Original Article

Underlying bone change in oral squamous cell carcinoma observed from magnetic resonance imaging and computed tomography: Potential implications for tumor aggressiveness and prognosis

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Abstract *Background: /purpose*In cases where oral squamous cell carcinoma (OSCC) invades the jawbone, clinicians frequently observe abnormal attenuation on computed tomography (CT) and pathologic signal intensity (SI) on magnetic resonance (MR) imaging of the affected underlying bone marrow. This study introduced a concept of "underlying bone change" to examine its association with clinicopathological features and prognosis of OSCC, as well as its correlation with medullary invasion.

Materials and methods: We enrolled 93 consecutive patients diagnosed with OSCC, who underwent mandibulectomy between 2010 and 2016. CT and MR images, along with electronic medical records, were reviewed to evaluate correlations between underlying bone changes, clinicopathological features, five-year overall survival, and medullary invasion.

Results: Of the 93 patients, 69 (74.2%) exhibited underlying bone sclerosis on CT, and 74 (79.6%) displayed pathological SI on MR images. These underlying bone changes correlated with the T stage and recurrence, but not with overall survival.

Medullary invasion, observed in 61 (65.6%) patients, was strongly associated with T and TNM stages and was linked to poorer overall survival.

The underlying bone changes on CT and MR images were positively associated with medullary

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invasion; however, no significant differences were found in the occurrence of underlying bone changes between the subtypes based on the extent of medullary invasion.

Conclusion: Underlying bone changes on CT and MR images can provide valuable insights into the aggressiveness of bone invasion by OSCC. Accurate interpretation of these imaging findings might be crucial for correctly delineating surgical margins and preventing the overestimation of tumor extent.

Introduction

The gingival mucosa is the second most prevalent site of oral squamous cell carcinoma (OSCC) next to the tongue; in this site, OSCC frequently infiltrates the mandible owing to its close anatomical proximity to the underlying bone.[1,2] The consequential bone invasion often categorizes gingival OSCC as stage IV at the time of presentation, necessitating treatment modalities involving resection of the involved bone.[3] Assessment of mandibular invasion in patients with OSCC commonly relies on computed tomography (CT) and magnetic resonance (MR) imaging.[4,5] The extent of invasion determined through these imaging modalities plays a crucial role in guiding decisions regarding whether to perform a marginal or segmental mandibulectomy.

In the clinical context, we frequently observe abnormal bone marrow attenuation on CT images and pathologic signal intensity (SI) of underlying bone on MR images in cases of OSCC.[6] This observation, termed "underlying bone change" in this study, makes it difficult to accurately delineate tumor margins and may contribute to the overestimation of mandibular invasion.[7–10] Uncertainty regarding the presence of malignant tumor cells in areas with underlying bone change further complicates the determination of surgical resection margins.

While existing studies have investigated peritumoral change in soft tissues and their implications for the potential overestimation of tumor size, understanding of peritumoral change in hard tissues, particularly in the bone, remains insufficient.[11,12] Unlike carcinomas outside the oral cavity, which rarely infiltrate adjacent bone, except in advanced stages, gingival carcinomas within the oral cavity have the potential to invade the bone, leading to frequent underlying bone changes due to tumor–bone interactions. Although medullary invasion, an imaging and histopathological biomarker, is a well-known prognostic factor in OSCC, research on peritumoral change in the bone marrow is scarce.[13–17] To the best of our knowledge, no study has been conducted on the correlation between underlying bone change and clinicopathological features, including overall survival or recurrence, in OSCC.

Hence, this study aimed to determine the association between underlying bone change and the clinicopathological features and prognosis of OSCC and to explore the correlation between underlying bone change and medullary invasion.

