs. 22.9 mm in average) (Fig. 16). Post-surgical mandibular height in the marginal resection group ranged from 8 mm to 18 mm, with an average of 11.2 mm.

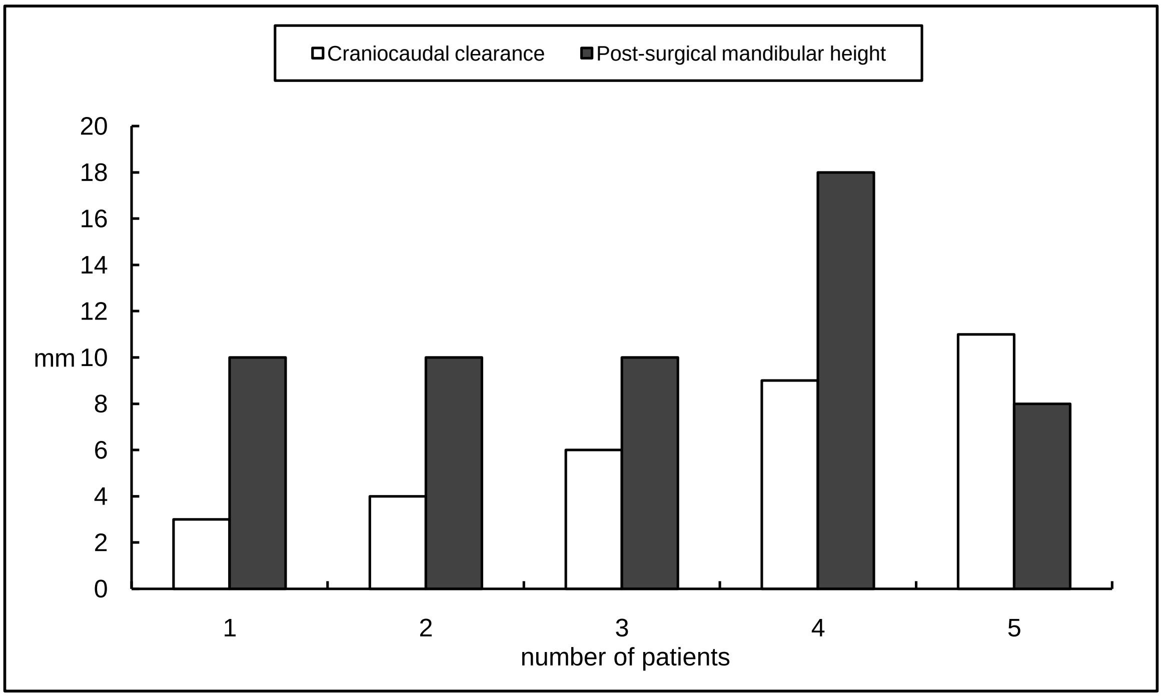


Fig. 16 - Craniocaudal surgical clearance and post-surgical mandibular height in marginal resection group

6. Discussion

6.1. Infiltration of oral squamous cell carcinoma into the mandible

Byars (1955) 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. Many further investigations regarding the topic were published. Larson et al (1966) and Marchetta et al (1971) proved there was no perineural or periosteal lymphatic spread into the mandible, and influenced the classic concept of ‘radical excision without hesitation and without considering function and esthetics’ (Modlin and Johnson 1955). O’Brien et al (1986) and Mueller and Slootweg (1989) noted that the infiltration of tumor occurred at the point of contact. Totsuka et al (1986) observed tumor infiltration through enlarged harversian canals, periodontal space and by direct resorption of cortical bone. Bhattathiri et al (1991) supported Totsuka’s findings and cited periodontal space as the major route to bone. In addition, the attached mucosa with its firm collagen attachment to bone was proposed as the main route of tumor entry into the mandible (Brown et al 1994). The occlusal ridge was the most favored portal of entry by McGregor and MacDonald (1987), 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. Spread of the tumor from occlusal ridge through periodontal space into medullary portion was also observed in case of dentate mandible. Spread of tumor never exceeded the limit on the mucosa, but it reached beyond the limit of the primary tumor in case with perineural spread through the mental foramen.

