206

Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445
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International Journal of
Oral & Maxillofacial Surgery
ISSN 0901-5027

mit echter Dankbarkeit
und meinem Lehrer
Prof. Sailer.

1.2.97
N. Kalavrezos.

Oncology

Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas

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N. D. Kalavrezos, K. W. Grätz, H. F. Sailer, W. A. Stahel: Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas. Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445. © Munksgaard, 1996

Abstract. The detection in the mandible of early local spreading of adjacent primary malignancies poses a difficult problem. A survey of 60 patients suspected of carcinomatous mandibular infiltration was undertaken, and the most important clinical and imaging data were studied. Tumor localization and bone scintigraphy proved to offer the most important predictive power. A decision tree and a logistic regression model which determines a score function combining these characteristics were designed. This decision tree improves the sensitivity and specificity of the preoperative assessment and provides the surgeon with an algorithm for the accurate estimation of early mandibular invasion.

Key words: bone scintigraphy; computed tomography; tumor localization; logistic regression; prediction.

Accepted for publication 12 June 1996

Oral malignancies constitute approximately 5% of all malignant neoplasms in the body, and the vast majority of them (91%) are squamous cell carcinomas (SCC)[25,30]. Early bone invasion is of paramount importance when treatment is considered, having also a great impact on the survival rate[26,35]. Inability to detect invasion of the tumor in the bone may lead to inadequate resection, resulting in local recurrence and potential regional or distant metastasis. The incidence of mandibular invasion by SCC depends on the size of the primary tumor and on the proximity of the tumor to the mandible, the incidence ranging from 12% to 56% according to various studies[2,4,13,18,21,24,31,32,36].

Several imaging methods such as conventional radiography, computed tomography (CT), radionuclide scans, and magnetic resonance imaging (MRI) have been used to delineate mandibular infiltration. All of these methods, however, seem to have specific limitations, and the preoperative assessment of possible bone infiltration is still based on clinical inspection combined with the data derived from these imaging methods.

Bone scintigraphy (BS) is generally regarded as one of the most reliable methods of assessment of bone invasion and detection of distant osseous metastasis[11,20]. Despite the high sensitivity of the method in relation to the detection of osseous infiltration, BS is associated with a high incidence of false-positive results due to its unspecificity[13,17,37]. Various studies have reported false-positive and -negative results and discussed the implications.

CT is regarded as a sensitive method of assessing primary SCC (size, location, spread in the soft tissues, and regional lymph-node metastasis). However, its ultimate usefulness in the delineation of invasion of SCC in the mandible remains questionable due to the irregular shape of the mandibular bone and the limitations caused by metal dental artifacts[9,28].

To compare the accuracy of BS and CT scanning, we undertook a study in which both methods were used in sequential order. The results were linked with the clinical assessment and the histopathologic findings. The aim was to develop a protocol allowing precise preoperative assessment of possible invasion of SCC in the mandible.

Material and methods

The records of 60 patients with oral carcinoma suspected of mandibular infiltration, treated surgically in the Cranio-Maxillofacial Surgery Department of the University Hospital of Zurich, Switzerland, between 1988 and 1995, were reviewed. The patient population consisted of 44 (73%) men and 16 (27%) women. The patient age range was 33–83

years; the average age was 60.18 years (59 for men and 64 for women). In 15 patients, preoperative radiotherapy was performed. The radiation was conventionally fractionated with a total dosis of 50–55 Gy. The interim period between radiation and surgery was less than 50 days in each case.

The criteria for inclusion of patients in the study were as follows:

1) primary SCC of the oral cavity adjacent to or near the mandible
2) general medical condition of the patient permitting radical tumor surgery.

The diagnostic presurgical imaging for the assessment of mandibular invasion included conventional plain radiographs, BS, and CT. Whole-body radionuclide bone scanning was performed in all patients, by the protocol of the Nuclear Medicine Department, with application of 500–800 MBq ^{99m}Tc-DPD (dicarboxypropane-diphosphonate), while imaging was done 3 h later (delayed phase) with a high-resolution collimator. The images were always interpreted independently by two observers skilled in nuclear imaging interpretation.

CT data were obtained in 47 patients. CT imaging of the suspected mandible was performed according to the standard procedure of the Neuroradiology Department, including CT scans in two planes (axial and coronal) in contiguous 5-mm slices. In suspected invaded bone areas, additional overlapping cuts of 3 or even of 1.5 mm were performed. Filming was done at both soft-tissue and bone-tissue settings. The mandibular area suspected of tumor invasion was filmed at 4000, rather than 2000, window settings, for better imaging in cases of minimal bone destruction.

Of the 60 patients, 37 underwent segmental and 18 marginal resection; in the remaining five patients, a sagittal resection of the lingual cortex of the mandible was performed. The specimens were demineralized with EDTA and cut in a routine fashion.

The clinical and imaging parameters included the primary tumor localization, staging and grading of the tumor, radionuclide bone-scan evaluation, CT scan data, surgical treatment, and correlation of the diagnostic findings with the histologic results. Tumors were staged according to the guidelines of the TNM system[14]. Tumors with periosteal involvement but intact osseous structures were classified as having no bone infiltration.

The dependence of the histologically determined bone infiltration and each of the preoperative variables were statistically tested by the chi-square test. To study joint effects of several variables for improving their diagnostic value, we devised a decision tree. In the first step, the patient population was split into two groups according to the variable which distinguished best between histologically negative and positive results. The division was stopped when further steps no longer led to improvement, as was the case after two steps. The method[8] was adapted to optimize predictive values and to improve interpretability. A logistic regression model which provides an alternative method for the prediction of bone infiltration on the basis of several preoperative characteristics of the patient was also submitted. A score function in the form of a linear combination of these characteristics was constructed. This function was then converted by the so-called logistic transformation into an estimated probability for any patient suspected of bone infiltration. Statistical calculations were performed by the program S/S-Plus.

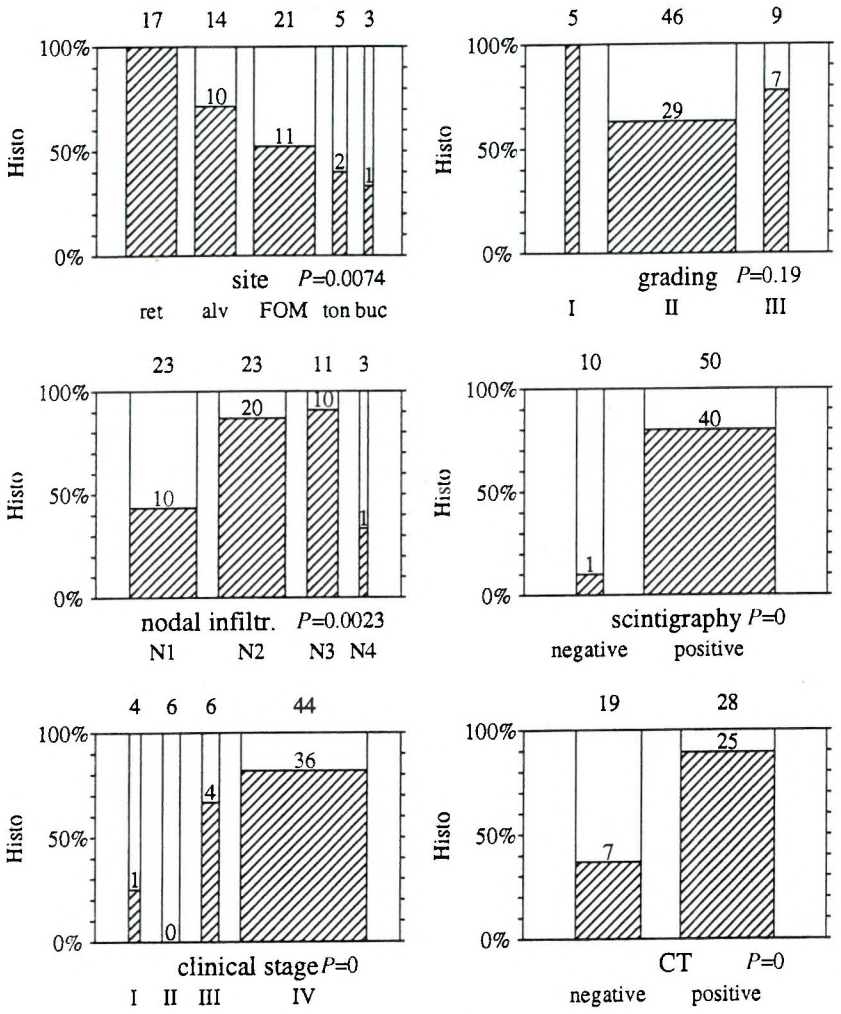


Fig. 1. Correlation between histologically verified bone infiltration and preoperative predictor variables. Shaded areas and numbers above them show number of patients with bone infiltration in each category of predictors. Total numbers are presented at top and are proportional to width of bars. *P* values refer to chi-square test for independence.

Results

Bone involvement was histologically proven in 41 patients (68%), while in 19 patients (32%) the tumor was in proximity to the bone but without infiltration of the cortex.

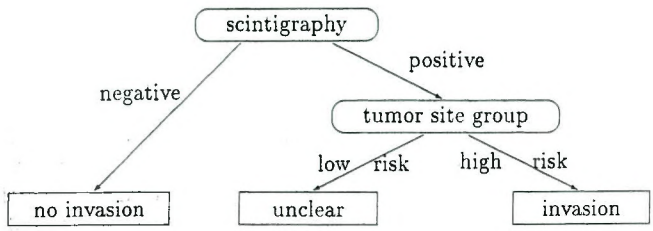


Fig. 2. Decision tree: branching is based statistically on two most important predictive factors – scintigraphy and tumor localization.

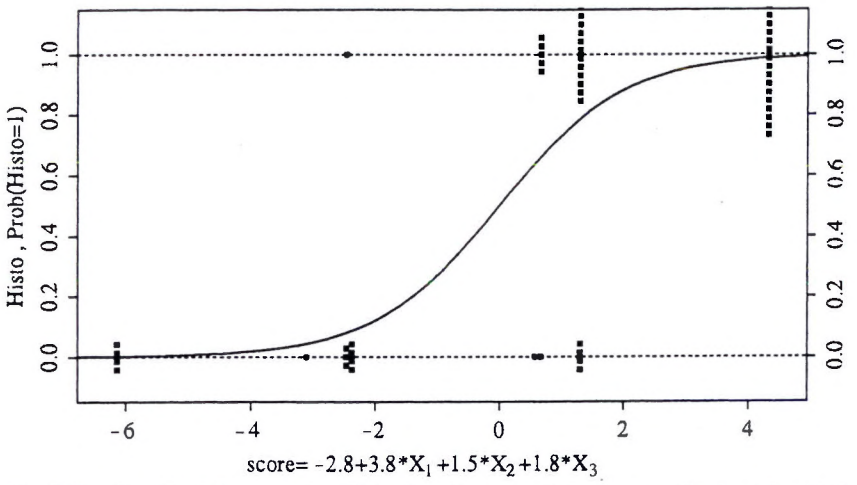


Fig. 3. Results of logistic regression. Dots show linear predictor or score (horizontal axis) for each patient with and without bone invasion (vertical axis). Line shows how this score is transformed into estimated probability of bone invasion based on three predictors, X_1, X_2, and X_3.

Localization

The tumors were localized in five different sites, including the retromolar area, the alveolar ridge, the floor of the mouth, the tongue, and the cheek mucosa. The tumors located in the retromolar area (17 patients, 28%) all showed histologic invasion of tumor in the bone (100%). Tumors of the alveolar process were found in 14 patients (23%). In 10 (71%) of them, bone invasion was histologically present. SCC in the floor of the mouth was present in 21 (35%) patients. In 11 (52%) of them, osseous infiltration was histologically evident. There were only five patients with SCC localized in the tongue, while in three patients, it was in the buccal mucosa. In two patients with tongue SCC and one with involvement of the buccal mucosa, bony invasion was histologically apparent (Fig. 1).

Nodal infiltration

On clinical and CT examination, 23 (38%) of the 60 patients showed no evidence of nodal disease (N0), 23 (38%) patients had N1 positive lymph nodes, 11 (18%) patients were classified as N2, and three (5%) patients were classified as N3. Ten (43%) patients of the first group had histologic evidence of bone involvement; in 20 (87%) of the 23 N1 patients, this was the case. In the N2 category, bone invasion was present in 10 (91%) of the 11 patients, but in only one patient in the N3 group (Fig. 1).

Stage

The relationship between stage of disease and bone invasion is presented in Table 1. It is evident that bony invasion correlated with the higher-stage groups (Fig. 1).

Grading

Differentiation of tumor cells was distributed into three grades[14]: grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated). Only five (8%) of the 60 patients presented with grade I lesions; in all of them (100%), mandibular involvement was confirmed. Of the 46 (77%) patients with grade II lesions, bone infiltration was found in 29 (63%). Of the remaining nine (15%) patients with poorly differentiated SCC, seven (78%) had evident bone infiltration. The results, however, were not statistically significant (Fig. 1).

Bone scintigraphy

Preoperative bone scans were positive in 40 (98%) of the 41 patients (Fig. 1). In only one (2%) patient was the result of bone scanning false-negative; i.e., the mandibular destruction was not detected. Increased radionuclide uptake in the BS was seen in 10 (52%) of the group of the 19 patients without histologically proven mandibular invasion. The results obtained with the univariate analysis verified the diagnostic accuracy and the sensitivity of BS, resulting in a negative predictive value (NPV) of 90% and a positive predictive value (PPV) of 80%, due to the incidence of false-positive findings.

Table 1. Clinical stage according to TNM system

Stage	Criteria	Bone invasion, no. of patients		
		No	Yes	Total
I	T1N0	3	1	4
II	T2N0	6	0	6
III	T2N1, T3N0, T3N1	2	4	6
IV	All T4 Any T with N2 or N3 Any T and N with M1	8	36	44

Table 2. Estimated coefficients for logistic model

	Estimate	Std. error	*P* value
Intercept	−2.788	1.4017	0.047
Scintigraphy	3.762	1.4577	0.010
Site group	1.515	0.6046	0.012
Stage 4	1.833	0.6265	0.003

Table 3. Estimated probabilities of bone invasion calculated from logistic model

Site group	Low risk		High risk	
Tumor stage	1–3	4	1–3	4
Sc. negative	0.2	7.8	4.3	63.7
Sc. positive	8.5	78.5	65.8	98.7

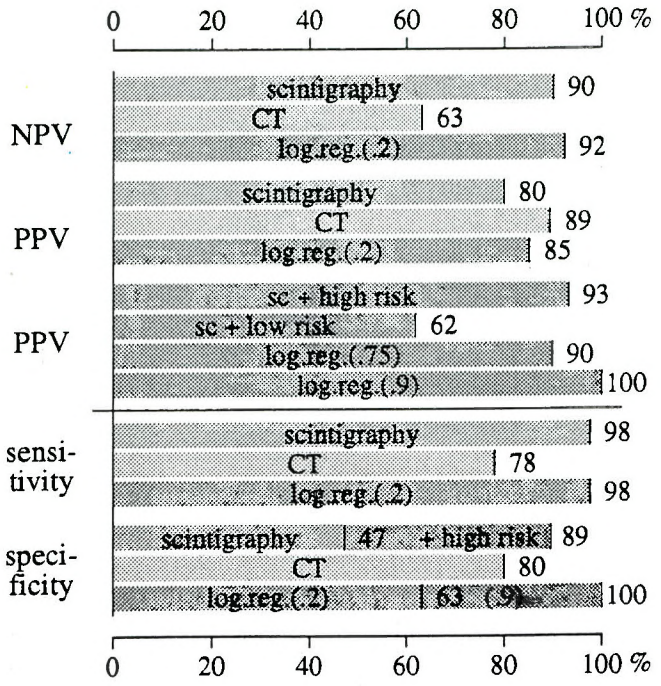


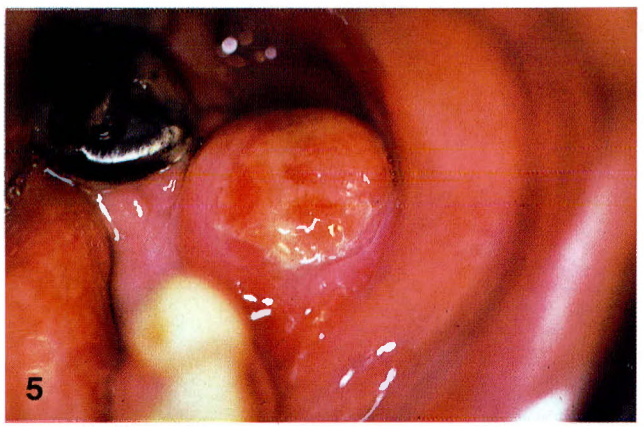
Fig. 4. Predictive values, sensitivities, and specificities for scintigraphy; for CT; for decision tree that permits category of uncertain decision (scintigraphy and low-risk site); and for various rules based on probability of bone invasion estimated by logistic regression.

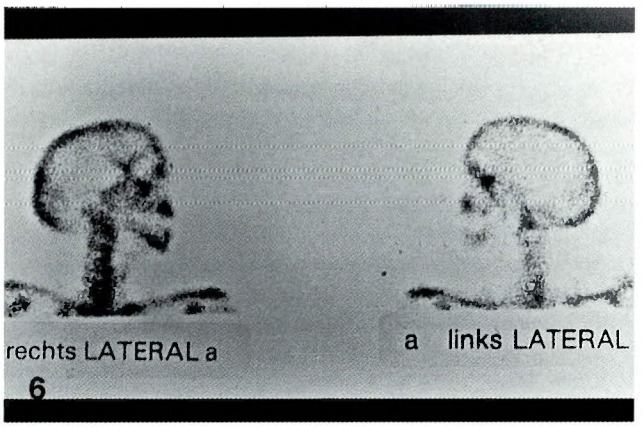
Computed tomography

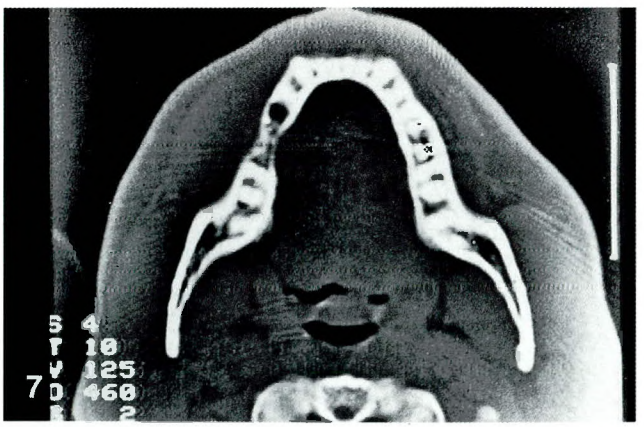
CT data were obtained in 47 patients. The imaging findings corresponded well with the histopathologic results in 37 (62%) patients. In 25 patients, mandibular invasion was properly diagnosed, whereas in 12 who had no histologic evidence of osseous infiltration, the results of CT were negative as well. There were seven (22%) patients in whom CT did not reveal bony erosion while the histology proved to be positive. There were only three patients with false-positive results (Fig. 1).