Materials and methods

Study population

This study was approved by the Institutional Review Board of Seoul National Dental Hospital (approval number: IRB007/01–15). Data collection and analyses conformed to institutional guidelines. This study included 93 consecutive patients diagnosed with OSCC who underwent mandibulectomy at Seoul National University Dental Hospital between 2010 and 2016. They were followed up for over 5 years. The inclusion and exclusion criteria were as follows: *Inclusion criteria* (a) lesion originating from the mandibular gingiva of the premolar and molar teeth or retromolar trigone; (b) availability of preoperative contrast-enhanced CT and MR images; (c) acquisition of fat-suppressed T2-weighted MR images. *Exclusion criteria* (a) recurrent lesion; (b) preoperative radiotherapy or chemotherapy; (c) previous surgical operation on the underlying bone; (d) images with severe artifacts impacting the accuracy of underlying bone evaluation; (e) progression of underlying bone destruction to the inferior cortex of the mandible.

Clinicopathological characteristics were retrieved from the patients' electronic medical records, including demographic information (age, sex), histological grade, pathological TNM stage, and 5-year locoregional recurrence. TNM stages were determined in accordance with the 7th American Joint Committee on Cancer Staging Manual.[3]

Image acquisition

CT images were obtained using a multidetector CT system (Somatom Sensation 10; Siemens Healthcare, Erlangen, Germany) with the following standard scan parameters: 120 kV, 150 mAs, 1-s rotation time, 0.75 pitch, and 1–2-mm section collimation. MR images were obtained using a 3.0-T scanner (Skyra; Siemens Healthcare) and a 1.5-T scanner (Signa HDxt; GE Medical Systems, Milwaukee, WI, USA). Furthermore, 32- and 16-channel phased-array head and neck coils were used for the 3.0- and 1.5-T machines, respectively. The imaging protocol included a section thickness of 4–6 mm, matrix size of 320 192 or 320, and a field of view measuring 22 × 22 or 19 × 19 cm. Axial and coronal fat-suppressed T2-weighted fast spin-echo sequences were acquired with repetition and echo times of 3000–5600 ms and 60–110 ms, respectively.

Evaluation of the underlying bone change

The underlying bone change caused by adjacent OSCC was assessed as underlying bone marrow sclerosis on CT images and as pathologic SI of underlying bone marrow on MR images. CT and MR images were independently evaluated by two oral and maxillofacial radiologists with over 10 years of experience using a picture archiving and communication system (INFINITT PACS; INFINITT Healthcare, Seoul, Korea). They were blinded to the clinical and histopathological information. In cases of disagreement, images were reassessed to reach a consensus.

Underlying bone marrow sclerosis on CT images
It is defined as increased attenuation and/or thickened trabeculae in the medullary cavity just beneath an OSCC mass on bone window CT images compared with the corresponding region of the contralateral side of the mandible. The presence of underlying bone sclerosis was evaluated as positive or negative.

Pathologic SI of the underlying bone marrow on MR images
It is defined as high SI in the underlying bone marrow just beneath an OSCC mass on fat-suppressed T2-weighted images compared with the corresponding region of the contralateral side of the mandible. The presence of pathologic SI was evaluated as positive or negative.

Evaluation of the type of invasion

The type of bone invasion was mainly assessed on bone window CT images by another oral and maxillofacial radiologist with over 10 years of experience and who had access to histopathological findings related to bone invasion. In cases of discrepancies regarding medullary invasion between the histopathological report and CT findings, an oral pathologist reviewed the histopathological slides again. Through the collaborative effort between the radiologist and pathologist, a consensus on the medullary invasion was reached.

No medullary invasion
It indicates a tumor that is superficially confined without invasion into the medullary space. This type is characterized by the tumor being either adjacent to or eroding only the cortex.

Medullary invasion
It indicates a tumor that spreads into the medullary space without a distinct border. This type is characterized by an ill-defined border with a broad transition zone and finger-like extensions into the surrounding trabecular bone. Medullary invasion is further classified into two subtypes based on the extent of tumor involvement with respect to the mandibular canal: "medullary invasion that extends over the mandibular canal" and "medullary invasion that does not extend over the mandibular canal".