The invasive group showed greater tumor size and deeper infiltrating depth than the erosive group. This finding was compatible to the results observed by Brown et al (1994).

The contributing factors of oral squamous cell carcinoma infiltration into the mandible were, predominantly, location and size of primary tumor. On the other hand, cervical lymph node metastasis was not correlated with mandibular infiltration of oral squamous cell carcinoma.

6.2. Surgical management of oral squamous cell carcinoma infiltrating mandible

Some extent of mandibular resection is mandatory when the tumor approaches or infiltrates the mandible. Most surgeons would like to adopt a modern conservative concept to spare mandibular continuity as long as possible, and to avoid postoperative morbidity accompanied by a complicated resection-reconstruction procedure. Therefore, there are several different opinions concerning the indication to marginal resection. Som and Nussbaum (1971), Flynn and Moore (1974) and Shaha (1992) conducted marginal resection when there was no evidence of osseous infiltration. Brown and Browne (1995) did not recommend marginal resection in the posterior edentulous mandible in the presence of tumor infiltration. McGregor and MacDonald (1993) suggested complete excision of the mandibular canal and its contents with no conservative approach to resection of the ramus in the case of tumor infiltration in the posterior mandible. A mobile tumor was the indication for marginal resection by Mazarella and Friedlander (1981). In contrast, Dubner and Heller (1993) applied marginal resection to the tumors which infiltrate the mandible, but not those that deeply infiltrate the mandible. It is obvious that the anterior mandible is more favorable for marginal resection due to its lack of neurovascular bundle and its greater post-resection height. Bartellbort et al (1987) and Larson and Sanger (1995) suggested that at least 1 cm margin of mandibular remnant is essential so that the marginal resection remains biomechanically sound. In most cases in our series, post-surgical mandibular height was greater than 1 cm and no pathologic fracture was reported during follow-up. Regarding the surgical clearance, Dubner and Heller's (1993) suggestion of at least 2 cm beyond all clinically evident tumors seems too big in head and neck region. However, McGregor and MacDonald (1989), Brown and Browne (1995) and Larson and Sanger (1995) proposed an oncologic safety margin of 5 - 10 mm, a more meaningful finding for the recent conservative concept. Despite their recommendation of 5 - 10 mm, the actual indication for marginal resection has restricted bounds, especially on the posterior mandible. However, 5 -10 mm surgical clearance was well conformed to our series, except when deciding the anteroposterior bony safety margin. Mean anteroposterior bony surgical clearance was 20.7 mm in our series and it was remarkably greater than that in the mucosa (mean 7.1 mm). However, reduction of surgical clearance in the mucosa should be taken into consideration, because the distances were measured on the shrunken specimens that have already been fixed in formalin solution. Despite this, a large amount of sound osseous tissue was removed as part of a partial mandibulectomy. The fact that it is impossible to gain direct sight into the medullary portion, coupled with fear for residual tumor in this inaccessible space resulted in needless functional defect. The discrepancy was also great between segmental (mean 22.9 mm) and marginal (mean 13.8 mm) resection groups. Craniocaudal surgical clearance in marginal resection group was yet smaller (mean 6.6 mm) but remained oncologically sound. Small craniocaudal surgical clearance could be mainly due to surgeon's desire to prevent pathologic fracture of mandible after marginal mandibulectomy. However, this small amount of surgical clearance (mean 6.6 mm) with no remarkable oncologic disadvantage in histopathologic examination implied that 5 - 10 mm of surgical clearance could also be applied in deciding the anteroposterior bony surgical margin. These findings were suggestive of a strong desire to establish a generalized protocol regarding surgical clearance not only in anteroposterior but also in craniocaudal dimensions.