Decision tree (Fig. 2)

To study the joint effects of the several variables which might enhance their diagnostic value, we devised a decision tree based on the two most statistically predictive criteria, scintigraphic find-







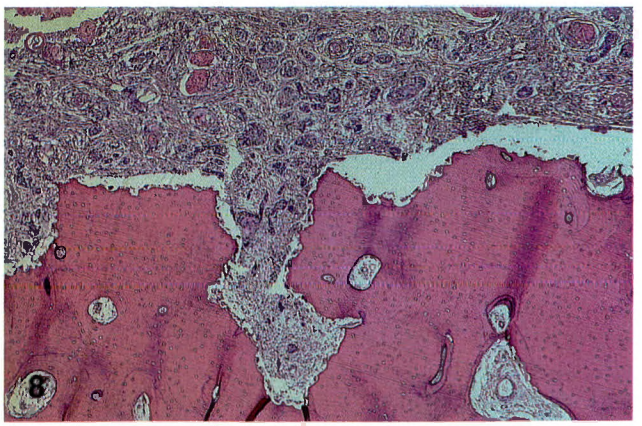


Fig. 5. Clinical view of exophytic SCC adjacent to alveolar crest of mandible.
Fig. 6. Bone scan of same patient with increased ^{99m}Tc uptake in right mandible, revealing bony invasion.
Fig. 7. CT scan of same patient showing osteolysis in right premolar region due to tumor invasion of mandible.
Fig. 8. Histologic findings of resected mandible showing deep penetration of tumor cells into bony structures (HE ×10).

ings and tumor localization. Two groups were chosen for the sake of simplicity. The high-risk group consisted of the retromolar area and the alveolar ridge, while the floor of the mouth, the tongue, and the buccal mucosa formed the low-risk group. The first decision was based on the scintigraphic results. For patients with negative bone scanning, the risk of osseous infiltration was low (estimated at 10%). For patients with positive scintigraphy, with a positive predictive value (PPV) of 80%, further branching helped. In tumors of a high-risk area, the PPV increased to 27/29 (93%). For patients with positive bone scanning but with tumors localized in low-risk areas, the prediction was uncertain, as the probability of osseous infiltration was 13/21 (61%). Further diagnostic tests were recommended. If this group of 21 patients had been further divided, improved results could have been obtained. Eighteen of this group had positive or negative CT. Of the nine patients with positive CT, only one had no bone infiltration, whereas this was the case for five of the nine patients with negative CT. All four patients with clinical tumor stage less than IV had no bone infiltration.

Logistic regression

On the basis of the results achieved, a logistic regression model, which allows one to obtain estimated probabilities of bone invasion from several predictive variables, was developed. The best result was found by using the three binary variables:

X_1=1 for patients with positive bone scanning; otherwise, X_1=0

X_2=1 for patients with tumor in a high risk site; otherwise, X_2=0

X_3=for patients with tumor stage IV; otherwise, X_3=0.

Estimated coefficients are presented in Table 2, while Table 3 shows the estimated probabilities for bone infiltration for the eight combinations of the characteristics.

The results suggest the following hypothesis. Positive bone scanning combined with tumor stage IV entails a very high probability of high-risk sites (98.7%) and still a high probability (78%) of low-risk sites. Patients with negative bone scanning have a low risk (4.3%) unless they have tumor stage IV in high-risk areas. For high-risk sites and either tumor stage IV or positive bone scanning (but not both), the outcome remains unclear. Fig. 3 shows the correlation between incidence of bone invasion and its estimated probability.

Discussion

Mandibular invasion is a determining factor for treatment planning, and it also affects the prognosis of the disease. Invasion of the bone by direct extension of an adjacent carcinoma which penetrates the thin mucosal layer of the alveolar ridge is the most common route of mandibular infiltration[18,19]. Brown & Browne[6] emphasize that the attached mucosa is the main potential route of tumor entry because of the lack of periosteum in this area of the mandible. Invasion by involvement of deeper tissues and secondary extension through the periosteum is rare[18]. Early tumor invasion of the mandible generally occurs when the lesion is located close to the buccal sulcus or the mylohyoid crest, thus bringing the tumor into direct proximity to the bone[19]. The bone is invaded in areas of cortical defects created by the fibrous attachment of the mucosa or by reactive inflammation associated with the tumor[6,19,23].

These findings suggest that it is justifiable to adopt a more conservative surgical approach, such as marginal resection, in cases of limited superficial bone involvement, thus avoiding aesthetic problems and reconstructive difficulties in low-risk cases[4,12,27]. However, when evidence of bone-marrow invasion exists, segmental resection has to be carried out[34]. Dubner & Heller[10] did not find differences in the recurrence rate of 130 patients who underwent either segmental or marginal mandibulectomy. They found that most recurrences after marginal mandibulectomy were in the adjacent soft tissues, not in the remaining mandible.

According to our findings, the primary tumor site appears to have a strong correlation with mandibular invasion. Of the five tumor localizations studied, tumors located in the retromolar area and alveolar ridge were found to involve the bone in a significant number of patients (88%). This finding agrees with the results of previous studies[7,13,36]. The strong predilection for bone invasion from tumors located in the retromolar zone/alveolar ridge can be explained by of the fact that early infiltrative growth may easily reach the 2–3 mm of soft tissue overlying the alveolar bone in these cases. As for tumors of the floor of the mouth, the high propensity for early bone invasion which is reported by Bahadur[2] could not be verified. Carcinomas of the floor of the mouth invaded the mandible at a rate of 52% in our group. The propensity for tumors of the buccal mucosa and the tongue to infiltrate the bone could not be determined because of the low numbers in this group.

A statistical assessment of the correlation of primary tumor size with bone infiltration could not be done, due to the low number of patients with T1 and T2. However, the data presented agree with those reported by Weisman & Kimmelman[37], supporting the view that larger tumors pose a greater risk of bone invasion.

The stage of tumor appears (P=0.0003) to be associated with mandibular bone involvement. Although it is reported[2,15,18,21] that only proximity to bone, not tumor size or stage, is the determining factor in mandibular involvement, larger tumors theoretically increase the surface area and therefore, through "fragile" osseous parts (cortical clefts or microvascular bone channels), can more easily erode the bony surface. Confirmation of this assumption would require a randomized, prospective study of a large group of patients with Stage IV SCC.

In this study, differentiation of SCC was found to have no bearing on whether or not bone was invaded. Lund[16] suggests that tumor aggressiveness is related to both invasion and cellular differentiation, whereas the presence of only one of these features is less significant. Brown & Browne[6] reported that tumors with an erosive pattern of infiltration tend to be related to grade I or II, while those with an invasive pattern are often related to grade III. Correlation of the degree of differentiation and infiltration patterns of the tumor has not been confirmed by other authors[2,15].

Bone scanning is sensitive for the detection of occult metastasis in the skeleton. The main radiopharmaceutic agent is technetium-99m dicarboxy-propane diphosphonate (^{99m}Tc-DPD). In SCC, increased bone turnover occurs, resulting in high uptake of ^{99m}Tc, correspond-

ing to the "hot spots" on the bone scan. Metastatic lesions are usually detected by radionuclide bone scan before they are detected by conventional plain radiographs because the chemical changes of a disease process usually occur before anatomic changes. Such chemical changes inducing bone reaction are detectable by radionuclide imaging[22].

The results on the value of BS for the detection of early mandibular invasion agree with the results of other studies[1–5,7,11,13,17,27,37], indicating high sensitivity. However, there were many (52%) false-positive results.

The present study found the predictability and reliability of CT scans in assessment of invasion of the mandible to be unsatisfactory. A false-negative rate of 22% was found, in comparison with an average of 12.5% reported in other studies[2,7,9,29]. Only Brown et al.[7] reported a higher incidence of 28% false-negative results in CT scans. Although CT scans can help to estimate the size of the primary tumor and the nodal status, their value in the detection of early invasion of the mandible seems to be limited. Artifacts, especially in the coronal planes, due to dental restorations, and failure to assess accurately the area of the inner cortex of the mandible due to its irregular shape make it difficult to draw conclusions.

Tumor delineation by MRI was used only in selected cases and mainly for the estimation of soft-tissue invasion. Brown et al.[7] reported a false-negative rate of only 6% for predictability of bone invasion. However, Tsue et al.[36] found MRI scans to be less accurate than CT scans in determining cortex involvement and bone-marrow invasion. These controversial reports indicate the need for further study of this more costly imaging modality in assessing bony invasion.

According to the results of the present study and information from the available literature, bone scanning still seems to be the most sensitive method for detection of early invasion of SCC in the mandible. According to Noyek[22] and Bergstedt et al.[5], virtually no false-positive results should be obtained and a distinction should be possible between cancers that involve the soft tissues and those that erode the mandible by comparing early and delayed uptake. These authors also state that the errors in interpretation of the integrity of the mandible are largely due to failure of careful correlation between clinical findings and areas of abnormal activity on the scan. Although this statement has been disputed by several authors[15,19,37], we believe that, with cautious correlation with the clinical features, at least misinterpretation because of periapical or pericoronal inflammatory disease should be avoidable.

As far as patients who have received radiation are concerned, the assessment of the mandible is particularly difficult, either by preoperative diagnostic imaging or clinically. The increased sensitivity of bone scanning in irradiated patients is due to the mechanism of radionuclide uptake and the primary effect of the irradiation itself. In these patients, decisions regarding segmental as opposed to marginal mandibulectomy should be generally based on the location of the tumor, its extent, and the presence or absence of induration around the mandible[29].

The statistical method of the study addresses the problem of false-positive results by allowing for an intermediate class of unclear cases. By the decision-tree approach, the decision, "no bone invasion", would have been made for 10 patients (17%) with one error (10%); "bone invasion" would have been decided for 29 (48%) with two misclassifications (7%); and for the remaining 21 patients (35%), the decision "unclear" would have been applied. By use of the estimated probabilities of the logistic regression, several decision rules can be derived by setting levels. The estimated probability was below 0.1 for 13 patients (22%). If the remaining 47 patients had been classified positive, the PPV would have been 40/47 (85%). All 22 patients (37%) with estimated probability higher than 0.9 showed positive histologic results (PPV=100%). Twenty-five patients (42%), showing probability of 0.1–0.9, remained "unclear". If the levels had been set to 25% and 75%, only eight (13%) patients would have remained unclassified. While the "no bone invasion" class would have been the same, the class with positive results would have contained 39 patients (65%) with only four false-positive cases.

Predictive values, sensitivities, and specificities of five prediction rules are compared in Fig. 4. As mentioned above, scintigraphy exhibited higher negative predictive value and higher sensitivity than CT. If the estimated probability in the logistic regression were cut anywhere between 0.1 and 0.5, the NPV would be 93%. However, bone scanning with a specificity of only 47% was less specific than CT (78%). If mandibular invasion were diagnosed only for those patients showing positive scintigraphy and a high-risk tumor site, the specificity would rise to 89% and the PPV to 93%. If the decision "further investigation necessary" were not allowed, one would have to assume bony infiltration and the decision tree would then coincide with the scintigraphic criterion. For the logistic regression, the positive predictive value would increase to 85% or 100% if only patients with estimated probability higher than 0.75 or 0.9, respectively, were called positive. The corresponding specificity values would be 79% and 100%.

In conclusion, bone scanning appeared to be the best predictive imaging parameter for bone invasion. When it was combined with specific clinical features, it provided the best prognostic means in most patients (Figs. 5–8). We suggest the selection of an intermediate group of patients in whom it is not clear whether bone infiltration is present and who need further examination. The "rules" derived from our data set of 60 patients may have given unduly promising predictive values. The small number of our patient population, however, should compel further studies to check and refine the procedure.

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Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445
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International Journal of
Oral & Maxillofacial Surgery
ISSN 0901-5027

Oncology

Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas

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N. D. Kalavrezos, K. W. Grätz, H. F. Sailer, W. A. Stahel: Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas. Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445. © Munksgaard, 1996

Abstract. The detection in the mandible of early local spreading of adjacent primary malignancies poses a difficult problem. A survey of 60 patients suspected of carcinomatous mandibular infiltration was undertaken, and the most important clinical and imaging data were studied. Tumor localization and bone scintigraphy proved to offer the most important predictive power. A decision tree and a logistic regression model which determines a score function combining these characteristics were designed. This decision tree improves the sensitivity and specificity of the preoperative assessment and provides the surgeon with an algorithm for the accurate estimation of early mandibular invasion.

Key words: bone scintigraphy; computed tomography; tumor localization; logistic regression; prediction.

Accepted for publication 12 June 1996

Oral malignancies constitute approximately 5% of all malignant neoplasms in the body, and the vast majority of them (91%) are squamous cell carcinomas (SCC)[25,30]. Early bone invasion is of paramount importance when treatment is considered, having also a great impact on the survival rate[26,35]. Inability to detect invasion of the tumor in the bone may lead to inadequate resection, resulting in local recurrence and potential regional or distant metastasis. The incidence of mandibular invasion by SCC depends on the size of the primary tumor and on the proximity of the tumor to the mandible, the incidence ranging from 12% to 56% according to various studies[2,4,13,18,21,24,31,32,36].

Several imaging methods such as conventional radiography, computed tomography (CT), radionuclide scans, and magnetic resonance imaging (MRI) have been used to delineate mandibular infiltration. All of these methods, however, seem to have specific limitations, and the preoperative assessment of possible bone infiltration is still based on clinical inspection combined with the data derived from these imaging methods.

Bone scintigraphy (BS) is generally regarded as one of the most reliable methods of assessment of bone invasion and detection of distant osseous metastasis[11,20]. Despite the high sensitivity of the method in relation to the detection of osseous infiltration, BS is associated with a high incidence of false-positive results due to its unspecificity[13,17,37]. Various studies have reported false-positive and -negative results and discussed the implications.

CT is regarded as a sensitive method of assessing primary SCC (size, location, spread in the soft tissues, and regional lymph-node metastasis). However, its ultimate usefulness in the delineation of invasion of SCC in the mandible remains questionable due to the irregular shape of the mandibular bone and the limitations caused by metal dental artifacts[9,28].

To compare the accuracy of BS and CT scanning, we undertook a study in which both methods were used in sequential order. The results were linked with the clinical assessment and the histopathologic findings. The aim was to develop a protocol allowing precise preoperative assessment of possible invasion of SCC in the mandible.

Material and methods

The records of 60 patients with oral carcinoma suspected of mandibular infiltration, treated surgically in the Cranio-Maxillofacial Surgery Department of the University Hospital of Zurich, Switzerland, between 1988 and 1995, were reviewed. The patient population consisted of 44 (73%) men and 16 (27%) women. The patient age range was 33–83

years; the average age was 60.18 years (59 for men and 64 for women). In 15 patients, preoperative radiotherapy was performed. The radiation was conventionally fractionated with a total dosis of 50–55 Gy. The interim period between radiation and surgery was less than 50 days in each case.

The criteria for inclusion of patients in the study were as follows:

1) primary SCC of the oral cavity adjacent to or near the mandible
2) general medical condition of the patient permitting radical tumor surgery.

The diagnostic presurgical imaging for the assessment of mandibular invasion included conventional plain radiographs, BS, and CT. Whole-body radionuclide bone scanning was performed in all patients, by the protocol of the Nuclear Medicine Department, with application of 500–800 MBq ^{99m}Tc-DPD (dicarboxypropane-diphosphonate), while imaging was done 3 h later (delayed phase) with a high-resolution collimator. The images were always interpreted independently by two observers skilled in nuclear imaging interpretation.

CT data were obtained in 47 patients. CT imaging of the suspected mandible was performed according to the standard procedure of the Neuroradiology Department, including CT scans in two planes (axial and coronal) in contiguous 5-mm slices. In suspected invaded bone areas, additional overlapping cuts of 3 or even of 1.5 mm were performed. Filming was done at both soft-tissue and bone-tissue settings. The mandibular area suspected of tumor invasion was filmed at 4000, rather than 2000, window settings, for better imaging in cases of minimal bone destruction.

Of the 60 patients, 37 underwent segmental and 18 marginal resection; in the remaining five patients, a sagittal resection of the lingual cortex of the mandible was performed. The specimens were demineralized with EDTA and cut in a routine fashion.

The clinical and imaging parameters included the primary tumor localization, staging and grading of the tumor, radionuclide bone-scan evaluation, CT scan data, surgical treatment, and correlation of the diagnostic findings with the histologic results. Tumors were staged according to the guidelines of the TNM system[14]. Tumors with periosteal involvement but intact osseous structures were classified as having no bone infiltration.

The dependence of the histologically determined bone infiltration and each of the preoperative variables were statistically tested by the chi-square test. To study joint effects of several variables for improving their diagnostic value, we devised a decision tree. In the first step, the patient population was split into two groups according to the variable which distinguished best between histologically negative and positive results. The division was stopped when further steps no longer led to improvement, as was the case after two steps. The method[8] was adapted to optimize predictive values and to improve interpretability. A logistic regression model which provides an alternative method for the prediction of bone infiltration on the basis of several preoperative characteristics of the patient was also submitted. A score function in the form of a linear combination of these characteristics was constructed. This function was then converted by the so-called logistic transformation into an estimated probability for any patient suspected of bone infiltration. Statistical calculations were performed by the program S/S-Plus.

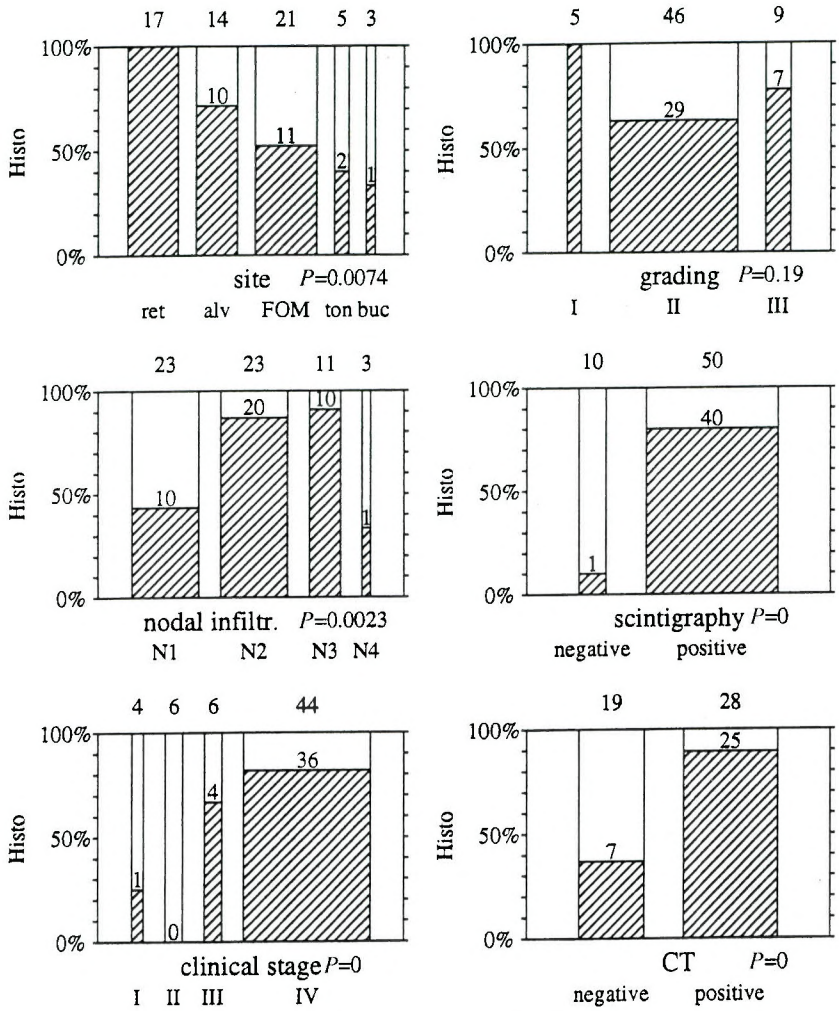


Fig. 1. Correlation between histologically verified bone infiltration and preoperative predictor variables. Shaded areas and numbers above them show number of patients with bone infiltration in each category of predictors. Total numbers are presented at top and are proportional to width of bars. *P* values refer to chi-square test for independence.