Statistical analysis

Interobserver agreement for the underlying bone change was assessed using Cohen's kappa coefficient. The strengths of this coefficient were having values > 0.80, an almost perfect reliability, and $0.60-0.80$, substantial reliability.[18] Pearson's chi-squared test or Fisher's exact test was conducted to evaluate the correlation between underlying bone change, clinicopathological features, and medullary invasion. Cumulative survival rates were calculated using the Kaplan–Meier method, and differences between the curves were analyzed using the log-rank test. $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were conducted using SPSS Statistics Version 21 (IBM, Armonk, NY, USA).

Results

Correlation between underlying bone changes and clinicopathological features in patients with OSCC

The clinicopathological features of 93 patients with OSCC are listed in Table 1 and the correlations of these features with the underlying bone change in Table 2. The interobserver agreement for the underlying bone change between the two

Table 1 Clinicopathological features of 93 patients with oral squamous cell carcinoma.

Variable	No. of cases (%)
Age (y); mean, 62.8	
30–39	1 (1.1)
40–49	13 (14.0)
50–59	20 (21.5)
60–69	30 (32.3)
70–79	24 (25.8)
80–89	5 (5.4)
Sex	
Male	62 (66.7)
Female	31 (33.3)
Differentiation status	
Well	85 (91.4)
Moderately	8 (8.6)
Poorly	0 (0.0)
T classification	
T1	11 (11.8)
T2	23 (24.7)
T3	1 (1.1)
T4	58 (62.4)
N classification	
N0	63 (67.7)
N1	10 (10.8)
N2	20 (21.5)
M classification	
M0	92 (98.9)
M1	1 (1.1)
Stage	
I	7 (7.5)
II	16 (17.2)
III	5 (5.4)
IV	65 (69.9)
Recurrence	
No	69 (74.2)
Yes	24 (25.8)

Table 2 Correlation between underlying bone change and clinicopathological factors in patients with oral squamous cell carcinoma.

Variable	No. cases (n = 93)	Sclerosis on CT		P	Pathologic SI on MR		P	Medullary invasion		P
		Negative (n = 24)	Positive (n = 69)		Negative (n = 19)	Positive (n = 74)		Negative (n = 32)	Positive (n = 61)	
Age (y)				0.218			0.476			0.354
<62	41	8	33		7	34		12	29	
≥62	52	16	36		12	40		20	32	
Sex				0.078			0.363			0.001*
Male	62	12	50		11	51		14	48	
Female	31	12	19		8	23		18	13	
Differentiation status				0.102			0.210			
Well	85	20	65		16	69		30	55	0.558
Moderately to poorly	8	4	4		3	5		2	6	
Tumor size				0.001*			0.016*			<0.001*
T1 + T2 + T3	35	15	17		11	21		32	0	
T4	58	9	52		8	53		0	61	
Lymph node metastasis				0.315			0.716			0.758
Negative	62	14	48		12	50		22	40	
Positive	31	10	21		7	24		10	21	
Distant metastasis				0.553			0.610			0.466
Negative	92	24	68		19	73		32	60	
Positive	1	0	1		0	1		0	1	
Stage				0.198			0.201			<0.001*
I + II + III	28	10	19		8	20		27	1	
IV	65	14	50		11	54		5	60	
Recurrence				0.438			0.017*			0.076
No	68	19	49		18	50		27	41	
Yes	25	5	20		1	24		5	20	

*Statistically significant.
Abbreviations: CT, computed tomography; SI, signal intensity; MR, magnetic resonance imaging.