6.3. Diagnosis and treatment planning

The role of immediate reconstruction during ablative oral cancer surgery becomes meaningful, because primary radical resection and simultaneous reconstructive procedure provided a better prognosis (Kerscher et al 1992, Lentrodt et al 1992, Mühling et al 1992, Schmelzeisen et al 1992), at least when the size of tumor was greater than 2 cm (Ehrenfeld et al 1992). Therefore, preoperative measurement of tumor infiltration into the mandible is of paramount importance to assure the surgical margin and to plan reconstruction. Location and size of the primary tumor are important contributing factors, but measuring the size of infiltrating tumor within the mandible is still very difficult and unreliable. Furthermore, small or lingually deviated early infiltration could not be easily detected. Clinical examination including direct inspection and palpation play the most important role in treatment planning. However, clinical judgment alone is not sufficient to locate the exact tumor margin in the mandible. Previous studies by Baker et al (1982), Weisman and Kimmelman (1982) and Ahuja et al (1990) emphasized the accuracy of scintigraphy. In our series, Tc-99m scintigraphy was most sensitive (100%) to changes in bone and was reliable when there was no tumor infiltration. However, its low specificity (78%) and high false positive predictability (28.6%) made not a very useful tool for measuring the extent of marginal resection,

Axial sections in computerized tomography were specific (98%) and gave more information than orthopantomogram. In our series, however, it showed lower sensitivity (72%) and higher false negative predictive value (39%). Such unfavorable results were mainly due to artifacts caused by metallic dental restorations.

With 88% sensitivity, 98% specificity and 96% positive predictive value, orthopantomogram was therefore in this series the most useful tool for precise diagnosis. Furthermore, comparison of proportional infiltrating depths (infiltrating depth of tumor / mandibular height) measured in orthopantomograms and pathologic specimens showed quite good accordance with each other in our series (Fig. 3).

Despite the high reliability of diagnostic values in our series, no diagnostic modality is yet perfect to fulfill this assignment. Thus the combination of orthopantomogram, computerized tomography and Tc-99m scintigraphy is necessary (Fig. 5). A Brown et al (1994) study on different imaging modalities indicated that the combination of orthopantomogram and skeletal scintigraphy provide an excellent means to screen for possible infiltration of oral squamous cell carcinoma into the mandible.