Results

Bone involvement was histologically proven in 41 patients (68%), while in 19 patients (32%) the tumor was in proximity to the bone but without infiltration of the cortex.

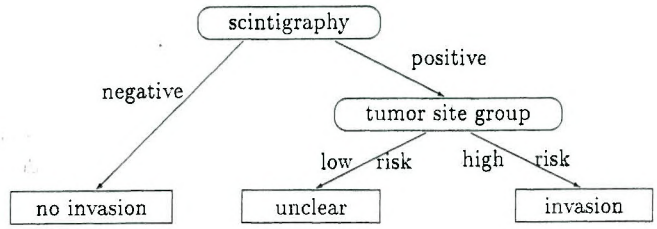


Fig. 2. Decision tree: branching is based statistically on two most important predictive factors – scintigraphy and tumor localization.

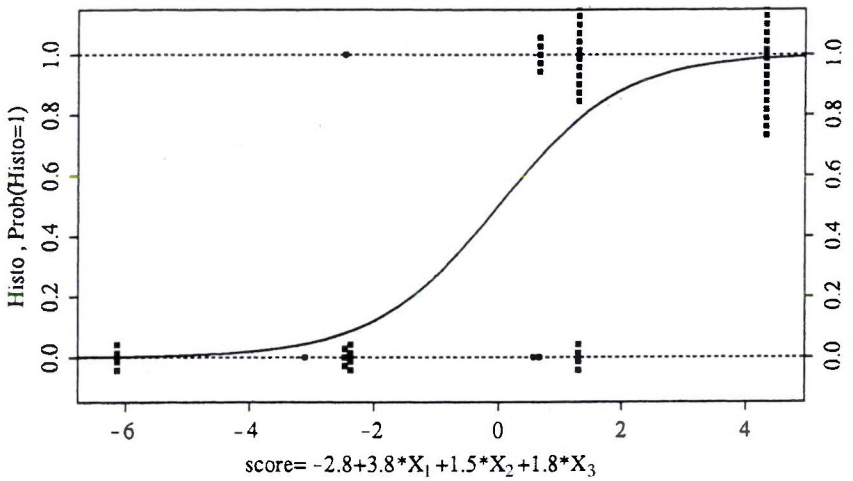


Fig. 3. Results of logistic regression. Dots show linear predictor or score (horizontal axis) for each patient with and without bone invasion (vertical axis). Line shows how this score is transformed into estimated probability of bone invasion based on three predictors, X_1, X_2, and X_3.

Localization

The tumors were localized in five different sites, including the retromolar area, the alveolar ridge, the floor of the mouth, the tongue, and the cheek mucosa. The tumors located in the retromolar area (17 patients, 28%) all showed histologic invasion of tumor in the bone (100%). Tumors of the alveolar process were found in 14 patients (23%). In 10 (71%) of them, bone invasion was histologically present. SCC in the floor of the mouth was present in 21 (35%) patients. In 11 (52%) of them, osseous infiltration was histologically evident. There were only five patients with SCC localized in the tongue, while in three patients, it was in the buccal mucosa. In two patients with tongue SCC and one with involvement of the buccal mucosa, bony invasion was histologically apparent (Fig. 1).

Nodal infiltration

On clinical and CT examination, 23 (38%) of the 60 patients showed no evidence of nodal disease (N0), 23 (38%) patients had N1 positive lymph nodes, 11 (18%) patients were classified as N2, and three (5%) patients were classified as N3. Ten (43%) patients of the first group had histologic evidence of bone involvement; in 20 (87%) of the 23 N1 patients, this was the case. In the N2 category, bone invasion was present in 10 (91%) of the 11 patients, but in only one patient in the N3 group (Fig. 1).

Stage

The relationship between stage of disease and bone invasion is presented in Table 1. It is evident that bony invasion correlated with the higher-stage groups (Fig. 1).

Grading

Differentiation of tumor cells was distributed into three grades[14]: grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated). Only five (8%) of the 60 patients presented with grade I lesions; in all of them (100%), mandibular involvement was confirmed. Of the 46 (77%) patients with grade II lesions, bone infiltration was found in 29 (63%). Of the remaining nine (15%) patients with poorly differentiated SCC, seven (78%) had evident bone infiltration. The results, however, were not statistically significant (Fig. 1).

Bone scintigraphy

Preoperative bone scans were positive in 40 (98%) of the 41 patients (Fig. 1). In only one (2%) patient was the result of bone scanning false-negative; i.e., the mandibular destruction was not detected. Increased radionuclide uptake in the BS was seen in 10 (52%) of the group of the 19 patients without histologically proven mandibular invasion. The results obtained with the univariate analysis verified the diagnostic accuracy and the sensitivity of BS, resulting in a negative predictive value (NPV) of 90% and a positive predictive value (PPV) of 80%, due to the incidence of false-positive findings.

Table 1. Clinical stage according to TNM system

Stage	Criteria	Bone invasion, no. of patients		
		No	Yes	Total
I	T1N0	3	1	4
II	T2N0	6	0	6
III	T2N1, T3N0, T3N1	2	4	6
IV	All T4 Any T with N2 or N3 Any T and N with M1	8	36	44

Table 2. Estimated coefficients for logistic model

	Estimate	Std. error	*P* value
Intercept	−2.788	1.4017	0.047
Scintigraphy	3.762	1.4577	0.010
Site group	1.515	0.6046	0.012
Stage 4	1.833	0.6265	0.003

Table 3. Estimated probabilities of bone invasion calculated from logistic model

Site group Tumor stage	Low risk		High risk	
	1–3	4	1–3	4
Sc. negative	0.2	7.8	4.3	63.7
Sc. positive	8.5	78.5	65.8	98.7

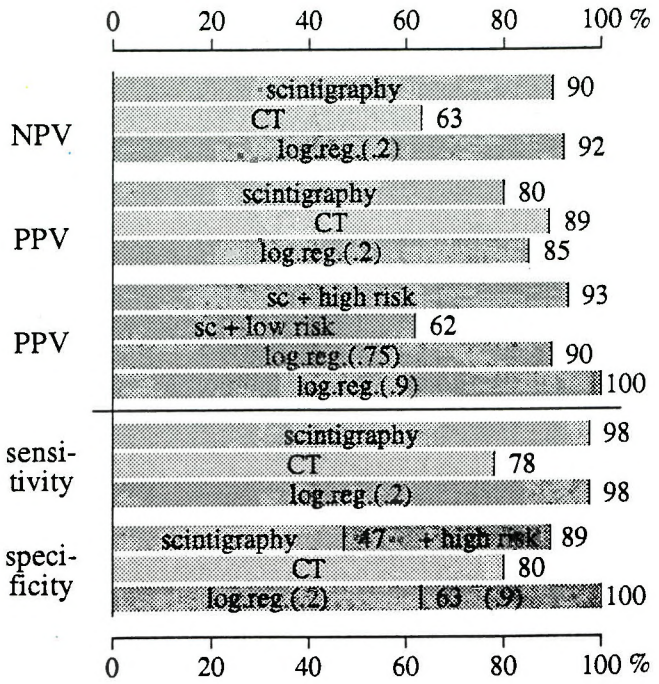


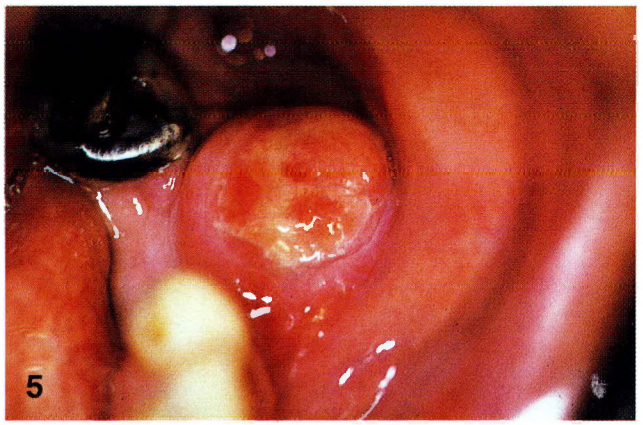
Fig. 4. Predictive values, sensitivities, and specificities for scintigraphy; for CT; for decision tree that permits category of uncertain decision (scintigraphy and low-risk site); and for various rules based on probability of bone invasion estimated by logistic regression.

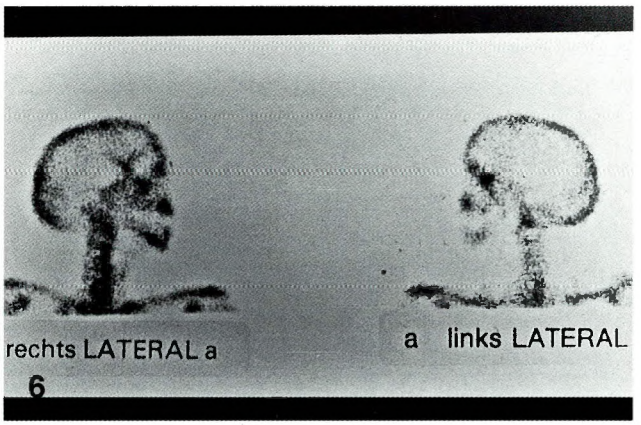
Computed tomography

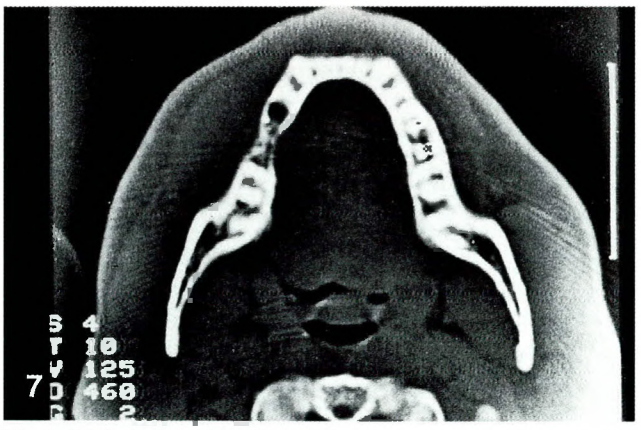
CT data were obtained in 47 patients. The imaging findings corresponded well with the histopathologic results in 37 (62%) patients. In 25 patients, mandibular invasion was properly diagnosed, whereas in 12 who had no histologic evidence of osseous infiltration, the results of CT were negative as well. There were seven (22%) patients in whom CT did not reveal bony erosion while the histology proved to be positive. There were only three patients with false-positive results (Fig. 1).

Decision tree (Fig. 2)

To study the joint effects of the several variables which might enhance their diagnostic value, we devised a decision tree based on the two most statistically predictive criteria, scintigraphic find-







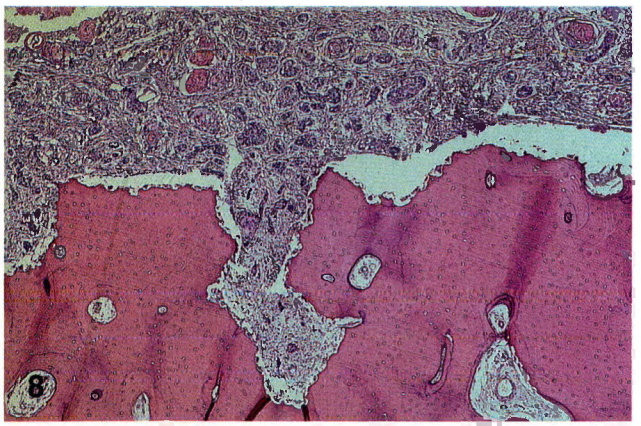


Fig. 5. Clinical view of exophytic SCC adjacent to alveolar crest of mandible.
Fig. 6. Bone scan of same patient with increased ^{99m}Tc uptake in right mandible, revealing bony invasion.
Fig. 7. CT scan of same patient showing osteolysis in right premolar region due to tumor invasion of mandible.
Fig. 8. Histologic findings of resected mandible showing deep penetration of tumor cells into bony structures (HE ×10).

ings and tumor localization. Two groups were chosen for the sake of simplicity. The high-risk group consisted of the retromolar area and the alveolar ridge, while the floor of the mouth, the tongue, and the buccal mucosa formed the low-risk group. The first decision was based on the scintigraphic results. For patients with negative bone scanning, the risk of osseous infiltration was low (estimated at 10%). For patients with positive scintigraphy, with a positive predictive value (PPV) of 80%, further branching helped. In tumors of a high-risk area, the PPV increased to 27/29 (93%). For patients with positive bone scanning but with tumors localized in low-risk areas, the prediction was uncertain, as the probability of osseous infiltration was 13/21 (61%). Further diagnostic tests were recommended. If this group of 21 patients had been further divided, improved results could have been obtained. Eighteen of this group had positive or negative CT. Of the nine patients with positive CT, only one had no bone infiltration, whereas this was the case for five of the nine patients with negative CT. All four patients with clinical tumor stage less than IV had no bone infiltration.

Logistic regression

On the basis of the results achieved, a logistic regression model, which allows one to obtain estimated probabilities of bone invasion from several predictive variables, was developed. The best result was found by using the three binary variables:

X_1=1 for patients with positive bone scanning; otherwise, X_1=0

X_2=1 for patients with tumor in a high risk site; otherwise, X_2=0

X_3=for patients with tumor stage IV; otherwise, X_3=0.

Estimated coefficients are presented in Table 2, while Table 3 shows the estimated probabilities for bone infiltration for the eight combinations of the characteristics.

The results suggest the following hypothesis. Positive bone scanning combined with tumor stage IV entails a very high probability of high-risk sites (98.7%) and still a high probability (78%) of low-risk sites. Patients with negative bone scanning have a low risk (4.3%) unless they have tumor stage IV in high-risk areas. For high-risk sites and either tumor stage IV or positive bone scanning (but not both), the outcome remains unclear. Fig. 3 shows the correlation between incidence of bone invasion and its estimated probability.

Discussion

Mandibular invasion is a determining factor for treatment planning, and it also affects the prognosis of the disease. Invasion of the bone by direct extension of an adjacent carcinoma which penetrates the thin mucosal layer of the alveolar ridge is the most common route of mandibular infiltration[18,19]. Brown & Browne[6] emphasize that the attached mucosa is the main potential route of tumor entry because of the lack of periosteum in this area of the mandible. Invasion by involvement of deeper tissues and secondary extension through the periosteum is rare[18]. Early tumor invasion of the mandible generally occurs when the lesion is located close to the buccal sulcus or the mylohyoid crest, thus bringing the tumor into direct proximity to the bone[19]. The bone is invaded in areas of cortical defects created by the fibrous attachment of the mucosa or by reactive inflammation associated with the tumor[6,19,23].

These findings suggest that it is justifiable to adopt a more conservative surgical approach, such as marginal resection, in cases of limited superficial bone involvement, thus avoiding aesthetic problems and reconstructive difficulties in low-risk cases[4,12,27]. However, when evidence of bone-marrow invasion exists, segmental resection has to be carried out[34]. Dubner & Heller[10] did not find differences in the recurrence rate of 130 patients who underwent either segmental or marginal mandibulectomy. They found that most recurrences after marginal mandibulectomy were in the adjacent soft tissues, not in the remaining mandible.

According to our findings, the primary tumor site appears to have a strong correlation with mandibular invasion. Of the five tumor localizations studied, tumors located in the retromolar area and alveolar ridge were found to involve the bone in a significant number of patients (88%). This finding agrees with the results of previous studies[7,13,36]. The strong predilection for bone invasion from tumors located in the retromolar zone/alveolar ridge can be explained by of the fact that early infiltrative growth may easily reach the 2–3 mm of soft tissue overlying the alveolar bone in these cases. As for tumors of the floor of the mouth, the high propensity for early bone invasion which is reported by Bahadur[2] could not be verified. Carcinomas of the floor of the mouth invaded the mandible at a rate of 52% in our group. The propensity for tumors of the buccal mucosa and the tongue to infiltrate the bone could not be determined because of the low numbers in this group.

A statistical assessment of the correlation of primary tumor size with bone infiltration could not be done, due to the low number of patients with T1 and T2. However, the data presented agree with those reported by Weisman & Kimmelman[37], supporting the view that larger tumors pose a greater risk of bone invasion.

The stage of tumor appears (P=0.0003) to be associated with mandibular bone involvement. Although it is reported[2,15,18,21] that only proximity to bone, not tumor size or stage, is the determining factor in mandibular involvement, larger tumors theoretically increase the surface area and therefore, through "fragile" osseous parts (cortical clefts or microvascular bone channels), can more easily erode the bony surface. Confirmation of this assumption would require a randomized, prospective study of a large group of patients with Stage IV SCC.

In this study, differentiation of SCC was found to have no bearing on whether or not bone was invaded. Lund[16] suggests that tumor aggressiveness is related to both invasion and cellular differentiation, whereas the presence of only one of these features is less significant. Brown & Browne[6] reported that tumors with an erosive pattern of infiltration tend to be related to grade I or II, while those with an invasive pattern are often related to grade III. Correlation of the degree of differentiation and infiltration patterns of the tumor has not been confirmed by other authors[2,15].

Bone scanning is sensitive for the detection of occult metastasis in the skeleton. The main radiopharmaceutic agent is technetium-99m dicarboxy-propane diphosphonate (^{99m}Tc-DPD). In SCC, increased bone turnover occurs, resulting in high uptake of ^{99m}Tc, correspond-

ing to the "hot spots" on the bone scan. Metastatic lesions are usually detected by radionuclide bone scan before they are detected by conventional plain radiographs because the chemical changes of a disease process usually occur before anatomic changes. Such chemical changes inducing bone reaction are detectable by radionuclide imaging[22].

The results on the value of BS for the detection of early mandibular invasion agree with the results of other studies[1–5,7,11,13,17,27,37], indicating high sensitivity. However, there were many (52%) false-positive results.

The present study found the predictability and reliability of CT scans in assessment of invasion of the mandible to be unsatisfactory. A false-negative rate of 22% was found, in comparison with an average of 12.5% reported in other studies[2,7,9,29]. Only Brown et al.[7] reported a higher incidence of 28% false-negative results in CT scans. Although CT scans can help to estimate the size of the primary tumor and the nodal status, their value in the detection of early invasion of the mandible seems to be limited. Artifacts, especially in the coronal planes, due to dental restorations, and failure to assess accurately the area of the inner cortex of the mandible due to its irregular shape make it difficult to draw conclusions.