readers was almost perfect (κ = 0.935 and κ = 0.959 on CT and MR, respectively). Underlying bone sclerosis was observed in 74.2% (69/93) of patients on CT images, whereas pathologic SI was observed in 79.6% (74/93) of patients on MR images (Fig. 1). Both underlying bone sclerosis and pathologic SI were correlated with the T stage ($P = 0.001$ and $P = 0.016$, respectively). Notably, pathologic SI was positively associated with recurrence ($P = 0.017$). No significant correlation was observed between the underlying bone change and other clinicopathological features. Of the 93 patients, 25 died, resulting in a 5-year survival rate of 73.1% (68/93). No significant difference was observed in overall survival between patients with and without underlying bone changes (Fig. 2).
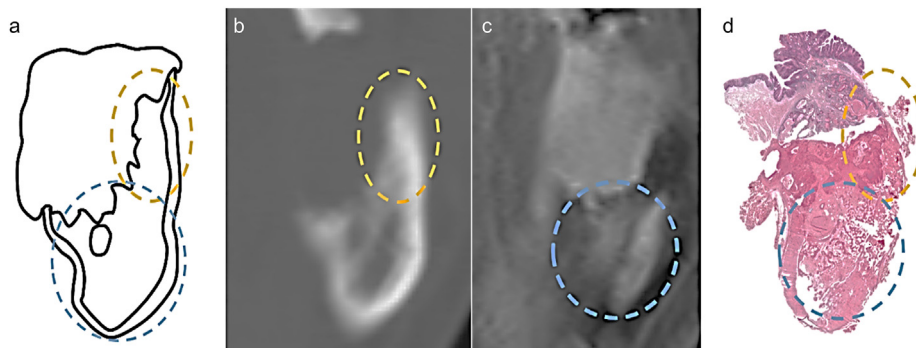

Figure 1 (a) Schematic illustration of the tumor mass and the underlying bone features. (b) The yellow circle indicates the underlying bone sclerosis on the CT image with