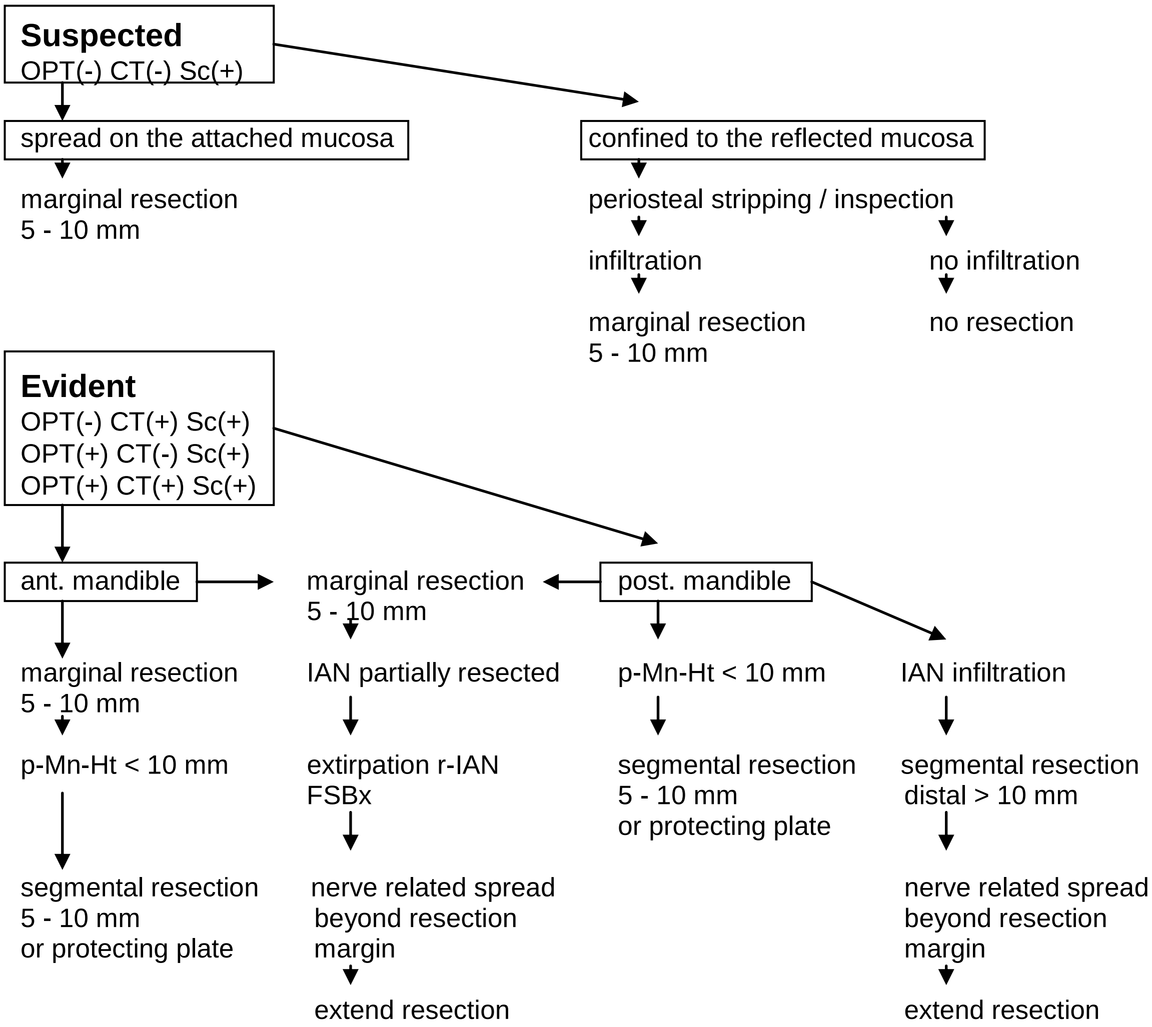
Investigations into ways to better diagnose tumor infiltration are common. Aitasalo and Neva (1985) recommended xeroradiography, as it seemed very helpful. Modern digital radiography could substitute for xeroradiography and it can be applied for further investigations. Primary positive findings or cortical breakdown and abnormal bone marrow signal were highly sensitive for periosteal / cortical invasion and medullary involvement in magnetic resonance image scan. The magnetic resonance image tomography gives important information in early phase of tumor infiltration, however, a high rate of false positive values hampered the accuracy of this technique (Chung et al 1994). In spite of this drawback, a negative value virtually excludes tumor infiltration in mandible and the merit of less amount of artifact could be an alternative. Bone SPECT (single photon emission computerized tomography) and Denta Scan could enhance the accuracy in assessing mandibular infiltration of oral squamous cell carcinoma (Chan et al 1996, Curran et al 1996, Talmi et al 1996).

Frozen section analysis of mucosal resection margin is a standard intraoperative diagnostic tool to eliminate surgical error. To address the adequacy of bony resection, frozen analysis of cancellous bone on both cutting ends could be adopted based on the histologic patterns of mandibular infiltration and spread of oral squamous cell carcinoma. Frozen section analysis of the cancellous bone yielded a predictability of 97% (Forrest et al 1995). In addition, frozen section analysis of remaining inferior alveolar nerve could prevent residues that are lying beyond the limit of resection when the perineural spread of the infiltrating tumor is strongly suspected or a part of inferior alveolar nerve is already sacrificed as a surgical specimen.

6.4. Prospective operating scheme

Based on the results of our study and a literature review, a logical prospective diagnostic and operative scheme was devised (Fig. 16). The operating scheme is divided into two categories: 1) when the mandibular infiltration of the tumor is suspected and 2) when the tumor infiltration is evident.

This scheme is not yet verified as adequate, but is applicable to prospective clinicopathologic study. Some changes in this scheme could be possible according to adoption of diagnostic alternatives.