Tumor delineation by MRI was used only in selected cases and mainly for the estimation of soft-tissue invasion. Brown et al.[7] reported a false-negative rate of only 6% for predictability of bone invasion. However, Tsue et al.[36] found MRI scans to be less accurate than CT scans in determining cortex involvement and bone-marrow invasion. These controversial reports indicate the need for further study of this more costly imaging modality in assessing bony invasion.

According to the results of the present study and information from the available literature, bone scanning still seems to be the most sensitive method for detection of early invasion of SCC in the mandible. According to Noyek[22] and Bergstedt et al.[5], virtually no false-positive results should be obtained and a distinction should be possible between cancers that involve the soft tissues and those that erode the mandible by comparing early and delayed uptake. These authors also state that the errors in interpretation of the integrity of the mandible are largely due to failure of careful correlation between clinical findings and areas of abnormal activity on the scan. Although this statement has been disputed by several authors[15,19,37], we believe that, with cautious correlation with the clinical features, at least misinterpretation because of periapical or pericoronal inflammatory disease should be avoidable.

As far as patients who have received radiation are concerned, the assessment of the mandible is particularly difficult, either by preoperative diagnostic imaging or clinically. The increased sensitivity of bone scanning in irradiated patients is due to the mechanism of radionuclide uptake and the primary effect of the irradiation itself. In these patients, decisions regarding segmental as opposed to marginal mandibulectomy should be generally based on the location of the tumor, its extent, and the presence or absence of induration around the mandible[29].

The statistical method of the study addresses the problem of false-positive results by allowing for an intermediate class of unclear cases. By the decision-tree approach, the decision, "no bone invasion", would have been made for 10 patients (17%) with one error (10%); "bone invasion" would have been decided for 29 (48%) with two misclassifications (7%); and for the remaining 21 patients (35%), the decision "unclear" would have been applied. By use of the estimated probabilities of the logistic regression, several decision rules can be derived by setting levels. The estimated probability was below 0.1 for 13 patients (22%). If the remaining 47 patients had been classified positive, the PPV would have been 40/47 (85%). All 22 patients (37%) with estimated probability higher than 0.9 showed positive histologic results (PPV=100%). Twenty-five patients (42%), showing probability of 0.1–0.9, remained "unclear". If the levels had been set to 25% and 75%, only eight (13%) patients would have remained unclassified. While the "no bone invasion" class would have been the same, the class with positive results would have contained 39 patients (65%) with only four false-positive cases.

Predictive values, sensitivities, and specificities of five prediction rules are compared in Fig. 4. As mentioned above, scintigraphy exhibited higher negative predictive value and higher sensitivity than CT. If the estimated probability in the logistic regression were cut anywhere between 0.1 and 0.5, the NPV would be 93%. However, bone scanning with a specificity of only 47% was less specific than CT (78%). If mandibular invasion were diagnosed only for those patients showing positive scintigraphy and a high-risk tumor site, the specificity would rise to 89% and the PPV to 93%. If the decision "further investigation necessary" were not allowed, one would have to assume bony infiltration and the decision tree would then coincide with the scintigraphic criterion. For the logistic regression, the positive predictive value would increase to 85% or 100% if only patients with estimated probability higher than 0.75 or 0.9, respectively, were called positive. The corresponding specificity values would be 79% and 100%.

In conclusion, bone scanning appeared to be the best predictive imaging parameter for bone invasion. When it was combined with specific clinical features, it provided the best prognostic means in most patients (Figs. 5–8). We suggest the selection of an intermediate group of patients in whom it is not clear whether bone infiltration is present and who need further examination. The "rules" derived from our data set of 60 patients may have given unduly promising predictive values. The small number of our patient population, however, should compel further studies to check and refine the procedure.

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Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445
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International Journal of
Oral & Maxillofacial Surgery
ISSN 0901-5027

Oncology

Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas

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N. D. Kalavrezos, K. W. Grätz, H. F. Sailer, W. A. Stahel: Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas. Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445. © Munksgaard, 1996

Abstract. The detection in the mandible of early local spreading of adjacent primary malignancies poses a difficult problem. A survey of 60 patients suspected of carcinomatous mandibular infiltration was undertaken, and the most important clinical and imaging data were studied. Tumor localization and bone scintigraphy proved to offer the most important predictive power. A decision tree and a logistic regression model which determines a score function combining these characteristics were designed. This decision tree improves the sensitivity and specificity of the preoperative assessment and provides the surgeon with an algorithm for the accurate estimation of early mandibular invasion.

Key words: bone scintigraphy; computed tomography; tumor localization; logistic regression; prediction.

Accepted for publication 12 June 1996

Oral malignancies constitute approximately 5% of all malignant neoplasms in the body, and the vast majority of them (91%) are squamous cell carcinomas (SCC)[25,30]. Early bone invasion is of paramount importance when treatment is considered, having also a great impact on the survival rate[26,35]. Inability to detect invasion of the tumor in the bone may lead to inadequate resection, resulting in local recurrence and potential regional or distant metastasis. The incidence of mandibular invasion by SCC depends on the size of the primary tumor and on the proximity of the tumor to the mandible, the incidence ranging from 12% to 56% according to various studies[2,4,13,18,21,24,31,32,36].

Several imaging methods such as conventional radiography, computed tomography (CT), radionuclide scans, and magnetic resonance imaging (MRI) have been used to delineate mandibular infiltration. All of these methods, however, seem to have specific limitations, and the preoperative assessment of possible bone infiltration is still based on clinical inspection combined with the data derived from these imaging methods.

Bone scintigraphy (BS) is generally regarded as one of the most reliable methods of assessment of bone invasion and detection of distant osseous metastasis[11,20]. Despite the high sensitivity of the method in relation to the detection of osseous infiltration, BS is associated with a high incidence of false-positive results due to its unspecificity[13,17,37]. Various studies have reported false-positive and -negative results and discussed the implications.

CT is regarded as a sensitive method of assessing primary SCC (size, location, spread in the soft tissues, and regional lymph-node metastasis). However, its ultimate usefulness in the delineation of invasion of SCC in the mandible remains questionable due to the irregular shape of the mandibular bone and the limitations caused by metal dental artifacts[9,28].

To compare the accuracy of BS and CT scanning, we undertook a study in which both methods were used in sequential order. The results were linked with the clinical assessment and the histopathologic findings. The aim was to develop a protocol allowing precise preoperative assessment of possible invasion of SCC in the mandible.

Material and methods

The records of 60 patients with oral carcinoma suspected of mandibular infiltration, treated surgically in the Cranio-Maxillofacial Surgery Department of the University Hospital of Zurich, Switzerland, between 1988 and 1995, were reviewed. The patient population consisted of 44 (73%) men and 16 (27%) women. The patient age range was 33–83

years; the average age was 60.18 years (59 for men and 64 for women). In 15 patients, preoperative radiotherapy was performed. The radiation was conventionally fractionated with a total dosis of 50–55 Gy. The interim period between radiation and surgery was less than 50 days in each case.

The criteria for inclusion of patients in the study were as follows:

1) primary SCC of the oral cavity adjacent to or near the mandible
2) general medical condition of the patient permitting radical tumor surgery.

The diagnostic presurgical imaging for the assessment of mandibular invasion included conventional plain radiographs, BS, and CT. Whole-body radionuclide bone scanning was performed in all patients, by the protocol of the Nuclear Medicine Department, with application of 500–800 MBq ^{99m}Tc-DPD (dicarboxypropane-diphosphonate), while imaging was done 3 h later (delayed phase) with a high-resolution collimator. The images were always interpreted independently by two observers skilled in nuclear imaging interpretation.

CT data were obtained in 47 patients. CT imaging of the suspected mandible was performed according to the standard procedure of the Neuroradiology Department, including CT scans in two planes (axial and coronal) in contiguous 5-mm slices. In suspected invaded bone areas, additional overlapping cuts of 3 or even of 1.5 mm were performed. Filming was done at both soft-tissue and bone-tissue settings. The mandibular area suspected of tumor invasion was filmed at 4000, rather than 2000, window settings, for better imaging in cases of minimal bone destruction.

Of the 60 patients, 37 underwent segmental and 18 marginal resection; in the remaining five patients, a sagittal resection of the lingual cortex of the mandible was performed. The specimens were demineralized with EDTA and cut in a routine fashion.

The clinical and imaging parameters included the primary tumor localization, staging and grading of the tumor, radionuclide bone-scan evaluation, CT scan data, surgical treatment, and correlation of the diagnostic findings with the histologic results. Tumors were staged according to the guidelines of the TNM system[14]. Tumors with periosteal involvement but intact osseous structures were classified as having no bone infiltration.

The dependence of the histologically determined bone infiltration and each of the preoperative variables were statistically tested by the chi-square test. To study joint effects of several variables for improving their diagnostic value, we devised a decision tree. In the first step, the patient population was split into two groups according to the variable which distinguished best between histologically negative and positive results. The division was stopped when further steps no longer led to improvement, as was the case after two steps. The method[8] was adapted to optimize predictive values and to improve interpretability. A logistic regression model which provides an alternative method for the prediction of bone infiltration on the basis of several preoperative characteristics of the patient was also submitted. A score function in the form of a linear combination of these characteristics was constructed. This function was then converted by the so-called logistic transformation into an estimated probability for any patient suspected of bone infiltration. Statistical calculations were performed by the program S/S-Plus.

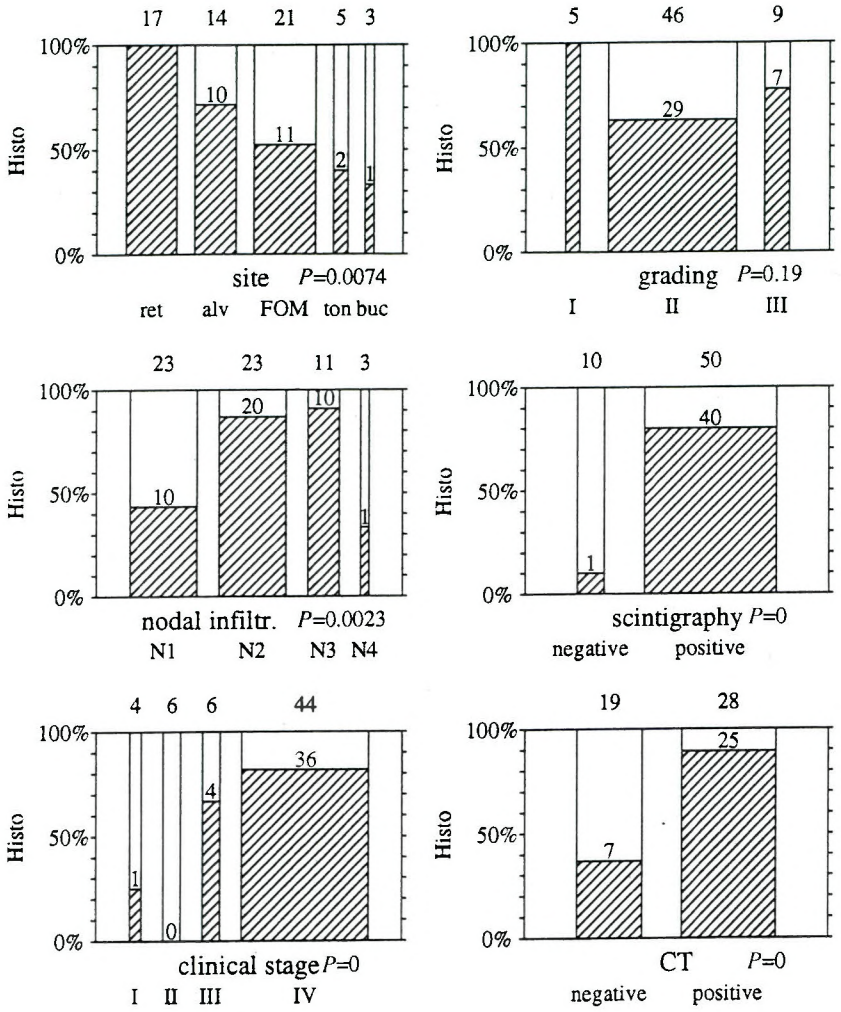


Fig. 1. Correlation between histologically verified bone infiltration and preoperative predictor variables. Shaded areas and numbers above them show number of patients with bone infiltration in each category of predictors. Total numbers are presented at top and are proportional to width of bars. *P* values refer to chi-square test for independence.

Results

Bone involvement was histologically proven in 41 patients (68%), while in 19 patients (32%) the tumor was in proximity to the bone but without infiltration of the cortex.

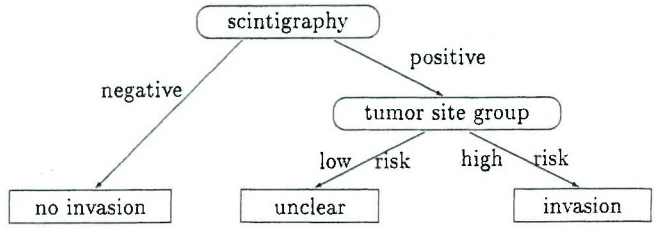


Fig. 2. Decision tree: branching is based statistically on two most important predictive factors – scintigraphy and tumor localization.

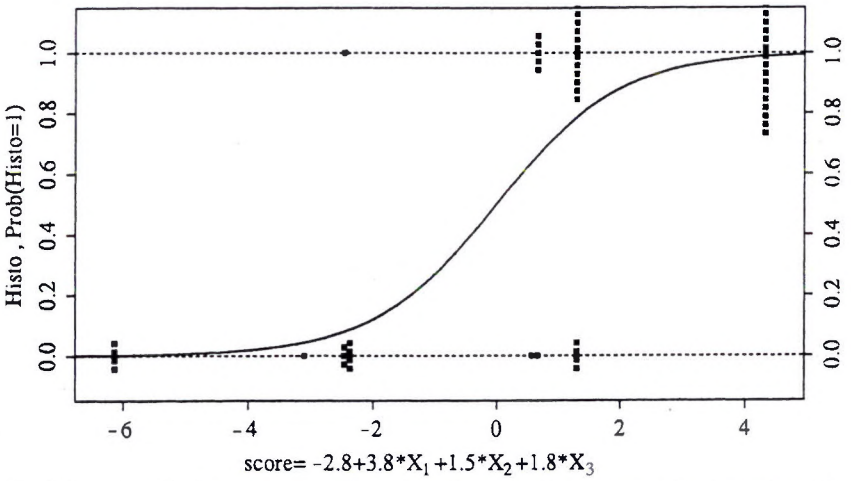


Fig. 3. Results of logistic regression. Dots show linear predictor or score (horizontal axis) for each patient with and without bone invasion (vertical axis). Line shows how this score is transformed into estimated probability of bone invasion based on three predictors, X_1, X_2, and X_3.

Localization

The tumors were localized in five different sites, including the retromolar area, the alveolar ridge, the floor of the mouth, the tongue, and the cheek mucosa. The tumors located in the retromolar area (17 patients, 28%) all showed histologic invasion of tumor in the bone (100%). Tumors of the alveolar process were found in 14 patients (23%). In 10 (71%) of them, bone invasion was histologically present. SCC in the floor of the mouth was present in 21 (35%) patients. In 11 (52%) of them, osseous infiltration was histologically evident. There were only five patients with SCC localized in the tongue, while in three patients, it was in the buccal mucosa. In two patients with tongue SCC and one with involvement of the buccal mucosa, bony invasion was histologically apparent (Fig. 1).

Nodal infiltration

On clinical and CT examination, 23 (38%) of the 60 patients showed no evidence of nodal disease (N0), 23 (38%) patients had N1 positive lymph nodes, 11 (18%) patients were classified as N2, and three (5%) patients were classified as N3. Ten (43%) patients of the first group had histologic evidence of bone involvement; in 20 (87%) of the 23 N1 patients, this was the case. In the N2 category, bone invasion was present in 10 (91%) of the 11 patients, but in only one patient in the N3 group (Fig. 1).

Stage

The relationship between stage of disease and bone invasion is presented in Table 1. It is evident that bony invasion correlated with the higher-stage groups (Fig. 1).

Grading

Differentiation of tumor cells was distributed into three grades[14]: grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated). Only five (8%) of the 60 patients presented with grade I lesions; in all of them (100%), mandibular involvement was confirmed. Of the 46 (77%) patients with grade II lesions, bone infiltration was found in 29 (63%). Of the remaining nine (15%) patients with poorly differentiated SCC, seven (78%) had evident bone infiltration. The results, however, were not statistically significant (Fig. 1).

Bone scintigraphy

Preoperative bone scans were positive in 40 (98%) of the 41 patients (Fig. 1). In only one (2%) patient was the result of bone scanning false-negative; i.e., the mandibular destruction was not detected. Increased radionuclide uptake in the BS was seen in 10 (52%) of the group of the 19 patients without histologically proven mandibular invasion. The results obtained with the univariate analysis verified the diagnostic accuracy and the sensitivity of BS, resulting in a negative predictive value (NPV) of 90% and a positive predictive value (PPV) of 80%, due to the incidence of false-positive findings.

Table 1. Clinical stage according to TNM system

Stage	Criteria	Bone invasion, no. of patients		
		No	Yes	Total
I	T1N0	3	1	4
II	T2N0	6	0	6
III	T2N1, T3N0, T3N1	2	4	6
IV	All T4 Any T with N2 or N3 Any T and N with M1	8	36	44

Table 2. Estimated coefficients for logistic model

	Estimate	Std. error	*P* value
Intercept	−2.788	1.4017	0.047
Scintigraphy	3.762	1.4577	0.010
Site group	1.515	0.6046	0.012
Stage 4	1.833	0.6265	0.003

Table 3. Estimated probabilities of bone invasion calculated from logistic model

Site group	Low risk		High risk	
Tumor stage	1–3	4	1–3	4
Sc. negative	0.2	7.8	4.3	63.7
Sc. positive	8.5	78.5	65.8	98.7

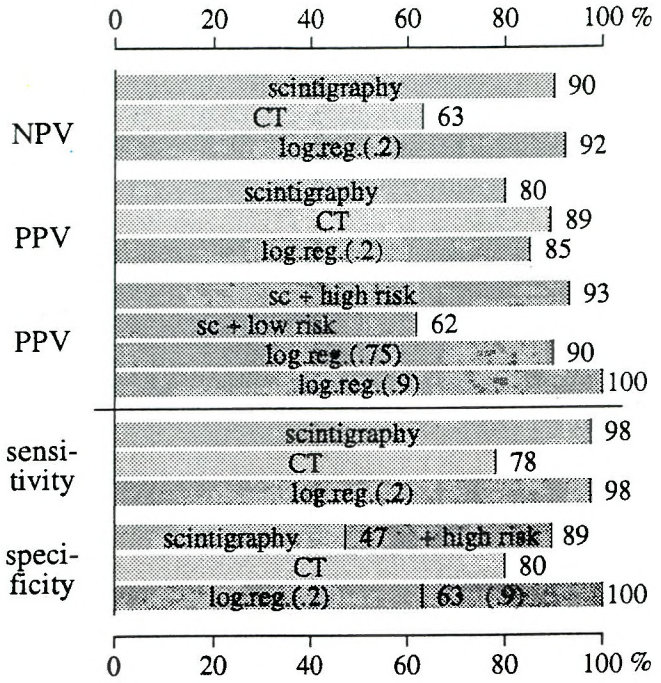


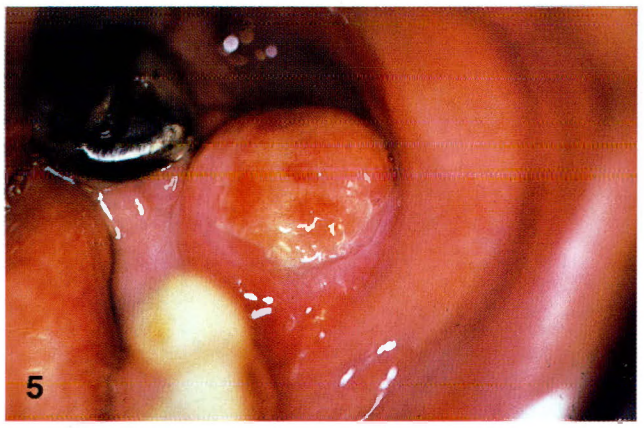
Fig. 4. Predictive values, sensitivities, and specificities for scintigraphy; for CT; for decision tree that permits category of uncertain decision (scintigraphy and low-risk site); and for various rules based on probability of bone invasion estimated by logistic regression.

