

Potential role of post-treatment follow-up FDG-PET CT to detect mandibular osteoradionecrosis: A case report

MASAYA AKASHI¹, SATOSHI WANIFUCHI¹, JUNYA KUSUMOTO¹, MEGUMI KISHIMOTO¹,
YASUMASA KAKEI¹, KAZUNOBU HASHIKAWA² and TAKAHIDE KOMORI¹

Departments of ¹Oral and Maxillofacial Surgery, and ²Plastic Surgery,
Kobe University Graduate School of Medicine, Kobe 650-0017, Japan

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Abstract. It was hypothesized that fluorodeoxyglucose (FDG) uptake on post-treatment follow-up positron emission tomography with computed tomography (PET CT; using PET CT to monitor and rule out recurrence and metastasis of head and neck carcinoma) would be useful for detecting and understanding the disease state of osteoradionecrosis (ORN) of the jaw. The present study included 14 patients who developed mandibular ORN following radiation therapy (RT) for head and neck cancer and underwent follow-up PET CT several times following RT. Areas exhibiting FDG uptake were retrospectively assessed on post-treatment follow-up PET CT images and were classified into three types: Spot type: Only spot accumulation of FDG; localized type: Accumulation of FDG restricted to within the bone resorption area; extensive type: Accumulation of FDG extending into surrounding soft tissue. PET classification at the time of clinical diagnosis of mandibular ORN in the 14 patients demonstrated the extensive type in 43%, localized type in 36% and spot type in 21%. An increased area of FDG uptake around the ORN was revealed retrospectively on post-treatment follow-up FDG PET-CT images in 50% of patients. Alterations in PET classification included spot type to localized type in 36% and localized type to extensive type in 14%. A significantly increased number of patients with extensive-type ORN ($P=0.026$) required surgery. Post-treatment follow-up FDG-PET CT may be useful for early detection and better understanding of ORN.

Introduction

Although the incidence of osteoradionecrosis (ORN) of the jaw seems to be progressively declining in recent years (1),

Correspondence to: Dr Masaya Akashi, Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
E-mail: akashim@med.kobe-u.ac.jp

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it remains one of the most serious complications of radiation therapy (RT) for head and neck malignancy. Patients with advanced ORN have nutrient insufficiency, pain, and chronic drainage, resulting in severely decreased quality of life (2).

Jacobson *et al* (3) classify ORN into stages I-III. Stage I (early stage) exhibits minimal soft tissue ulceration and limited exposure of cortical bone. It should be treated conservatively. Stage I ORN rarely progresses to stage II [3]. Stage II (intermediate stage) exhibits pathologic changes localized in the mandibular cortex and underlying medullary bone. Most stage II ORN resolves with conservative treatment or minimal surgical intervention (3). Stage III (advanced stage) shows full-thickness involvement of the bone, including the inferior border (e.g., pathologic fracture may be present). Surgical intervention (i.e., bone and/or soft tissue replacement) is the definitive treatment for stage III (3).

Early detection and intervention are essential to prevent progression to advanced ORN. A previous study showed that panoramic radiography was useful for monitoring ORN, despite underestimating ORN on these images (4). In fact, patients whose pathologic changes are shown on panoramic radiographs sometimes develop intermediate or advanced ORN.

A recent study demonstrated that fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET CT) detects local and diffuse metabolic changes that may not be revealed on plain radiography in patients with medication-related osteonecrosis of the jaw (MRONJ) (5). Another previous study showed that FDG-PET reflects the disease course and indicates the point of clinical remission in patients with mandibular chronic osteomyelitis (6). The role of FDG-PET in infectious diseases has been attracting attention, and its usefulness in the diagnosis of active osteomyelitis in various regions of the body (e.g., legs, lumbar spine) has recently been reported (7,8).

In the present study, we focus on post-treatment follow-up PET CT imaging (i.e., PET CT for monitoring and ruling out recurrence and metastasis of head and neck cancer) to detect and understand the pathologic state of ORN. The main objective of our retrospective case series study was to evaluate the FDG accumulation on post-treatment follow-up PET CT imaging in patients who developed mandibular ORN. The authors hypothesized that the FDG uptake would be detected

on PET images before the clinicians found and diagnosed mandibular ORN.

Patients and methods

Study population. All patients with head and neck malignancies included in this study were mainly treated by otolaryngologists, radiation oncologists, and medical oncologists in our hospital. Oral and maxillofacial surgeons performed pre-RT dental examinations and prophylactic extraction of unrestorable teeth before initiating RT. After completion of the treatment for head and neck malignancies (RT with chemotherapy or surgery), attending clinicians in each department performed routine follow-up. During this post-treatment observation period, imaging examinations were applied as necessary to rule out local recurrence and metastasis. The timing, frequency, and type of imaging examinations were decided by the attending otolaryngologist, radiation oncologist, and medical oncologist. Patients suspected of having ORN by attending clinicians were re-introduced to our department. In this study, these second introductions to us from other departments for the diagnosis and treatment of ORN were designated 'second visit' cases.