bone setting, which corresponds to thickened trabecular bone in histopathology. (c) The blue circle indicates the high signal intensity of the underlying bone marrow on fat-suppressed T2-weighted MR image, correlating with fibrosis and inflammatory cell infiltration in histopathology. (d) Hematoxylin−eosin staining of the specimen from a partial mandibulectomy represents sclerosis, fibrosis, and inflammatory changes in the underlying bone. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
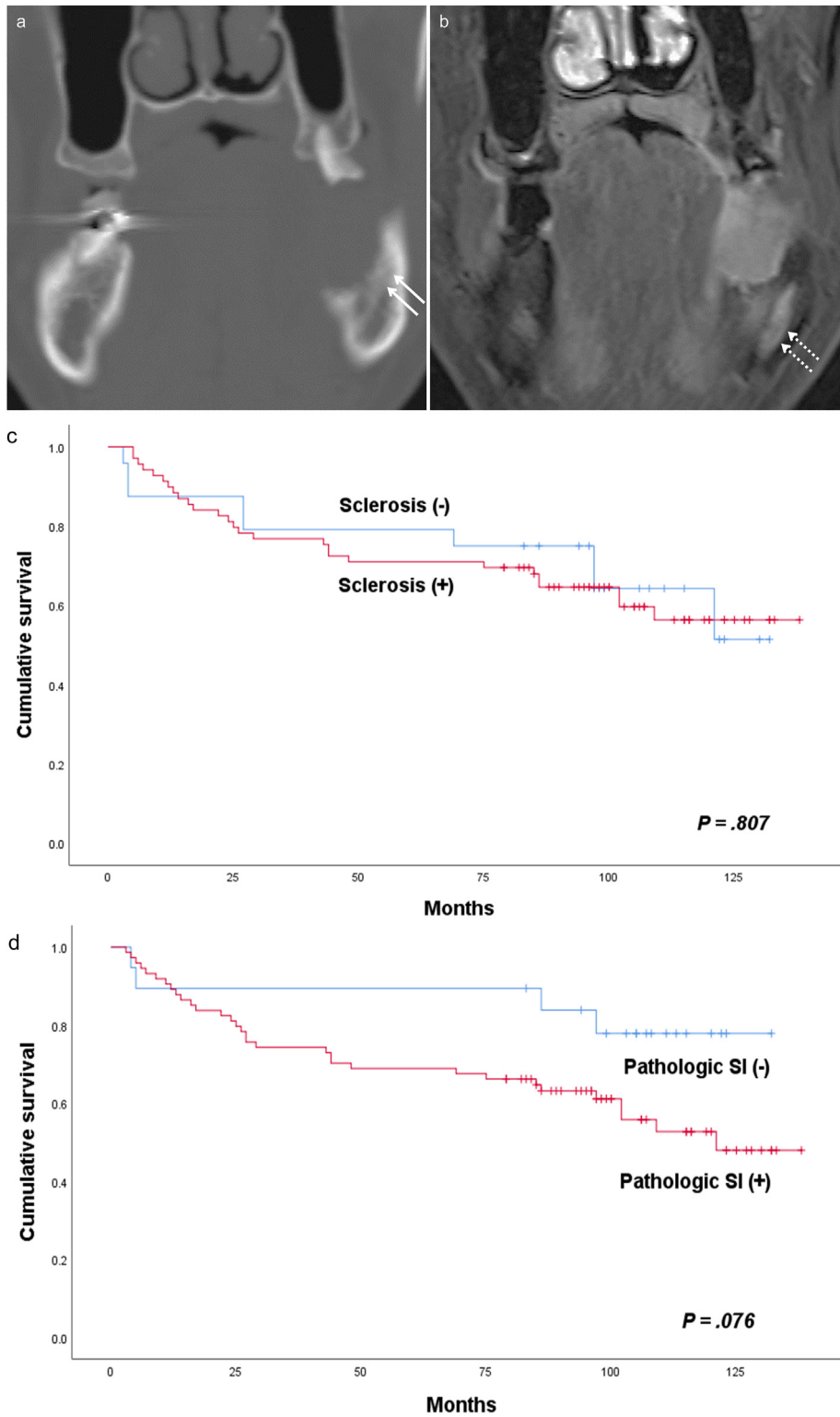
Figure 2 Underlying bone change accompanied by bone invasion by oral squamous cell carcinoma. (a) Underlying bone sclerosis on CT image with bone setting (arrow). (b) High signal intensity of the underlying bone marrow on fat-suppressed T2-weighted MR image (dashed arrows). (c) and (d) Kaplan—Meier curves for 93 patients with or without underlying bone sclerosis on CT image (c) and pathologic signal intensity on MR image (d). SI: signal intensity.