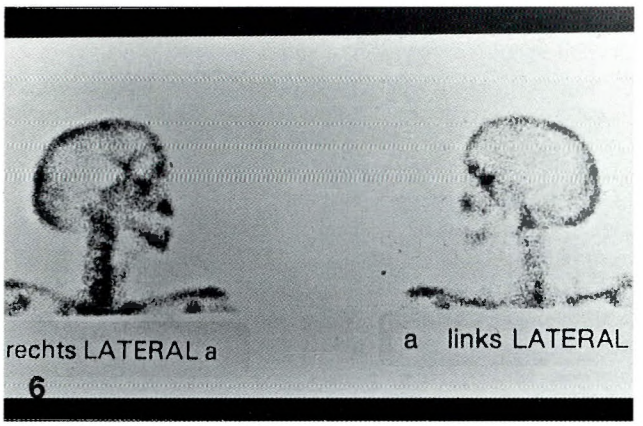
Computed tomography

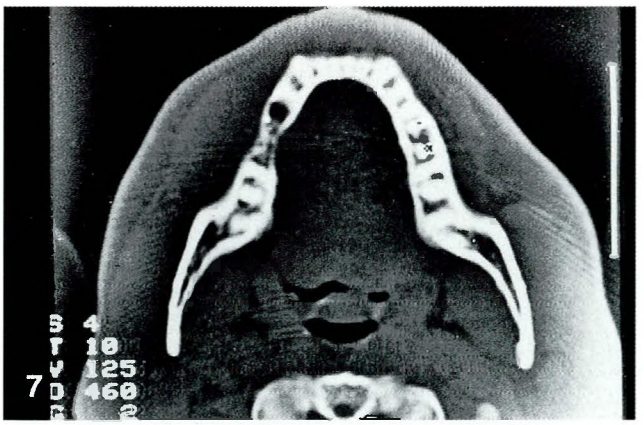
CT data were obtained in 47 patients. The imaging findings corresponded well with the histopathologic results in 37 (62%) patients. In 25 patients, mandibular invasion was properly diagnosed, whereas in 12 who had no histologic evidence of osseous infiltration, the results of CT were negative as well. There were seven (22%) patients in whom CT did not reveal bony erosion while the histology proved to be positive. There were only three patients with false-positive results (Fig. 1).

Decision tree (Fig. 2)

To study the joint effects of the several variables which might enhance their diagnostic value, we devised a decision tree based on the two most statistically predictive criteria, scintigraphic find-







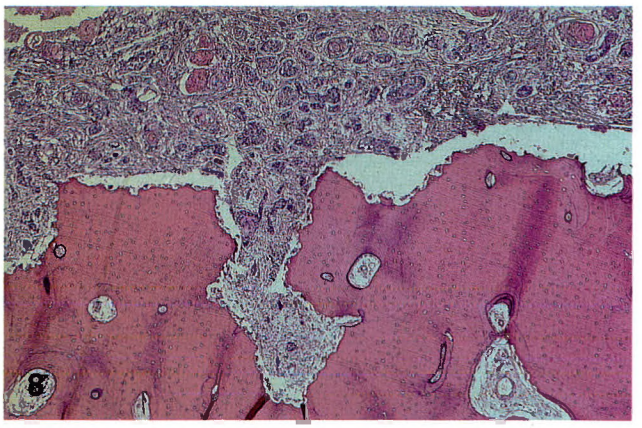


Fig. 5. Clinical view of exophytic SCC adjacent to alveolar crest of mandible.
Fig. 6. Bone scan of same patient with increased ^{99m}Tc uptake in right mandible, revealing bony invasion.
Fig. 7. CT scan of same patient showing osteolysis in right premolar region due to tumor invasion of mandible.
Fig. 8. Histologic findings of resected mandible showing deep penetration of tumor cells into bony structures (HE ×10).

ings and tumor localization. Two groups were chosen for the sake of simplicity. The high-risk group consisted of the retromolar area and the alveolar ridge, while the floor of the mouth, the tongue, and the buccal mucosa formed the low-risk group. The first decision was based on the scintigraphic results. For patients with negative bone scanning, the risk of osseous infiltration was low (estimated at 10%). For patients with positive scintigraphy, with a positive predictive value (PPV) of 80%, further branching helped. In tumors of a high-risk area, the PPV increased to 27/29 (93%). For patients with positive bone scanning but with tumors localized in low-risk areas, the prediction was uncertain, as the probability of osseous infiltration was 13/21 (61%). Further diagnostic tests were recommended. If this group of 21 patients had been further divided, improved results could have been obtained. Eighteen of this group had positive or negative CT. Of the nine patients with positive CT, only one had no bone infiltration, whereas this was the case for five of the nine patients with negative CT. All four patients with clinical tumor stage less than IV had no bone infiltration.

Logistic regression

On the basis of the results achieved, a logistic regression model, which allows one to obtain estimated probabilities of bone invasion from several predictive variables, was developed. The best result was found by using the three binary variables:

X_1=1 for patients with positive bone scanning; otherwise, X_1=0

X_2=1 for patients with tumor in a high risk site; otherwise, X_2=0

X_3=for patients with tumor stage IV; otherwise, X_3=0.

Estimated coefficients are presented in Table 2, while Table 3 shows the estimated probabilities for bone infiltration for the eight combinations of the characteristics.

The results suggest the following hypothesis. Positive bone scanning combined with tumor stage IV entails a very high probability of high-risk sites (98.7%) and still a high probability (78%) of low-risk sites. Patients with negative bone scanning have a low risk (4.3%) unless they have tumor stage IV in high-risk areas. For high-risk sites and either tumor stage IV or positive bone scanning (but not both), the outcome remains unclear. Fig. 3 shows the correlation between incidence of bone invasion and its estimated probability.

Discussion

Mandibular invasion is a determining factor for treatment planning, and it also affects the prognosis of the disease. Invasion of the bone by direct extension of an adjacent carcinoma which penetrates the thin mucosal layer of the alveolar ridge is the most common route of mandibular infiltration[18,19]. Brown & Browne[6] emphasize that the attached mucosa is the main potential route of tumor entry because of the lack of periosteum in this area of the mandible. Invasion by involvement of deeper tissues and secondary extension through the periosteum is rare[18]. Early tumor invasion of the mandible generally occurs when the lesion is located close to the buccal sulcus or the mylohyoid crest, thus bringing the tumor into direct proximity to the bone[19]. The bone is invaded in areas of cortical defects created by the fibrous attachment of the mucosa or by reactive inflammation associated with the tumor[6,19,23].

These findings suggest that it is justifiable to adopt a more conservative surgical approach, such as marginal resection, in cases of limited superficial bone involvement, thus avoiding aesthetic problems and reconstructive difficulties in low-risk cases[4,12,27]. However, when evidence of bone-marrow invasion exists, segmental resection has to be carried out[34]. Dubner & Heller[10] did not find differences in the recurrence rate of 130 patients who underwent either segmental or marginal mandibulectomy. They found that most recurrences after marginal mandibulectomy were in the adjacent soft tissues, not in the remaining mandible.

According to our findings, the primary tumor site appears to have a strong correlation with mandibular invasion. Of the five tumor localizations studied, tumors located in the retromolar area and alveolar ridge were found to involve the bone in a significant number of patients (88%). This finding agrees with the results of previous studies[7,13,36]. The strong predilection for bone invasion from tumors located in the retromolar zone/alveolar ridge can be explained by of the fact that early infiltrative growth may easily reach the 2–3 mm of soft tissue overlying the alveolar bone in these cases. As for tumors of the floor of the mouth, the high propensity for early bone invasion which is reported by Bahadur[2] could not be verified. Carcinomas of the floor of the mouth invaded the mandible at a rate of 52% in our group. The propensity for tumors of the buccal mucosa and the tongue to infiltrate the bone could not be determined because of the low numbers in this group.

A statistical assessment of the correlation of primary tumor size with bone infiltration could not be done, due to the low number of patients with T1 and T2. However, the data presented agree with those reported by Weisman & Kimmelman[37], supporting the view that larger tumors pose a greater risk of bone invasion.

The stage of tumor appears (P=0.0003) to be associated with mandibular bone involvement. Although it is reported[2,15,18,21] that only proximity to bone, not tumor size or stage, is the determining factor in mandibular involvement, larger tumors theoretically increase the surface area and therefore, through "fragile" osseous parts (cortical clefts or microvascular bone channels), can more easily erode the bony surface. Confirmation of this assumption would require a randomized, prospective study of a large group of patients with Stage IV SCC.

In this study, differentiation of SCC was found to have no bearing on whether or not bone was invaded. Lund[16] suggests that tumor aggressiveness is related to both invasion and cellular differentiation, whereas the presence of only one of these features is less significant. Brown & Browne[6] reported that tumors with an erosive pattern of infiltration tend to be related to grade I or II, while those with an invasive pattern are often related to grade III. Correlation of the degree of differentiation and infiltration patterns of the tumor has not been confirmed by other authors[2,15].

Bone scanning is sensitive for the detection of occult metastasis in the skeleton. The main radiopharmaceutic agent is technetium-99m dicarboxy-propane diphosphonate (^{99m}Tc-DPD). In SCC, increased bone turnover occurs, resulting in high uptake of ^{99m}Tc, correspond-

ing to the "hot spots" on the bone scan. Metastatic lesions are usually detected by radionuclide bone scan before they are detected by conventional plain radiographs because the chemical changes of a disease process usually occur before anatomic changes. Such chemical changes inducing bone reaction are detectable by radionuclide imaging[22].

The results on the value of BS for the detection of early mandibular invasion agree with the results of other studies[1–5,7,11,13,17,27,37], indicating high sensitivity. However, there were many (52%) false-positive results.

The present study found the predictability and reliability of CT scans in assessment of invasion of the mandible to be unsatisfactory. A false-negative rate of 22% was found, in comparison with an average of 12.5% reported in other studies[2,7,9,29]. Only Brown et al.[7] reported a higher incidence of 28% false-negative results in CT scans. Although CT scans can help to estimate the size of the primary tumor and the nodal status, their value in the detection of early invasion of the mandible seems to be limited. Artifacts, especially in the coronal planes, due to dental restorations, and failure to assess accurately the area of the inner cortex of the mandible due to its irregular shape make it difficult to draw conclusions.

Tumor delineation by MRI was used only in selected cases and mainly for the estimation of soft-tissue invasion. Brown et al.[7] reported a false-negative rate of only 6% for predictability of bone invasion. However, Tsue et al.[36] found MRI scans to be less accurate than CT scans in determining cortex involvement and bone-marrow invasion. These controversial reports indicate the need for further study of this more costly imaging modality in assessing bony invasion.

According to the results of the present study and information from the available literature, bone scanning still seems to be the most sensitive method for detection of early invasion of SCC in the mandible. According to Noyek[22] and Bergstedt et al.[5], virtually no false-positive results should be obtained and a distinction should be possible between cancers that involve the soft tissues and those that erode the mandible by comparing early and delayed uptake. These authors also state that the errors in interpretation of the integrity of the mandible are largely due to failure of careful correlation between clinical findings and areas of abnormal activity on the scan. Although this statement has been disputed by several authors[15,19,37], we believe that, with cautious correlation with the clinical features, at least misinterpretation because of periapical or pericoronal inflammatory disease should be avoidable.

As far as patients who have received radiation are concerned, the assessment of the mandible is particularly difficult, either by preoperative diagnostic imaging or clinically. The increased sensitivity of bone scanning in irradiated patients is due to the mechanism of radionuclide uptake and the primary effect of the irradiation itself. In these patients, decisions regarding segmental as opposed to marginal mandibulectomy should be generally based on the location of the tumor, its extent, and the presence or absence of induration around the mandible[29].

The statistical method of the study addresses the problem of false-positive results by allowing for an intermediate class of unclear cases. By the decision-tree approach, the decision, "no bone invasion", would have been made for 10 patients (17%) with one error (10%); "bone invasion" would have been decided for 29 (48%) with two misclassifications (7%); and for the remaining 21 patients (35%), the decision "unclear" would have been applied. By use of the estimated probabilities of the logistic regression, several decision rules can be derived by setting levels. The estimated probability was below 0.1 for 13 patients (22%). If the remaining 47 patients had been classified positive, the PPV would have been 40/47 (85%). All 22 patients (37%) with estimated probability higher than 0.9 showed positive histologic results (PPV=100%). Twenty-five patients (42%), showing probability of 0.1–0.9, remained "unclear". If the levels had been set to 25% and 75%, only eight (13%) patients would have remained unclassified. While the "no bone invasion" class would have been the same, the class with positive results would have contained 39 patients (65%) with only four false-positive cases.

Predictive values, sensitivities, and specificities of five prediction rules are compared in Fig. 4. As mentioned above, scintigraphy exhibited higher negative predictive value and higher sensitivity than CT. If the estimated probability in the logistic regression were cut anywhere between 0.1 and 0.5, the NPV would be 93%. However, bone scanning with a specificity of only 47% was less specific than CT (78%). If mandibular invasion were diagnosed only for those patients showing positive scintigraphy and a high-risk tumor site, the specificity would rise to 89% and the PPV to 93%. If the decision "further investigation necessary" were not allowed, one would have to assume bony infiltration and the decision tree would then coincide with the scintigraphic criterion. For the logistic regression, the positive predictive value would increase to 85% or 100% if only patients with estimated probability higher than 0.75 or 0.9, respectively, were called positive. The corresponding specificity values would be 79% and 100%.

In conclusion, bone scanning appeared to be the best predictive imaging parameter for bone invasion. When it was combined with specific clinical features, it provided the best prognostic means in most patients (Figs. 5–8). We suggest the selection of an intermediate group of patients in whom it is not clear whether bone infiltration is present and who need further examination. The "rules" derived from our data set of 60 patients may have given unduly promising predictive values. The small number of our patient population, however, should compel further studies to check and refine the procedure.

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Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445
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International Journal of
Oral & Maxillofacial Surgery
ISSN 0901-5027

Oncology

Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas

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N. D. Kalavrezos, K. W. Grätz, H. F. Sailer, W. A. Stahel: Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas. Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445. © Munksgaard, 1996

Abstract. The detection in the mandible of early local spreading of adjacent primary malignancies poses a difficult problem. A survey of 60 patients suspected of carcinomatous mandibular infiltration was undertaken, and the most important clinical and imaging data were studied. Tumor localization and bone scintigraphy proved to offer the most important predictive power. A decision tree and a logistic regression model which determines a score function combining these characteristics were designed. This decision tree improves the sensitivity and specificity of the preoperative assessment and provides the surgeon with an algorithm for the accurate estimation of early mandibular invasion.

Key words: bone scintigraphy; computed tomography; tumor localization; logistic regression; prediction.

Accepted for publication 12 June 1996

Oral malignancies constitute approximately 5% of all malignant neoplasms in the body, and the vast majority of them (91%) are squamous cell carcinomas (SCC)[25,30]. Early bone invasion is of paramount importance when treatment is considered, having also a great impact on the survival rate[26,35]. Inability to detect invasion of the tumor in the bone may lead to inadequate resection, resulting in local recurrence and potential regional or distant metastasis. The incidence of mandibular invasion by SCC depends on the size of the primary tumor and on the proximity of the tumor to the mandible, the incidence ranging from 12% to 56% according to various studies[2,4,13,18,21,24,31,32,36].

Several imaging methods such as conventional radiography, computed tomography (CT), radionuclide scans, and magnetic resonance imaging (MRI) have been used to delineate mandibular infiltration. All of these methods, however, seem to have specific limitations, and the preoperative assessment of possible bone infiltration is still based on clinical inspection combined with the data derived from these imaging methods.

Bone scintigraphy (BS) is generally regarded as one of the most reliable methods of assessment of bone invasion and detection of distant osseous metastasis[11,20]. Despite the high sensitivity of the method in relation to the detection of osseous infiltration, BS is associated with a high incidence of false-positive results due to its unspecificity[13,17,37]. Various studies have reported false-positive and -negative results and discussed the implications.

CT is regarded as a sensitive method of assessing primary SCC (size, location, spread in the soft tissues, and regional lymph-node metastasis). However, its ultimate usefulness in the delineation of invasion of SCC in the mandible remains questionable due to the irregular shape of the mandibular bone and the limitations caused by metal dental artifacts[9,28].

To compare the accuracy of BS and CT scanning, we undertook a study in which both methods were used in sequential order. The results were linked with the clinical assessment and the histopathologic findings. The aim was to develop a protocol allowing precise preoperative assessment of possible invasion of SCC in the mandible.

Material and methods

The records of 60 patients with oral carcinoma suspected of mandibular infiltration, treated surgically in the Cranio-Maxillofacial Surgery Department of the University Hospital of Zurich, Switzerland, between 1988 and 1995, were reviewed. The patient population consisted of 44 (73%) men and 16 (27%) women. The patient age range was 33–83

years; the average age was 60.18 years (59 for men and 64 for women). In 15 patients, preoperative radiotherapy was performed. The radiation was conventionally fractionated with a total dosis of 50–55 Gy. The interim period between radiation and surgery was less than 50 days in each case.

The criteria for inclusion of patients in the study were as follows:

1) primary SCC of the oral cavity adjacent to or near the mandible
2) general medical condition of the patient permitting radical tumor surgery.

The diagnostic presurgical imaging for the assessment of mandibular invasion included conventional plain radiographs, BS, and CT. Whole-body radionuclide bone scanning was performed in all patients, by the protocol of the Nuclear Medicine Department, with application of 500–800 MBq ^{99m}Tc-DPD (dicarboxypropane-diphosphonate), while imaging was done 3 h later (delayed phase) with a high-resolution collimator. The images were always interpreted independently by two observers skilled in nuclear imaging interpretation.