To elucidate the usefulness of FDG-PET CT for diagnosing mandibular ORN, we excluded patients who had not undergone FDG-PET CT several times during the post-treatment observation period. Patients with maxillary ORN were also excluded. Only cancer patients who achieved a complete response to treatment were included. Patients with recurrent cancer after treatment were excluded. In all, 14 patients who re-visited our department for the treatment of mandibular ORN from October 2011 to April 2016 were included in the study. Because of the retrospective nature of this study, the institutional review board in our hospital granted an exemption (in writing) from requiring written informed consent from the patients in the study.

ORN was defined as exposure of the bone for >6 months (9). The following epidemiologic data were retrospectively gathered from the medical charts: Age, sex, histologic diagnosis and site of the primary tumor, radiation dose, chemotherapy, surgery for head and neck cancer, interval between completion of RT and the second visit to our department for the treatment of ORN, frequency of FDG-PET CT during observation follow-up periods, and type of treatment of mandibular ORN. The latter was divided into conservative and surgical interventions. The former included repeated local wound irrigation, antibiotic administration, and hyperbaric oxygen therapy (HBO). The latter included surgical debridement with or without free tissue transfer.

FDG-PET CT evaluation. Evaluation of FDG uptake by PET CT during the observation follow-up periods was performed by three observers (J.K., S.W., M.K.). Observer 1 (J.K.) is a specialist in oral and maxillofacial surgery with more than 10 years of experience, and observers 2 and 3 (S.W. and M.K.) are graduate fellows in the Department of Oral and Maxillofacial Surgery. A Microsoft® Office PowerPoint presentation (PPT) had been prepared by the first author (M.A.). The areas exhibiting FDG uptake were classified into three types: (1) spot type, with only spot accumulation of FDG that did not extend to the labial or lingual sides of

Table I. Patient data.

Characteristic	Values ^a (n=14)
Age (years), median (range)	64 (41-87)
Sex	
Male	12 (86)
Female	2 (14)
Histology	
Squamous cell carcinoma	13 (93)
Adenoid cystic carcinoma	1 (7)
Primary tumor site	
Oropharynx	6 (44)
Oral cavity	2 (14)
Nasopharynx	2 (14)
Neck (unknown primary)	2 (14)
Paranasal cavity	1 (7)
Submandibular gland	1 (7)
Radiation dose (Gy)	
70	9 (64)
60-70	5 (36)
Chemotherapy	13 (93)
Surgery for head and neck cancer	6 (43)
Period from completion of RT and second visit ^b (months), median (range)	45 (5-76)
No. of FDG PET-CT sessions during follow-up period, median (range)	3 (2-9)
Location of mandibular osteoradionecrosis	
Unilateral posterior	10 (72)
Bilateral posterior	2 (14)
Anterior	1 (7)
Bilateral posterior and anterior	1 (7)

^aUnless otherwise noted, data are reported as the number (percentage) of study patients. ^b'Second visit' indicates the second time that patients came to our department for treatment for mandibular osteoradionecrosis.

mandibular cortices (Fig. 1A); (2) localized type, with accumulation of FDG restricted to within the bone resorption area in the mandible (Fig. 1B); (3) extensive type, in which the FDG accumulation extended from the mandible into the surrounding soft tissue (Fig. 1C). Slight uptake of FDG along the mandible outward was regarded as 'non-specific' (Fig. 1). To differentiate between 'specific' and 'non-specific' accumulation of FDG, the features of 'specific' accumulation were defined as follows: The shape of the FDG accumulation was circular or elliptical, with its center located in the mandible (Fig. 1). In patients with bilateral ORN, the lesions accompanied by clinical symptoms were evaluated. Three observers reviewed the PPT individually. After one week, order of the PPT slides was randomly changed, and assessed again by the same observers to allow to evaluate intra-observer reliability. The results of the second reviews were edited according to the first reviews to enable comparison between the first and second