OPT: Orthopantomogram CT: Computerized tomography Sc: Tc-99m scintigraphy
p-Mn-Ht: Post-surgical mandibular height r-IAN: Remaining inferior alveolar nerve
FSBx: Frozen section biopsy 5 - 10 mm: Surgical clearance

Fig. 17 - Operating scheme

7. 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 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, histologic 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.

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9. Abstract

Progression of recent trends in mandible-preserving operations for the management of oral squamous cell carcinomas that infiltrate the mandible is rapid and accompanying studies give invaluable information concerning behavioral understanding of oral squamous cell carcinoma within the mandible. However, a large amount of sound osseous tissue is removed as part of partial mandibulectomy, because it is difficult to gain direct sight into the medullary portion and as a result of fear for residual tumor in this inaccessible space. Thus, needless defects are not seldom. For that reason, there still exists a strong demand for an operating protocol regarding precise surgical clearance which fulfills the surgeons' desire to be more conservative.

Twenty-one with evidence of intraosseous tumor spread of 82 resected mandibles were radiologically and histologically reexamined to compare discrepancies among clinical, radiologic and histologic entities of oral squamous cell carcinoma infiltration. Size and location of primary tumor were dominant correlating factors of oral squamous cell carcinoma infiltration into the mandible and were statistically significant ($p < 0.05$). Larger tumors are more likely to infiltrate the mandible. Gingiva and retromolar trigone were the prevalent locations which facilitated tumor infiltration. Direct contact of the tumor on the attached mucosa usually provides portal of entry of the tumor through the cortex 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 early phase of infiltration and then followed by invasive type in the deeper portion of mandible. Infiltrating tumors usually do not exceed the limit of the primary on the mucosa, but it becomes unpredictable when inferior alveolar nerve related spread is once 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 mandible is inevitable when nerve involvement is evident.

A combination of orthopantomogram, computerized tomography and Tc-99m skeletal scintigraphy provide a good assessment of the tumor infiltration in the mandible. Distance measurement in orthopantomogram is reliable in localizing the tumor and in planning the surgical margin. An operating scheme based on the biologic behavior of oral squamous cell carcinoma within the mandible is devised as a result of this study.

Key words: oral squamous cell carcinoma, mandibular infiltration, marginal resection

10. Zusammenfassung

Die Entwicklungen in der Behandlung des Plattenepithelkarzinoms des Unterkiefers zielen darauf ab, einen möglichst großen Teil des Unterkiefers zu erhalten. Wissenschaftliche Ergebnisse aus zahlreichen Studien über das biologische Verhalten des Plattenepithelkarzinoms des Unterkiefers bieten mehrere wichtige Informationen. Trotz dieser Forschungen geht oftmals ein großer Teil des *gesunden* Unterkiefers durch die übermäßige Resektion verloren. Diese zum Teil zu ausgedehnte Resektion hat ihre Ursache in der Befürchtung, daß man den möglichen Resttumor in den Zwischenräumen des Knochenmarkes nicht direkt erkennen kann. Aus diesem Grund hat sich die folgende Arbeit zum Ziel gesetzt, dem Operateur ein angemessenes Operationsprotokoll für einen möglichst großen Erhalt des Unterkiefers anzubieten.
Nach retrospektiver Bewertung von klinischen, radiologischen und pathologischen Untersuchungen an 21 histologisch nachgewiesenen Infiltrationen von Unterkiefern durch ein Plattenepithelkarzinom wurden die folgenden Ergebnisse gefunden.
Die Größe eines Tumors und die Lokalisation des Primärtumors zeigen in Bezug auf die Infiltration des Unterkiefers durch ein Plattenepithelkarzinom eine statistisch signifikante Korrelation ($p < 0.05$). Je größer ein Tumor, desto größer ist die Wahrscheinlichkeit für eine Infiltration des Knochens. Je nach Lokalisation dringen die Tumorzellen häufig durch den Alveolarfortsatz- und Kieferwinkelbereich in den Unterkiefer ein.
Ein direkter Kontakt des Tumors zur fest anhaftenden Schleimhaut des Unterkiefers (attached gingiva) begünstigt das Eindringen des Tumors über die Kompakta in den Bereich der Unterkieferspongiosa. Eine weitere Prädilektionsstelle für die Infiltration liegt im Bereich des Zahnhalteapparates.
Der erosive Typ der Knocheninfiltration wurde in der Frühphase der Unterkieferinfiltration in dem kortikalisnahen Teil, der invasive Typ in fortgeschrittenen Stadien im Bereich der tiefen Spongiosa beobachtet. Nach der histologischen Aufarbeitung war üblicherweise die Größe des in den Kiefer eingedrungenen Tumors nicht größer als die des auf der Schleimhaut stehenden Primärtumors.