CT data were obtained in 47 patients. CT imaging of the suspected mandible was performed according to the standard procedure of the Neuroradiology Department, including CT scans in two planes (axial and coronal) in contiguous 5-mm slices. In suspected invaded bone areas, additional overlapping cuts of 3 or even of 1.5 mm were performed. Filming was done at both soft-tissue and bone-tissue settings. The mandibular area suspected of tumor invasion was filmed at 4000, rather than 2000, window settings, for better imaging in cases of minimal bone destruction.

Of the 60 patients, 37 underwent segmental and 18 marginal resection; in the remaining five patients, a sagittal resection of the lingual cortex of the mandible was performed. The specimens were demineralized with EDTA and cut in a routine fashion.

The clinical and imaging parameters included the primary tumor localization, staging and grading of the tumor, radionuclide bone-scan evaluation, CT scan data, surgical treatment, and correlation of the diagnostic findings with the histologic results. Tumors were staged according to the guidelines of the TNM system[14]. Tumors with periosteal involvement but intact osseous structures were classified as having no bone infiltration.

The dependence of the histologically determined bone infiltration and each of the preoperative variables were statistically tested by the chi-square test. To study joint effects of several variables for improving their diagnostic value, we devised a decision tree. In the first step, the patient population was split into two groups according to the variable which distinguished best between histologically negative and positive results. The division was stopped when further steps no longer led to improvement, as was the case after two steps. The method[8] was adapted to optimize predictive values and to improve interpretability. A logistic regression model which provides an alternative method for the prediction of bone infiltration on the basis of several preoperative characteristics of the patient was also submitted. A score function in the form of a linear combination of these characteristics was constructed. This function was then converted by the so-called logistic transformation into an estimated probability for any patient suspected of bone infiltration. Statistical calculations were performed by the program S/S-Plus.

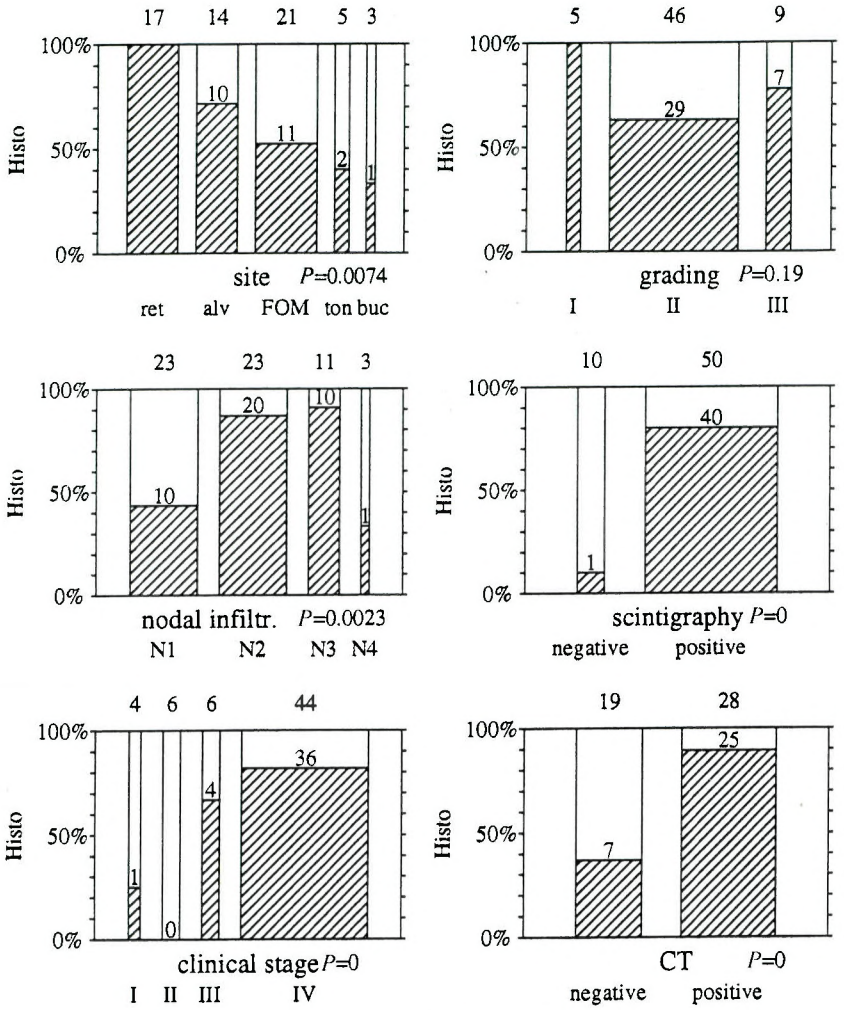


Fig. 1. Correlation between histologically verified bone infiltration and preoperative predictor variables. Shaded areas and numbers above them show number of patients with bone infiltration in each category of predictors. Total numbers are presented at top and are proportional to width of bars. *P* values refer to chi-square test for independence.

Results

Bone involvement was histologically proven in 41 patients (68%), while in 19 patients (32%) the tumor was in proximity to the bone but without infiltration of the cortex.

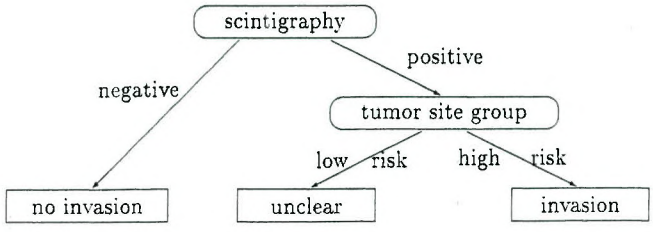


Fig. 2. Decision tree: branching is based statistically on two most important predictive factors – scintigraphy and tumor localization.

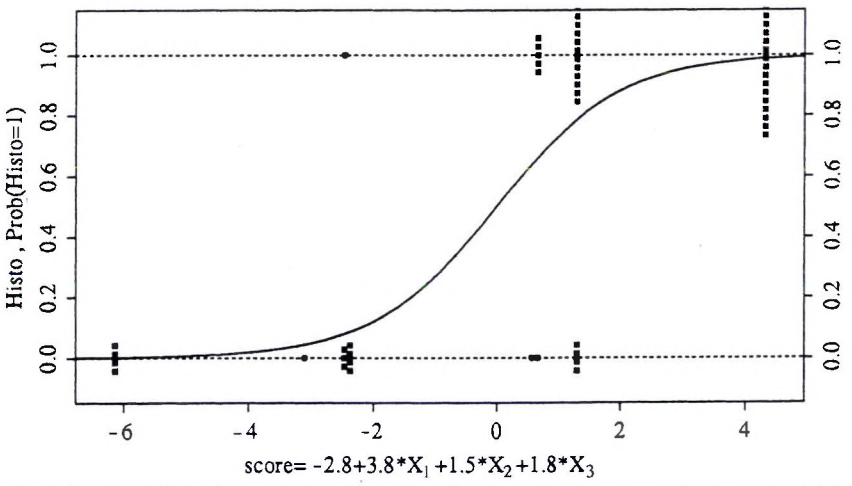


Fig. 3. Results of logistic regression. Dots show linear predictor or score (horizontal axis) for each patient with and without bone invasion (vertical axis). Line shows how this score is transformed into estimated probability of bone invasion based on three predictors, X_1, X_2, and X_3.

Localization

The tumors were localized in five different sites, including the retromolar area, the alveolar ridge, the floor of the mouth, the tongue, and the cheek mucosa. The tumors located in the retromolar area (17 patients, 28%) all showed histologic invasion of tumor in the bone (100%). Tumors of the alveolar process were found in 14 patients (23%). In 10 (71%) of them, bone invasion was histologically present. SCC in the floor of the mouth was present in 21 (35%) patients. In 11 (52%) of them, osseous infiltration was histologically evident. There were only five patients with SCC localized in the tongue, while in three patients, it was in the buccal mucosa. In two patients with tongue SCC and one with involvement of the buccal mucosa, bony invasion was histologically apparent (Fig. 1).

Nodal infiltration

On clinical and CT examination, 23 (38%) of the 60 patients showed no evidence of nodal disease (N0), 23 (38%) patients had N1 positive lymph nodes, 11 (18%) patients were classified as N2, and three (5%) patients were classified as N3. Ten (43%) patients of the first group had histologic evidence of bone involvement; in 20 (87%) of the 23 N1 patients, this was the case. In the N2 category, bone invasion was present in 10 (91%) of the 11 patients, but in only one patient in the N3 group (Fig. 1).

Stage

The relationship between stage of disease and bone invasion is presented in Table 1. It is evident that bony invasion correlated with the higher-stage groups (Fig. 1).

Grading

Differentiation of tumor cells was distributed into three grades[14]: grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated). Only five (8%) of the 60 patients presented with grade I lesions; in all of them (100%), mandibular involvement was confirmed. Of the 46 (77%) patients with grade II lesions, bone infiltration was found in 29 (63%). Of the remaining nine (15%) patients with poorly differentiated SCC, seven (78%) had evident bone infiltration. The results, however, were not statistically significant (Fig. 1).

Bone scintigraphy

Preoperative bone scans were positive in 40 (98%) of the 41 patients (Fig. 1). In only one (2%) patient was the result of bone scanning false-negative; i.e., the mandibular destruction was not detected. Increased radionuclide uptake in the BS was seen in 10 (52%) of the group of the 19 patients without histologically proven mandibular invasion. The results obtained with the univariate analysis verified the diagnostic accuracy and the sensitivity of BS, resulting in a negative predictive value (NPV) of 90% and a positive predictive value (PPV) of 80%, due to the incidence of false-positive findings.

Table 1. Clinical stage according to TNM system

Stage	Criteria	Bone invasion, no. of patients		
		No	Yes	Total
I	T1N0	3	1	4
II	T2N0	6	0	6
III	T2N1, T3N0, T3N1	2	4	6
IV	All T4 Any T with N2 or N3 Any T and N with M1	8	36	44

Table 2. Estimated coefficients for logistic model

	Estimate	Std. error	*P* value
Intercept	−2.788	1.4017	0.047
Scintigraphy	3.762	1.4577	0.010
Site group	1.515	0.6046	0.012
Stage 4	1.833	0.6265	0.003

Table 3. Estimated probabilities of bone invasion calculated from logistic model

Site group	Low risk		High risk	
Tumor stage	1–3	4	1–3	4
Sc. negative	0.2	7.8	4.3	63.7
Sc. positive	8.5	78.5	65.8	98.7

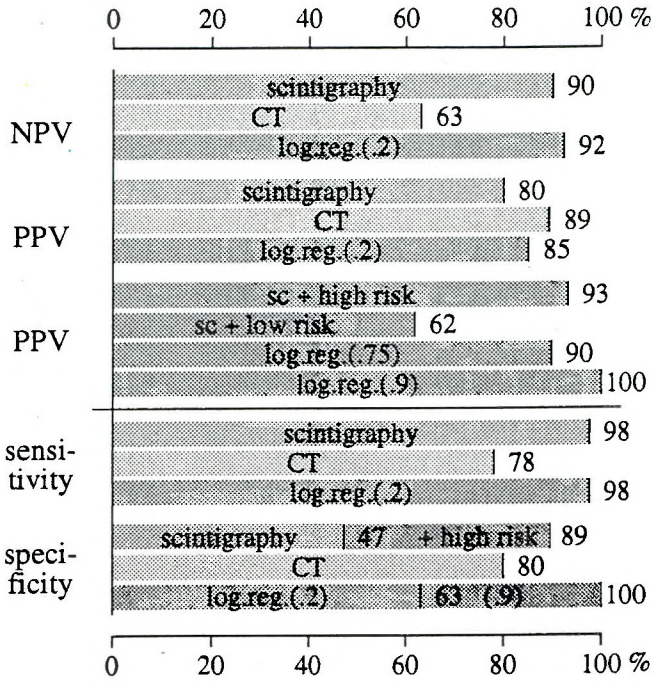


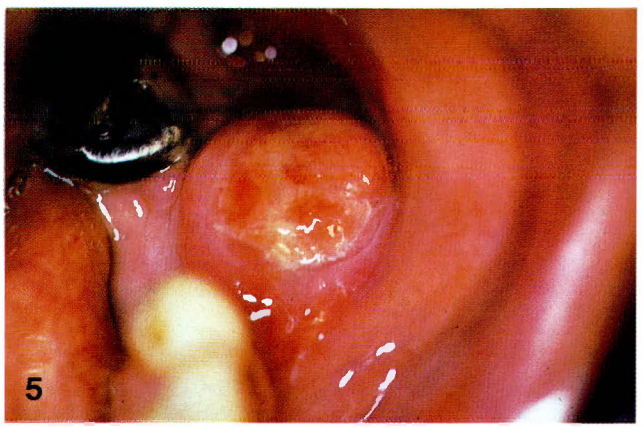
Fig. 4. Predictive values, sensitivities, and specificities for scintigraphy; for CT; for decision tree that permits category of uncertain decision (scintigraphy and low-risk site); and for various rules based on probability of bone invasion estimated by logistic regression.

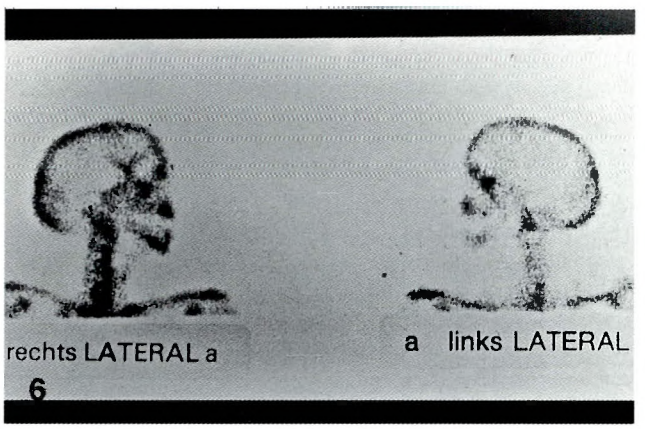
Computed tomography

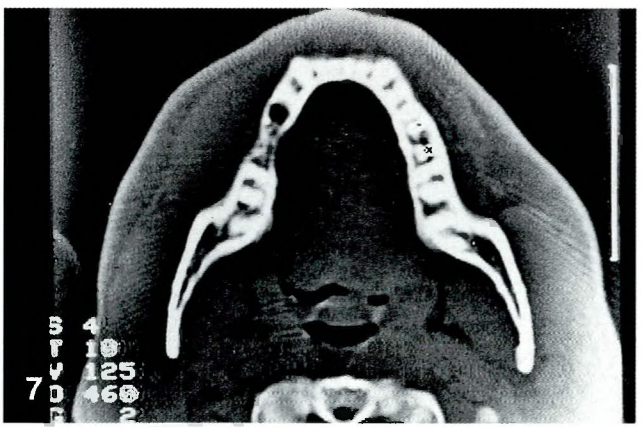
CT data were obtained in 47 patients. The imaging findings corresponded well with the histopathologic results in 37 (62%) patients. In 25 patients, mandibular invasion was properly diagnosed, whereas in 12 who had no histologic evidence of osseous infiltration, the results of CT were negative as well. There were seven (22%) patients in whom CT did not reveal bony erosion while the histology proved to be positive. There were only three patients with false-positive results (Fig. 1).

Decision tree (Fig. 2)

To study the joint effects of the several variables which might enhance their diagnostic value, we devised a decision tree based on the two most statistically predictive criteria, scintigraphic find-







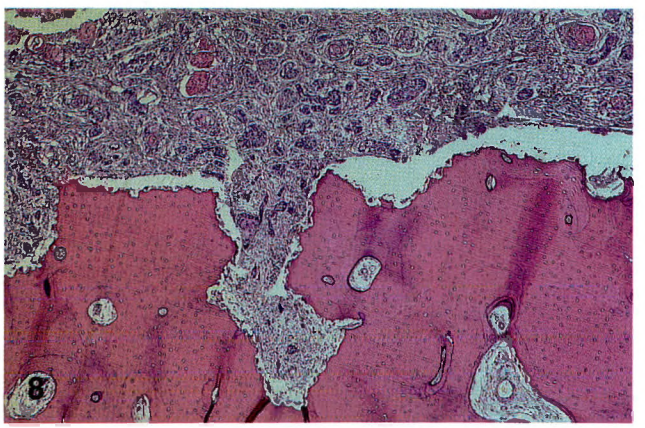


Fig. 5. Clinical view of exophytic SCC adjacent to alveolar crest of mandible.
Fig. 6. Bone scan of same patient with increased ^{99m}Tc uptake in right mandible, revealing bony invasion.
Fig. 7. CT scan of same patient showing osteolysis in right premolar region due to tumor invasion of mandible.
Fig. 8. Histologic findings of resected mandible showing deep penetration of tumor cells into bony structures (HE ×10).

ings and tumor localization. Two groups were chosen for the sake of simplicity. The high-risk group consisted of the retromolar area and the alveolar ridge, while the floor of the mouth, the tongue, and the buccal mucosa formed the low-risk group. The first decision was based on the scintigraphic results. For patients with negative bone scanning, the risk of osseous infiltration was low (estimated at 10%). For patients with positive scintigraphy, with a positive predictive value (PPV) of 80%, further branching helped. In tumors of a high-risk area, the PPV increased to 27/29 (93%). For patients with positive bone scanning but with tumors localized in low-risk areas, the prediction was uncertain, as the probability of osseous infiltration was 13/21 (61%). Further diagnostic tests were recommended. If this group of 21 patients had been further divided, improved results could have been obtained. Eighteen of this group had positive or negative CT. Of the nine patients with positive CT, only one had no bone infiltration, whereas this was the case for five of the nine patients with negative CT. All four patients with clinical tumor stage less than IV had no bone infiltration.

Logistic regression

On the basis of the results achieved, a logistic regression model, which allows one to obtain estimated probabilities of bone invasion from several predictive variables, was developed. The best result was found by using the three binary variables:

X_1=1 for patients with positive bone scanning; otherwise, X_1=0

X_2=1 for patients with tumor in a high risk site; otherwise, X_2=0

X_3=for patients with tumor stage IV; otherwise, X_3=0.

Estimated coefficients are presented in Table 2, while Table 3 shows the estimated probabilities for bone infiltration for the eight combinations of the characteristics.

The results suggest the following hypothesis. Positive bone scanning combined with tumor stage IV entails a very high probability of high-risk sites (98.7%) and still a high probability (78%) of low-risk sites. Patients with negative bone scanning have a low risk (4.3%) unless they have tumor stage IV in high-risk areas. For high-risk sites and either tumor stage IV or positive bone scanning (but not both), the outcome remains unclear. Fig. 3 shows the correlation between incidence of bone invasion and its estimated probability.

Discussion

Mandibular invasion is a determining factor for treatment planning, and it also affects the prognosis of the disease. Invasion of the bone by direct extension of an adjacent carcinoma which penetrates the thin mucosal layer of the alveolar ridge is the most common route of mandibular infiltration[18,19]. Brown & Browne[6] emphasize that the attached mucosa is the main potential route of tumor entry because of the lack of periosteum in this area of the mandible. Invasion by involvement of deeper tissues and secondary extension through the periosteum is rare[18]. Early tumor invasion of the mandible generally occurs when the lesion is located close to the buccal sulcus or the mylohyoid crest, thus bringing the tumor into direct proximity to the bone[19]. The bone is invaded in areas of cortical defects created by the fibrous attachment of the mucosa or by reactive inflammation associated with the tumor[6,19,23].