Correlation between medullary invasion and clinicopathological features in patients with OSCC

Of the 93 patients, 61 (65.6%) and 32 (34.4%) had positive and negative medullary invasion, respectively. Medullary invasion was significantly correlated with the T ($P < 0.001$) and TNM ($P < 0.001$) stages. However, no significant correlation was observed between medullary invasion and other clinicopathological features (Table 2). Patients with medullary invasion exhibited poorer overall survival than those without it ($P = 0.003$; Fig. 3).
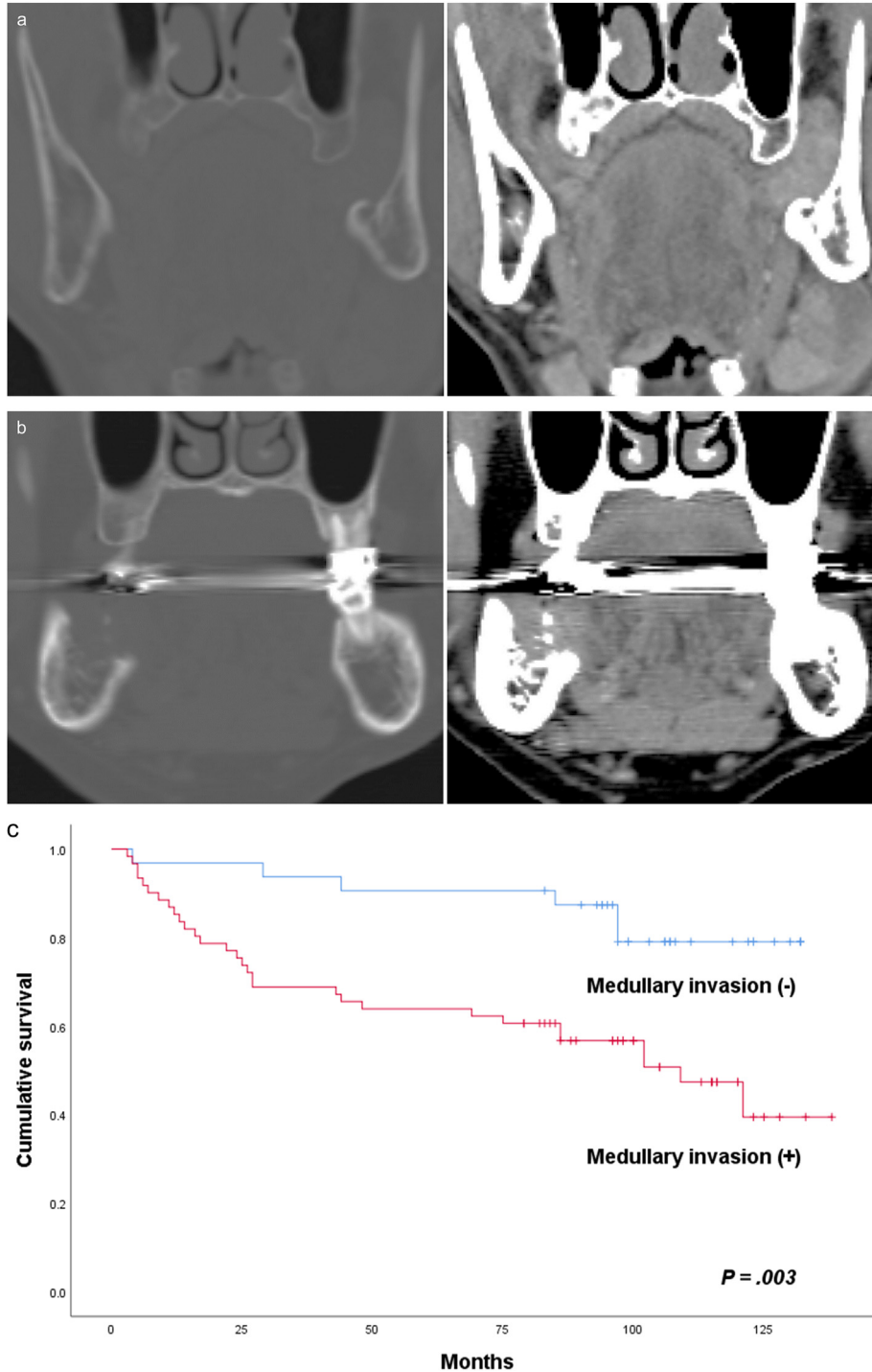

Figure 3 Bone invasion by oral squamous cell carcinoma. (a) A case of oral squamous cell carcinoma showing negative medullary invasion. A well-defined border adjoining the cortex or eroding only the cortex (CT images with bone and soft tissue setting). (b) A case of oral squamous cell carcinoma showing positive medullary invasion. Ill-defined border with fingerlike extension into the bone (CT images with bone and soft tissue settings). (c) Kaplan—Meier curves for 93 patients with or without medullary invasion.

Correlation between the underlying bone change and medullary invasion

The presence of underlying bone change on CT and MR images was positively correlated with medullary invasion ($P = 0.001$ and $P = 0.016$, respectively; Table 3). However, there were no statistically significant differences in the occurrence of underlying bone changes between the subtypes based on the extent of medullary invasion.

Discussion

This study explored the correlation of underlying bone marrow changes on CT and MR images with clinicopathological features and medullary invasion in patients with OSCC. Compared with medullary invasion, a well-known imaging and histopathological biomarker, little is known about underlying bone marrow changes. In this study, underlying bone change was observed in approximately 75% of CT and 80% of MR images and was positively correlated with medullary invasion. The underlying bone change was correlated with the T stage and recurrence but not with overall survival.

Medullary invasion is a crucial factor in predicting the extent of bone resection and patient prognosis. Compared with cortical bone invasion, medullary bone invasion is more likely to necessitate segmental resection than marginal resection, sacrificing the mandibular rim.[13−15] Furthermore, medullary invasion is associated with a statistically significant decrease in prognostic and overall survival rates.[15−17] To enhance margin control and survival rates, a deeper understanding of bone invasion is needed, and investigation of its associated underlying bone change might be beneficial for the identification of another imaging biomarker. However, the present study demonstrated no significant difference in patients' overall survival according to the underlying bone change. Nevertheless, it may provide additional information on medullary invasion and tumor recurrence.