Im Fall der Infiltration des Nervus alveolaris inferior war die Ausdehnung der

Infiltration nicht vorhersagbar.
Der in der Literatur für Weichgewebsresektionen ausgegebene Sicherheitsabstand von 5 bis 10 mm ist im Fall der Unterkieferinfiltration durch ein Plattenepithelkarzinom auf die Knochenresektion anwendbar.
Bei Verdacht auf muß bei der Operationsplannung und bei der Durchfuhrung der Knochenresektion mit intraoperative Schnellschnittdiagnostik aus dem angrenzenden Inhalt des Kanalis mandibularis besondere Sorgfalt angewandt werden, da eine entsprechende Erweiterung der Unterkieferteilresektion aus Sicherheitsgründen erforderlich werden kann.
Durch eine Kombination von Orthopantomogramm, Computer-Tomographie, und Tc-99m Szintigraphie kann die Unterkieferinfiltration des Plattenepithelkarzinoms der Mundhöhle präziser diagnostiziert werden.
Mit Hilfe der Messung der Tumorgröße im Orthopantomogramm kann die Resektionsgrenze im Unterkiefer noch sicherer festgelegt werden.
Diese Ergebnisse könnten dem Operateur ein angemessenes Vorgehen für den möglichst großen Erhalt des Unterkiefers vermitteln.

Schlüsselwörter: Plattenepithelkarzinom der Mundhöhle, Unterkieferinfiltration, Unterkieferteilresektion

11. Acknowledgment

Design and embodiment on this dissertation began in September, 1996, when I was a second year fellow at the Department of Oral and Maxillofacial Surgery in Yonsei University, Seoul, Korea. The work was come along when I moved to Munich in October of 1997 to carry on a further surgical training at the Department of Oral and Maxillofacial Surgery in the Ludwig-Maximilians-University. That it was finished is due, in no small measures, to the help and support which I received from numerous people.

I am grateful to Professor Dr. med. Dr. med. dent. Michael Ehrenfeld for his concern and guidance throughout my stay in the Department. He gave me a wonderful perspective on the depth and range of current concept in Oral and Maxillofacial Surgery. Dr. med. Dr. med. dent. Wolfgang A. Winter has provided much help, advice, teaching, and influence in head and neck oncologic surgery. My friends Prof. Dr. med. Dr. med. dent. Dirk Nolte and Dr. med. dent. Lars Helfrich, their invaluable friendship will remain in my heart. Professor Dr. med. Udo Löhrs generously allowed me to proceed histopathologic examination in his institute. I would like to thank Dr. med. Stephan Ihrler for very enthusiastic cooperation in histopathologic evaluation. Frau Andrea Hinkelmann in Promotion bureau, whom I owe so much in completing this Doctorate, I should remember her kindness as long as I can. I am grateful to my parents, my wife and daughters, whose love and good natured tolerance have been indispensable to the completion of this project. I must thank my teachers in Yonsei University, for their encouragement and trust from the beginning. Finally, I thank German Academic Exchange Service for the grant of scholarship. Part of efforts required for this work rightfully belongs to all those I mentioned, and I will now try to repay some of what I owe them.

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Munich, December, 2008

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