These findings suggest that it is justifiable to adopt a more conservative surgical approach, such as marginal resection, in cases of limited superficial bone involvement, thus avoiding aesthetic problems and reconstructive difficulties in low-risk cases[4,12,27]. However, when evidence of bone-marrow invasion exists, segmental resection has to be carried out[34]. Dubner & Heller[10] did not find differences in the recurrence rate of 130 patients who underwent either segmental or marginal mandibulectomy. They found that most recurrences after marginal mandibulectomy were in the adjacent soft tissues, not in the remaining mandible.

According to our findings, the primary tumor site appears to have a strong correlation with mandibular invasion. Of the five tumor localizations studied, tumors located in the retromolar area and alveolar ridge were found to involve the bone in a significant number of patients (88%). This finding agrees with the results of previous studies[7,13,36]. The strong predilection for bone invasion from tumors located in the retromolar zone/alveolar ridge can be explained by of the fact that early infiltrative growth may easily reach the 2–3 mm of soft tissue overlying the alveolar bone in these cases. As for tumors of the floor of the mouth, the high propensity for early bone invasion which is reported by Bahadur[2] could not be verified. Carcinomas of the floor of the mouth invaded the mandible at a rate of 52% in our group. The propensity for tumors of the buccal mucosa and the tongue to infiltrate the bone could not be determined because of the low numbers in this group.

A statistical assessment of the correlation of primary tumor size with bone infiltration could not be done, due to the low number of patients with T1 and T2. However, the data presented agree with those reported by Weisman & Kimmelman[37], supporting the view that larger tumors pose a greater risk of bone invasion.

The stage of tumor appears (P=0.0003) to be associated with mandibular bone involvement. Although it is reported[2,15,18,21] that only proximity to bone, not tumor size or stage, is the determining factor in mandibular involvement, larger tumors theoretically increase the surface area and therefore, through "fragile" osseous parts (cortical clefts or microvascular bone channels), can more easily erode the bony surface. Confirmation of this assumption would require a randomized, prospective study of a large group of patients with Stage IV SCC.

In this study, differentiation of SCC was found to have no bearing on whether or not bone was invaded. Lund[16] suggests that tumor aggressiveness is related to both invasion and cellular differentiation, whereas the presence of only one of these features is less significant. Brown & Browne[6] reported that tumors with an erosive pattern of infiltration tend to be related to grade I or II, while those with an invasive pattern are often related to grade III. Correlation of the degree of differentiation and infiltration patterns of the tumor has not been confirmed by other authors[2,15].

Bone scanning is sensitive for the detection of occult metastasis in the skeleton. The main radiopharmaceutic agent is technetium-99m dicarboxy-propane diphosphonate (^{99m}Tc-DPD). In SCC, increased bone turnover occurs, resulting in high uptake of ^{99m}Tc, correspond-

ing to the "hot spots" on the bone scan. Metastatic lesions are usually detected by radionuclide bone scan before they are detected by conventional plain radiographs because the chemical changes of a disease process usually occur before anatomic changes. Such chemical changes inducing bone reaction are detectable by radionuclide imaging[22].

The results on the value of BS for the detection of early mandibular invasion agree with the results of other studies[1–5,7,11,13,17,27,37], indicating high sensitivity. However, there were many (52%) false-positive results.

The present study found the predictability and reliability of CT scans in assessment of invasion of the mandible to be unsatisfactory. A false-negative rate of 22% was found, in comparison with an average of 12.5% reported in other studies[2,7,9,29]. Only Brown et al.[7] reported a higher incidence of 28% false-negative results in CT scans. Although CT scans can help to estimate the size of the primary tumor and the nodal status, their value in the detection of early invasion of the mandible seems to be limited. Artifacts, especially in the coronal planes, due to dental restorations, and failure to assess accurately the area of the inner cortex of the mandible due to its irregular shape make it difficult to draw conclusions.

Tumor delineation by MRI was used only in selected cases and mainly for the estimation of soft-tissue invasion. Brown et al.[7] reported a false-negative rate of only 6% for predictability of bone invasion. However, Tsue et al.[36] found MRI scans to be less accurate than CT scans in determining cortex involvement and bone-marrow invasion. These controversial reports indicate the need for further study of this more costly imaging modality in assessing bony invasion.

According to the results of the present study and information from the available literature, bone scanning still seems to be the most sensitive method for detection of early invasion of SCC in the mandible. According to Noyek[22] and Bergstedt et al.[5], virtually no false-positive results should be obtained and a distinction should be possible between cancers that involve the soft tissues and those that erode the mandible by comparing early and delayed uptake. These authors also state that the errors in interpretation of the integrity of the mandible are largely due to failure of careful correlation between clinical findings and areas of abnormal activity on the scan. Although this statement has been disputed by several authors[15,19,37], we believe that, with cautious correlation with the clinical features, at least misinterpretation because of periapical or pericoronal inflammatory disease should be avoidable.

As far as patients who have received radiation are concerned, the assessment of the mandible is particularly difficult, either by preoperative diagnostic imaging or clinically. The increased sensitivity of bone scanning in irradiated patients is due to the mechanism of radionuclide uptake and the primary effect of the irradiation itself. In these patients, decisions regarding segmental as opposed to marginal mandibulectomy should be generally based on the location of the tumor, its extent, and the presence or absence of induration around the mandible[29].

The statistical method of the study addresses the problem of false-positive results by allowing for an intermediate class of unclear cases. By the decision-tree approach, the decision, "no bone invasion", would have been made for 10 patients (17%) with one error (10%); "bone invasion" would have been decided for 29 (48%) with two misclassifications (7%); and for the remaining 21 patients (35%), the decision "unclear" would have been applied. By use of the estimated probabilities of the logistic regression, several decision rules can be derived by setting levels. The estimated probability was below 0.1 for 13 patients (22%). If the remaining 47 patients had been classified positive, the PPV would have been 40/47 (85%). All 22 patients (37%) with estimated probability higher than 0.9 showed positive histologic results (PPV=100%). Twenty-five patients (42%), showing probability of 0.1–0.9, remained "unclear". If the levels had been set to 25% and 75%, only eight (13%) patients would have remained unclassified. While the "no bone invasion" class would have been the same, the class with positive results would have contained 39 patients (65%) with only four false-positive cases.

Predictive values, sensitivities, and specificities of five prediction rules are compared in Fig. 4. As mentioned above, scintigraphy exhibited higher negative predictive value and higher sensitivity than CT. If the estimated probability in the logistic regression were cut anywhere between 0.1 and 0.5, the NPV would be 93%. However, bone scanning with a specificity of only 47% was less specific than CT (78%). If mandibular invasion were diagnosed only for those patients showing positive scintigraphy and a high-risk tumor site, the specificity would rise to 89% and the PPV to 93%. If the decision "further investigation necessary" were not allowed, one would have to assume bony infiltration and the decision tree would then coincide with the scintigraphic criterion. For the logistic regression, the positive predictive value would increase to 85% or 100% if only patients with estimated probability higher than 0.75 or 0.9, respectively, were called positive. The corresponding specificity values would be 79% and 100%.

In conclusion, bone scanning appeared to be the best predictive imaging parameter for bone invasion. When it was combined with specific clinical features, it provided the best prognostic means in most patients (Figs. 5–8). We suggest the selection of an intermediate group of patients in whom it is not clear whether bone infiltration is present and who need further examination. The "rules" derived from our data set of 60 patients may have given unduly promising predictive values. The small number of our patient population, however, should compel further studies to check and refine the procedure.

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Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445
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International Journal of
Oral & Maxillofacial Surgery
ISSN 0901-5027

Oncology

Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas

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N. D. Kalavrezos, K. W. Grätz, H. F. Sailer, W. A. Stahel: Correlation of imaging and clinical features in the assessment of mandibular invasion of oral carcinomas. Int. J. Oral Maxillofac. Surg. 1996; 25: 439–445. © Munksgaard, 1996

Abstract. The detection in the mandible of early local spreading of adjacent primary malignancies poses a difficult problem. A survey of 60 patients suspected of carcinomatous mandibular infiltration was undertaken, and the most important clinical and imaging data were studied. Tumor localization and bone scintigraphy proved to offer the most important predictive power. A decision tree and a logistic regression model which determines a score function combining these characteristics were designed. This decision tree improves the sensitivity and specificity of the preoperative assessment and provides the surgeon with an algorithm for the accurate estimation of early mandibular invasion.

Key words: bone scintigraphy; computed tomography; tumor localization; logistic regression; prediction.

Accepted for publication 12 June 1996

Oral malignancies constitute approximately 5% of all malignant neoplasms in the body, and the vast majority of them (91%) are squamous cell carcinomas (SCC)[25,30]. Early bone invasion is of paramount importance when treatment is considered, having also a great impact on the survival rate[26,35]. Inability to detect invasion of the tumor in the bone may lead to inadequate resection, resulting in local recurrence and potential regional or distant metastasis. The incidence of mandibular invasion by SCC depends on the size of the primary tumor and on the proximity of the tumor to the mandible, the incidence ranging from 12% to 56% according to various studies[2,4,13,18,21,24,31,32,36].

Several imaging methods such as conventional radiography, computed tomography (CT), radionuclide scans, and magnetic resonance imaging (MRI) have been used to delineate mandibular infiltration. All of these methods, however, seem to have specific limitations, and the preoperative assessment of possible bone infiltration is still based on clinical inspection combined with the data derived from these imaging methods.

Bone scintigraphy (BS) is generally regarded as one of the most reliable methods of assessment of bone invasion and detection of distant osseous metastasis[11,20]. Despite the high sensitivity of the method in relation to the detection of osseous infiltration, BS is associated with a high incidence of false-positive results due to its unspecificity[13,17,37]. Various studies have reported false-positive and -negative results and discussed the implications.

CT is regarded as a sensitive method of assessing primary SCC (size, location, spread in the soft tissues, and regional lymph-node metastasis). However, its ultimate usefulness in the delineation of invasion of SCC in the mandible remains questionable due to the irregular shape of the mandibular bone and the limitations caused by metal dental artifacts[9,28].

To compare the accuracy of BS and CT scanning, we undertook a study in which both methods were used in sequential order. The results were linked with the clinical assessment and the histopathologic findings. The aim was to develop a protocol allowing precise preoperative assessment of possible invasion of SCC in the mandible.

Material and methods

The records of 60 patients with oral carcinoma suspected of mandibular infiltration, treated surgically in the Cranio-Maxillofacial Surgery Department of the University Hospital of Zurich, Switzerland, between 1988 and 1995, were reviewed. The patient population consisted of 44 (73%) men and 16 (27%) women. The patient age range was 33–83

years; the average age was 60.18 years (59 for men and 64 for women). In 15 patients, preoperative radiotherapy was performed. The radiation was conventionally fractionated with a total dosis of 50–55 Gy. The interim period between radiation and surgery was less than 50 days in each case.

The criteria for inclusion of patients in the study were as follows:

1) primary SCC of the oral cavity adjacent to or near the mandible
2) general medical condition of the patient permitting radical tumor surgery.

The diagnostic presurgical imaging for the assessment of mandibular invasion included conventional plain radiographs, BS, and CT. Whole-body radionuclide bone scanning was performed in all patients, by the protocol of the Nuclear Medicine Department, with application of 500–800 MBq ^{99m}Tc-DPD (dicarboxypropane-diphosphonate), while imaging was done 3 h later (delayed phase) with a high-resolution collimator. The images were always interpreted independently by two observers skilled in nuclear imaging interpretation.

CT data were obtained in 47 patients. CT imaging of the suspected mandible was performed according to the standard procedure of the Neuroradiology Department, including CT scans in two planes (axial and coronal) in contiguous 5-mm slices. In suspected invaded bone areas, additional overlapping cuts of 3 or even of 1.5 mm were performed. Filming was done at both soft-tissue and bone-tissue settings. The mandibular area suspected of tumor invasion was filmed at 4000, rather than 2000, window settings, for better imaging in cases of minimal bone destruction.

Of the 60 patients, 37 underwent segmental and 18 marginal resection; in the remaining five patients, a sagittal resection of the lingual cortex of the mandible was performed. The specimens were demineralized with EDTA and cut in a routine fashion.

The clinical and imaging parameters included the primary tumor localization, staging and grading of the tumor, radionuclide bone-scan evaluation, CT scan data, surgical treatment, and correlation of the diagnostic findings with the histologic results. Tumors were staged according to the guidelines of the TNM system[14]. Tumors with periosteal involvement but intact osseous structures were classified as having no bone infiltration.

The dependence of the histologically determined bone infiltration and each of the preoperative variables were statistically tested by the chi-square test. To study joint effects of several variables for improving their diagnostic value, we devised a decision tree. In the first step, the patient population was split into two groups according to the variable which distinguished best between histologically negative and positive results. The division was stopped when further steps no longer led to improvement, as was the case after two steps. The method[8] was adapted to optimize

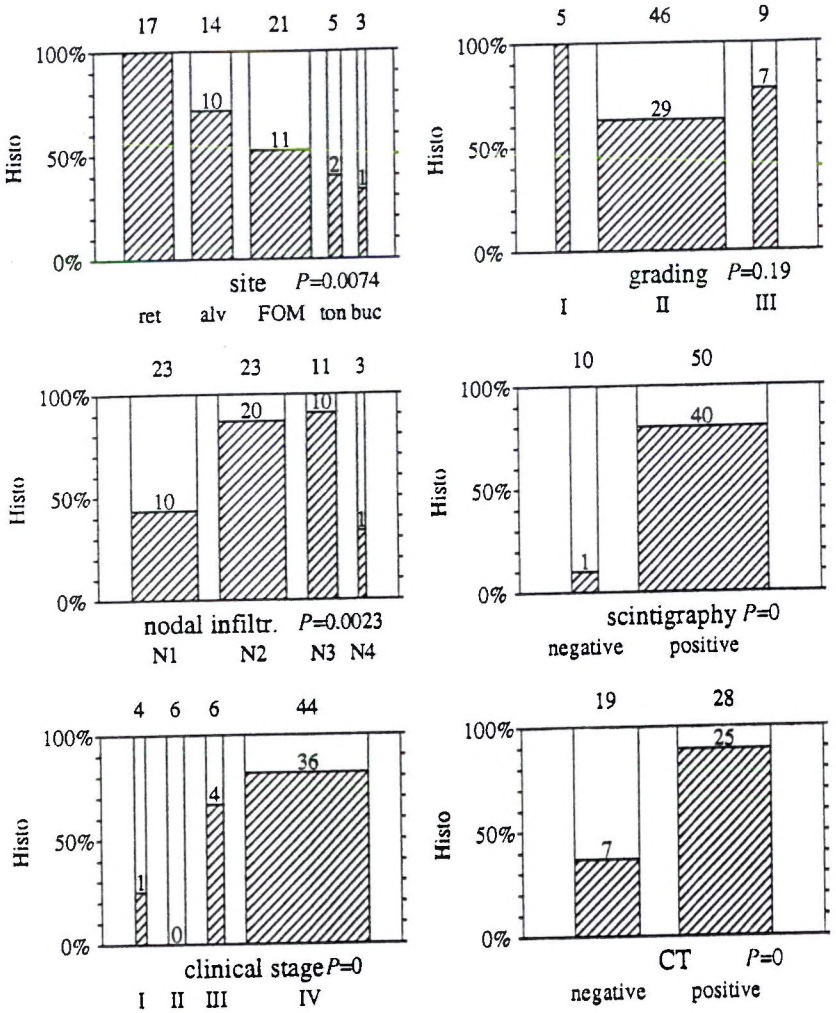


Fig. 1. Correlation between histologically verified bone infiltration and preoperative predictor variables. Shaded areas and numbers above them show number of patients with bone infiltration in each category of predictors. Total numbers are presented at top and are proportional to width of bars. *P* values refer to chi-square test for independence.

predictive values and to improve interpretability. A logistic regression model which provides an alternative method for the prediction of bone infiltration on the basis of several preoperative characteristics of the patient was also submitted. A score function in the form of a linear combination of these characteristics was constructed. This function was then converted by the so-called logistic transformation into an estimated probability for any patient suspected of bone infiltration. Statistical calculations were performed by the program S/S-Plus.

Results

Bone involvement was histologically proven in 41 patients (68%), while in 19 patients (32%) the tumor was in proximity to the bone but without infiltration of the cortex.

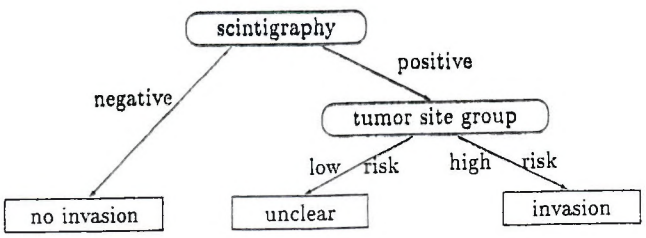


Fig. 2. Decision tree: branching is based statistically on two most important predictive factors – scintigraphy and tumor localization.

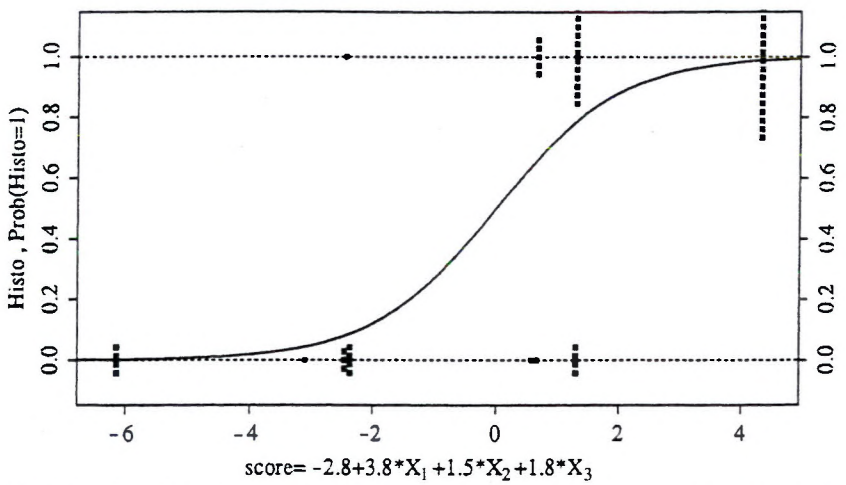


Fig. 3. Results of logistic regression. Dots show linear predictor or score (horizontal axis) for each patient with and without bone invasion (vertical axis). Line shows how this score is transformed into estimated probability of bone invasion based on three predictors, X_1, X_2, and X_3.

Localization

The tumors were localized in five different sites, including the retromolar area, the alveolar ridge, the floor of the mouth, the tongue, and the cheek mucosa. The tumors located in the retromolar area (17 patients, 28%) all showed histologic invasion of tumor in the bone (100%). Tumors of the alveolar process were found in 14 patients (23%). In 10 (71%) of them, bone invasion was histologically present. SCC in the floor of the mouth was present in 21 (35%) patients. In 11 (52%) of them, osseous infiltration was histologically evident. There were only five patients with SCC localized in the tongue, while in three patients, it was in the buccal mucosa. In two patients with tongue SCC and one with involvement of the buccal mucosa, bony invasion was histologically apparent (Fig. 1).