The process of bone invasion by malignant tumors involves various molecular mechanisms, including the secretion of enzymes and factors that degrade the bone matrix, the induction of osteoclasts, and the alteration of bone cell signaling pathways.[19] Recent studies on the molecular

mechanisms underlying bone invasion by OSCC may support the findings of the present study.[20] According to the research conducted by Elmusrati et al., a fibrous stroma was found to intervene between the tumor and bone in most OSCC cases. Two key proteins in osteoclastogenesis, RANKL (Receptor Activator for Nuclear Factor κB Ligand) and osteoprotegerin, were expressed not only in tumor cells but also in the fibrous stroma adjacent to the bone. Consistent infiltration of myofibroblastic cancer-associated fibroblasts into the bone ahead of tumor cells was also observed. We believe that this phenomenon is likely associated with the underlying bone changes found in the present study, which were characterized by hyperintense T2 SI in the underlying bone marrow space on MR images. Further studies investigating the pathogenesis of the underlying bone change are warranted to better understand the microenvironment adjacent to bone invasion.

While the exact mechanism remains not fully understood, previous studies on the underlying bone changes in patients with oral squamous cell carcinoma (OSCC) have reported two implications. The first implication is the presence of a nearby tumor, which indicates the response of the bone to an adjacent tumor. Such an underlying bone change can be considered an indicator of the presence of a nearby tumor. Shatzkes et al. reported that nearly 60% of patients with nasopharyngeal carcinoma developed sclerosis in the pterygoid process adjacent to the tumor mass.[21] Another study suggested that the presence of sclerosis in the mandible indicates microscopic disease and raise suspicion of mandibular invasion by OSCC.[6,22] The second implication is overestimation of tumor extent due to desmoplastic reaction or inflammatory changes in the affected bone marrow. The affected bone marrow may exhibit SI similar to that of the tumor mass and can be interpreted as marrow invasion or surrounding inflammation in the bone marrow that may obscure the actual tumor margins.[23,24] Radiologists should be aware of the implications of underlying bone change observed on CT and MR images, particularly when determining the tumor extent.

The present study has several limitations. First, only mandibular OSCC was included in the study because the maxilla has a relatively small volume of bone marrow space and it is difficult to determine the underlying bone marrow change in the maxilla. Second, underlying bone marrow changes on CT and MR images were qualitatively analyzed

Table 3 Correlation between medullary invasion and underlying bone changes.

Variable	No. cases (n = 93)	No medullary invasion (n = 32)	Medullary invasion (n = 61)		P
			Subtype I[a] (n = 29)	Subtype II[b] (n = 32)	
Sclerosis on CT					0.001[a]
Negative	24	15	5	4	
Positive	69	17	24	28	
Pathologic SI on MR					0.016*
Negative	19	11	5	3	
Positive	74	21	24	29	

Abbreviations: CT, computed tomography; SI, signal intensity; MR, magnetic resonance imaging.
*Statistically significant.
[a] Subtype I: medullary invasion that does not extend over the mandibular canal.
[b] Subtype II: medullary invasion that extends over the mandibular canal.

as positive or negative only based on comparison with the corresponding region on the contralateral side of the mandible. Future studies should conduct more detailed quantitative analysis using Hounsfield units on CT and gray values on MR images. Third, this was a retrospective study; therefore, the radiological and histopathological correlations of the underlying bone marrow space, other than medullary invasion, could not be performed. Such correlations are important to elucidate the characteristics of the underlying bone change.

Underlying bone changes on CT and MR images can provide valuable insights into the aggressiveness of bone invasion by OSCC. Accurate interpretation of these imaging findings might be crucial for correctly delineating surgical margins and preventing the overestimation of tumor extent.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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