Nodal infiltration

On clinical and CT examination, 23 (38%) of the 60 patients showed no evidence of nodal disease (N0), 23 (38%) patients had N1 positive lymph nodes, 11 (18%) patients were classified as N2, and three (5%) patients were classified as N3. Ten (43%) patients of the first group had histologic evidence of bone involvement; in 20 (87%) of the 23 N1 patients, this was the case. In the N2 category, bone invasion was present in 10 (91%) of the 11 patients, but in only one patient in the N3 group (Fig. 1).

Stage

The relationship between stage of disease and bone invasion is presented in Table 1. It is evident that bony invasion correlated with the higher-stage groups (Fig. 1).

Grading

Differentiation of tumor cells was distributed into three grades[14]: grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated). Only five (8%) of the 60 patients presented with grade I lesions; in all of them (100%), mandibular involvement was confirmed. Of the 46 (77%) patients with grade II lesions, bone infiltration was found in 29 (63%). Of the remaining nine (15%) patients with poorly differentiated SCC, seven (78%) had evident bone infiltration. The results, however, were not statistically significant (Fig. 1).

Bone scintigraphy

Preoperative bone scans were positive in 40 (98%) of the 41 patients (Fig. 1). In only one (2%) patient was the result of bone scanning false-negative; i.e., the mandibular destruction was not detected. Increased radionuclide uptake in the BS was seen in 10 (52%) of the group of the 19 patients without histologically proven mandibular invasion. The results obtained with the univariate analysis verified the diagnostic accuracy and the sensitivity of BS, resulting in a negative predictive value (NPV) of 90% and a positive predictive value (PPV) of 80%, due to the incidence of false-positive findings.

Table 1. Clinical stage according to TNM system

Stage	Criteria	Bone invasion, no. of patients		
		No	Yes	Total
I	T1N0	3	1	4
II	T2N0	6	0	6
III	T2N1, T3N0, T3N1	2	4	6
IV	All T4 Any T with N2 or N3 Any T and N with M1	8	36	44

Table 2. Estimated coefficients for logistic model

	Estimate	Std. error	*P* value
Intercept	−2.788	1.4017	0.047
Scintigraphy	3.762	1.4577	0.010
Site group	1.515	0.6046	0.012
Stage 4	1.833	0.6265	0.003

Table 3. Estimated probabilities of bone invasion calculated from logistic model

Site group	Low risk		High risk	
Tumor stage	1–3	4	1–3	4
Sc. negative	0.2	7.8	4.3	63.7
Sc. positive	8.5	78.5	65.8	98.7

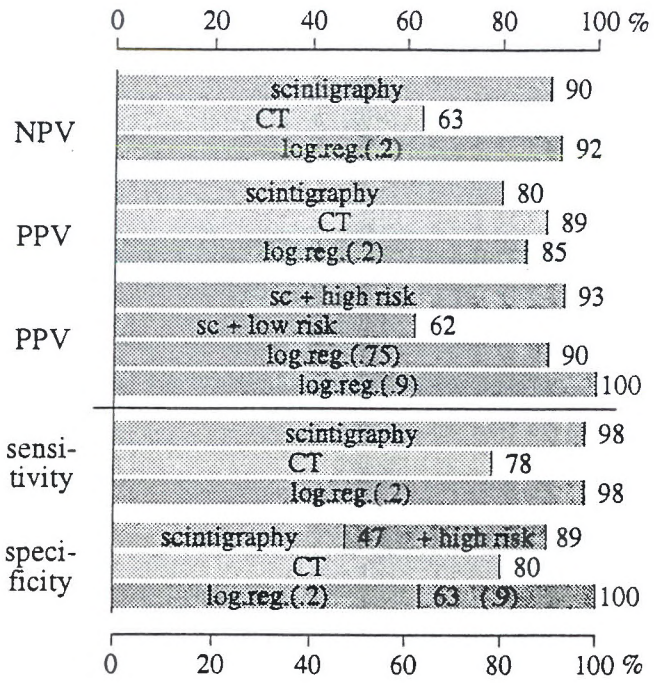


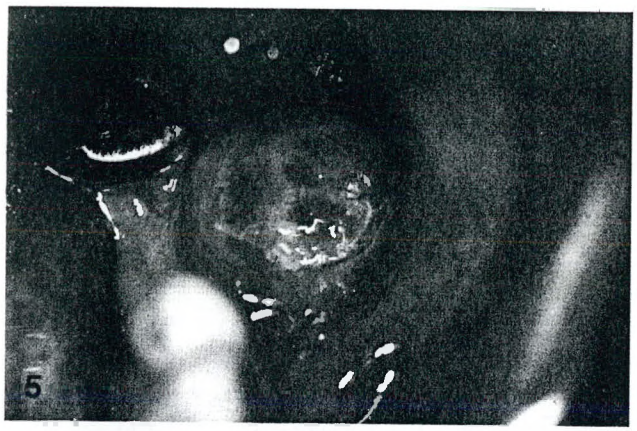
Fig. 4. Predictive values, sensitivities, and specificities for scintigraphy; for CT; for decision tree that permits category of uncertain decision (scintigraphy and low-risk site); and for various rules based on probability of bone invasion estimated by logistic regression.

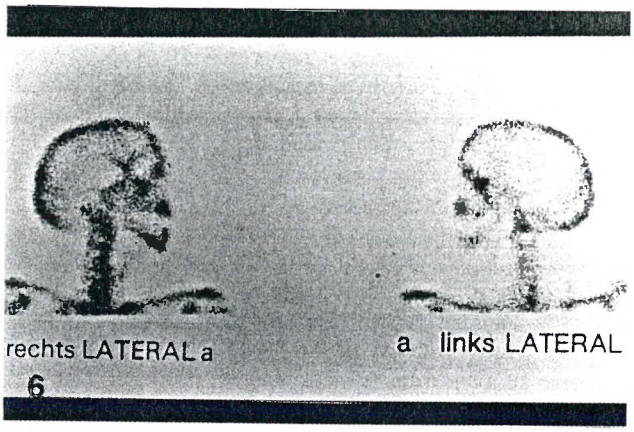
Computed tomography

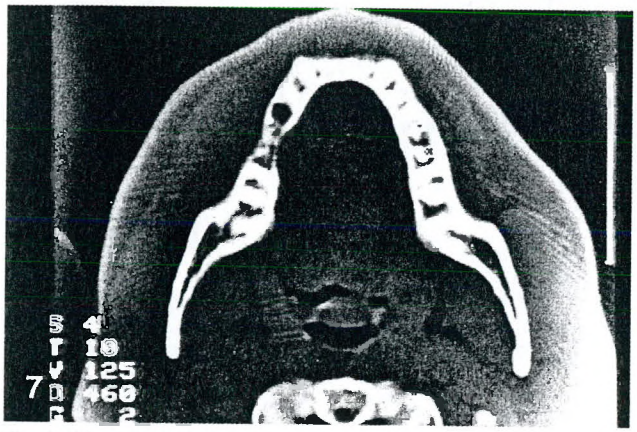
CT data were obtained in 47 patients. The imaging findings corresponded well with the histopathologic results in 37 (62%) patients. In 25 patients, mandibular invasion was properly diagnosed, whereas in 12 who had no histologic evidence of osseous infiltration, the results of CT were negative as well. There were seven (22%) patients in whom CT did not reveal bony erosion while the histology proved to be positive. There were only three patients with false-positive results (Fig. 1).

Decision tree (Fig. 2)

To study the joint effects of the several variables which might enhance their diagnostic value, we devised a decision tree based on the two most statistically predictive criteria, scintigraphic find-







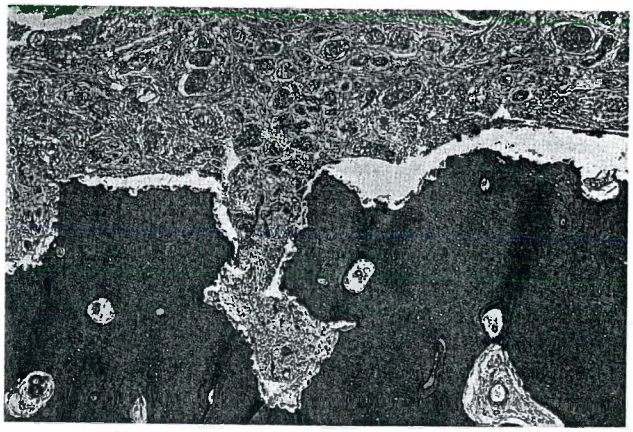


Fig. 5. Clinical view of exophytic SCC adjacent to alveolar crest of mandible.
Fig. 6. Bone scan of same patient with increased ^{99m}Tc uptake in right mandible, revealing bony invasion.
Fig. 7. CT scan of same patient showing osteolysis in right premolar region due to tumor invasion of mandible.
Fig. 8. Histologic findings of resected mandible showing deep penetration of tumor cells into bony structures (HE ×10).

ings and tumor localization. Two groups were chosen for the sake of simplicity. The high-risk group consisted of the retromolar area and the alveolar ridge, while the floor of the mouth, the tongue, and the buccal mucosa formed the low-risk group. The first decision was based on the scintigraphic results. For patients with negative bone scanning, the risk of osseous infiltration was low (estimated at 10%). For patients with positive scintigraphy, with a positive predictive value (PPV) of 80%, further branching helped. In tumors of a high-risk area, the PPV increased to 27/29 (93%). For patients with positive bone scanning but with tumors localized in low-risk areas, the prediction was uncertain, as the probability of osseous infiltration was 13/21 (61%). Further diagnostic tests were recommended. If this group of 21 patients had been further divided, improved results could have been obtained. Eighteen of this group had positive or negative CT. Of the nine patients with positive CT, only one had no bone infiltration, whereas this was the case for five of the nine patients with negative CT. All four patients with clinical tumor stage less than IV had no bone infiltration.

Logistic regression

On the basis of the results achieved, a logistic regression model, which allows one to obtain estimated probabilities of bone invasion from several predictive variables, was developed. The best result was found by using the three binary variables:

X_1=1 for patients with positive bone scanning; otherwise, X_1=0

X_2=1 for patients with tumor in a high risk site; otherwise, X_2=0

X_3=for patients with tumor stage IV; otherwise, X_3=0.

Estimated coefficients are presented in Table 2, while Table 3 shows the estimated probabilities for bone infiltration for the eight combinations of the characteristics.

The results suggest the following hypothesis. Positive bone scanning combined with tumor stage IV entails a very high probability of high-risk sites (98.7%) and still a high probability (78%) of low-risk sites. Patients with negative bone scanning have a low risk (4.3%) unless they have tumor stage IV in high-risk areas. For high-risk sites and either tumor stage IV or positive bone scanning (but not both), the outcome remains unclear. Fig. 3 shows the correlation between incidence of bone invasion and its estimated probability.

Discussion

Mandibular invasion is a determining factor for treatment planning, and it also affects the prognosis of the disease. Invasion of the bone by direct extension of an adjacent carcinoma which penetrates the thin mucosal layer of the alveolar ridge is the most common route of mandibular infiltration[18,19]. Brown & Browne[6] emphasize that the attached mucosa is the main potential route of tumor entry because of the lack of periosteum in this area of the mandible. Invasion by involvement of deeper tissues and secondary extension through the periosteum is rare[18]. Early tumor invasion of the mandible generally occurs when the lesion is located close to the buccal sulcus or the mylohyoid crest, thus bringing the tumor into direct proximity to the bone[19]. The bone is invaded in areas of cortical defects created by the fibrous attachment of the mucosa or by reactive inflammation associated with the tumor[6,19,23].

These findings suggest that it is justifiable to adopt a more conservative surgical approach, such as marginal resection, in cases of limited superficial bone involvement, thus avoiding aesthetic problems and reconstructive difficulties in low-risk cases[4,12,27]. However, when evidence of bone-marrow invasion exists, segmental resection has to be carried out[34]. Dubner & Heller[10] did not find differences in the recurrence rate of 130 patients who underwent either segmental or marginal mandibulectomy. They found that most recurrences after marginal mandibulectomy were in the adjacent soft tissues, not in the remaining mandible.

According to our findings, the primary tumor site appears to have a strong correlation with mandibular invasion. Of the five tumor localizations studied, tumors located in the retromolar area and alveolar ridge were found to involve the bone in a significant number of patients (88%). This finding agrees with the results of previous studies[7,13,36]. The strong predilection for bone invasion from tumors located in the retromolar zone/alveolar ridge can be explained by of the fact that early infiltrative growth may easily reach the 2–3 mm of soft tissue overlying the alveolar bone in these cases. As for tumors of the floor of the mouth, the high propensity for early bone invasion which is reported by Bahadur[2] could not be verified. Carcinomas of the floor of the mouth invaded the mandible at a rate of 52% in our group. The propensity for tumors of the buccal mucosa and the tongue to infiltrate the bone could not be determined because of the low numbers in this group.

A statistical assessment of the correlation of primary tumor size with bone infiltration could not be done, due to the low number of patients with T1 and T2. However, the data presented agree with those reported by Weisman & Kimmelman[37], supporting the view that larger tumors pose a greater risk of bone invasion.

The stage of tumor appears (P=0.0003) to be associated with mandibular bone involvement. Although it is reported[2,15,18,21] that only proximity to bone, not tumor size or stage, is the determining factor in mandibular involvement, larger tumors theoretically increase the surface area and therefore, through "fragile" osseous parts (cortical clefts or microvascular bone channels), can more easily erode the bony surface. Confirmation of this assumption would require a randomized, prospective study of a large group of patients with Stage IV SCC.

In this study, differentiation of SCC was found to have no bearing on whether or not bone was invaded. Lund[16] suggests that tumor aggressiveness is related to both invasion and cellular differentiation, whereas the presence of only one of these features is less significant. Brown & Browne[6] reported that tumors with an erosive pattern of infiltration tend to be related to grade I or II, while those with an invasive pattern are often related to grade III. Correlation of the degree of differentiation and infiltration patterns of the tumor has not been confirmed by other authors[2,15].

Bone scanning is sensitive for the detection of occult metastasis in the skeleton. The main radiopharmaceutic agent is technetium-99m dicarboxy-propane diphosphonate (^{99m}Tc-DPD). In SCC, increased bone turnover occurs, resulting in high uptake of ^{99m}Tc, correspond-

ing to the "hot spots" on the bone scan. Metastatic lesions are usually detected by radionuclide bone scan before they are detected by conventional plain radiographs because the chemical changes of a disease process usually occur before anatomic changes. Such chemical changes inducing bone reaction are detectable by radionuclide imaging[22].

The results on the value of BS for the detection of early mandibular invasion agree with the results of other studies[1–5,7,11,13,17,27,37], indicating high sensitivity. However, there were many (52%) false-positive results.

The present study found the predictability and reliability of CT scans in assessment of invasion of the mandible to be unsatisfactory. A false-negative rate of 22% was found, in comparison with an average of 12.5% reported in other studies[2,7,9,29]. Only Brown et al.[7] reported a higher incidence of 28% false-negative results in CT scans. Although CT scans can help to estimate the size of the primary tumor and the nodal status, their value in the detection of early invasion of the mandible seems to be limited. Artifacts, especially in the coronal planes, due to dental restorations, and failure to assess accurately the area of the inner cortex of the mandible due to its irregular shape make it difficult to draw conclusions.

Tumor delineation by MRI was used only in selected cases and mainly for the estimation of soft-tissue invasion. Brown et al.[7] reported a false-negative rate of only 6% for predictability of bone invasion. However, Tsue et al.[36] found MRI scans to be less accurate than CT scans in determining cortex involvement and bone-marrow invasion. These controversial reports indicate the need for further study of this more costly imaging modality in assessing bony invasion.

According to the results of the present study and information from the available literature, bone scanning still seems to be the most sensitive method for detection of early invasion of SCC in the mandible. According to Noyek[22] and Bergstedt et al.[5], virtually no false-positive results should be obtained and a distinction should be possible between cancers that involve the soft tissues and those that erode the mandible by comparing early and delayed uptake. These authors also state that the errors in interpretation of the integrity of the mandible are largely due to failure of careful correlation between clinical findings and areas of abnormal activity on the scan. Although this statement has been disputed by several authors[15,19,37], we believe that, with cautious correlation with the clinical features, at least misinterpretation because of periapical or pericoronal inflammatory disease should be avoidable.

As far as patients who have received radiation are concerned, the assessment of the mandible is particularly difficult, either by preoperative diagnostic imaging or clinically. The increased sensitivity of bone scanning in irradiated patients is due to the mechanism of radionuclide uptake and the primary effect of the irradiation itself. In these patients, decisions regarding segmental as opposed to marginal mandibulectomy should be generally based on the location of the tumor, its extent, and the presence or absence of induration around the mandible[29].

The statistical method of the study addresses the problem of false-positive results by allowing for an intermediate class of unclear cases. By the decision-tree approach, the decision, "no bone invasion", would have been made for 10 patients (17%) with one error (10%); "bone invasion" would have been decided for 29 (48%) with two misclassifications (7%); and for the remaining 21 patients (35%), the decision "unclear" would have been applied. By use of the estimated probabilities of the logistic regression, several decision rules can be derived by setting levels. The estimated probability was below 0.1 for 13 patients (22%). If the remaining 47 patients had been classified positive, the PPV would have been 40/47 (85%). All 22 patients (37%) with estimated probability higher than 0.9 showed positive histologic results (PPV=100%). Twenty-five patients (42%), showing probability of 0.1–0.9, remained "unclear". If the levels had been set to 25% and 75%, only eight (13%) patients would have remained unclassified. While the "no bone invasion" class would have been the same, the class with positive results would have contained 39 patients (65%) with only four false-positive cases.

Predictive values, sensitivities, and specificities of five prediction rules are compared in Fig. 4. As mentioned above, scintigraphy exhibited higher negative predictive value and higher sensitivity than CT. If the estimated probability in the logistic regression were cut anywhere between 0.1 and 0.5, the NPV would be 93%. However, bone scanning with a specificity of only 47% was less specific than CT (78%). If mandibular invasion were diagnosed only for those patients showing positive scintigraphy and a high-risk tumor site, the specificity would rise to 89% and the PPV to 93%. If the decision "further investigation necessary" were not allowed, one would have to assume bony infiltration and the decision tree would then coincide with the scintigraphic criterion. For the logistic regression, the positive predictive value would increase to 85% or 100% if only patients with estimated probability higher than 0.75 or 0.9, respectively, were called positive. The corresponding specificity values would be 79% and 100%.

In conclusion, bone scanning appeared to be the best predictive imaging parameter for bone invasion. When it was combined with specific clinical features, it provided the best prognostic means in most patients (Figs. 5–8). We suggest the selection of an intermediate group of patients in whom it is not clear whether bone infiltration is present and who need further examination. The "rules" derived from our data set of 60 patients may have given unduly promising predictive values. The small number of our patient population, however, should compel further studies to check and refine the procedure.

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