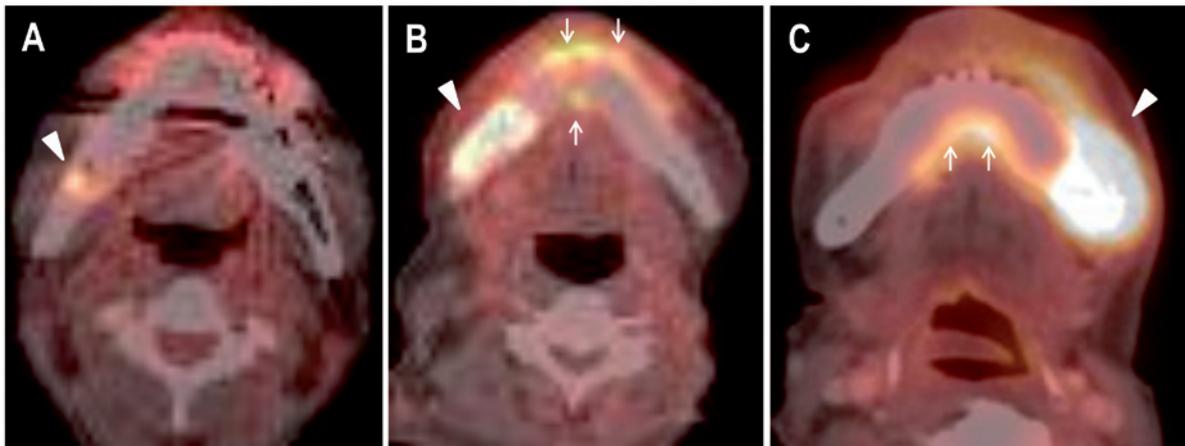


Figure 1. Positron emission tomography (PET) classification. (A) Spot-type accumulation, defined as spots of accumulation of fluorodeoxyglucose (FDG). (B) Localized type, defined as localized accumulation of FDG within the bone resorption area. (C) Extensive type, defined as the FDG accumulation extending into surrounding soft tissue. Arrowheads, specific FDG uptake; arrows, non-specific FDG uptake.

observation. Discrepant results were solved with reassessment by a first author and three observers.

Both the mean and maximum standard uptake value (SUV_{mean} and SUV_{max}) were analyzed quantitatively in the axial planes by using DICOM workstation (Yokogawa Medical Solutions Corporation, Tokyo, Japan).

Statistical analysis. Fisher's exact test was used to compare associations between the type of FDG accumulation and the type of treatment (conservative or surgical intervention). Kruskal-Wallis test with Steel-Dwass multiple comparisons was used to compare the values of SUV among three types of FDG accumulation (i.e., spot, localized, and extensive type). Intra-observer reliability was evaluated by calculating Cohen's Kappa, and inter-observer reliability was assessed with Fleiss' Kappa. Statistical significance was accepted at $P < 0.05$, and statistical analyses were performed using R software (R Development Core Team, 2011).

Results

Patient data are detailed in Table I. Overall, 93% of the patients included in this study underwent concomitant chemoradiotherapy (CCRT). Cisplatin was used in all of these patients.

Fleiss' kappa value (inter-observer reliability) was 0.77. Cohen's kappa values (intra-observer reliability) of observer 1, 2, and 3 were 1, 0.81, and 0.76, respectively. At the second visit (i.e., the time when patients were reintroduced to our department for the treatment of mandibular ORN), the most common ORN type, according to the PET classification, was the extensive type (43%), followed by the localized type (36%) and the spot type (21%). The significant difference of SUV_{mean} ($P = 0.022$) but not SUV_{max} ($P = 0.075$) among three types was found. However, there was no significant difference in both SUV_{mean} and SUV_{max} between extensive and localized types, extensive and spot types, and localized and spot types. The increased area of FDG uptake around mandibular ORN was found retrospectively on post-treatment follow-up FDG-PET CT in 50% of patients. The types of changes of PET

classification were the spot type to localized type in 36% and the localized type to extensive type in 14% (Table II).

In Table III, data are presented regarding the association between the range of FDG accumulation and the type of treatment used for mandibular ORN. In this study, 57% of the patients were treated conservatively. Among them, only one patient underwent HBO. In all, 6 of the 14 patients (43%) required surgical intervention. Four underwent segmental mandibulectomy for extirpation of the disease with simultaneous reconstruction using a free fibula osteocutaneous flap, and two underwent segmental mandibulectomy to control severe infection. Among the six patients classified as having extensive type ORN at the second visit, four had a pathologic fracture and an orocutaneous fistula. Significantly more patients with extensive-type ORN at the second visit required surgical intervention ($P = 0.026$).

Representative cases are shown in Figs. 2 and 3. A 58-year-old man was re-referred to our department for evaluation of left lower jaw pain. He previously underwent CCRT for right maxillary carcinoma in our hospital (Fig. 2). Prophylactic tooth extraction was performed before initiating CCRT in our department (Fig. 2). The patient had pain and swelling in the left mental region at 4 years 5 months after CCRT completion. Retrospective evaluation of the post-treatment follow-up PET CT revealed sequential uptake of FDG (Fig. 2). The extent of FDG uptake was slight (same signal as non-specific uptake) on PET CT at 2 years 2 months after CCRT completion (Fig. 2). On PET CT at 3 years 1 month after CCRT, we found localized accumulation of FDG around the left mandibular canine (Fig. 2). On PET CT 4 years after CCRT, the areas of FDG accumulation had increased around the osteolytic region and protruded into the lingual soft tissue. Hence, the type of FDG accumulation was extensive (PET classification) (Fig. 2). At the second visit, only a small fistula with pus discharge was found in the left mandibular molar region (Fig. 2). However, the panoramic radiographic image obtained at the second visit showed bone resorption in the left mandibular molar region (Fig. 2). It was diagnosed as mandibular ORN. The patient is currently undergoing conservative therapy that includes repeated local

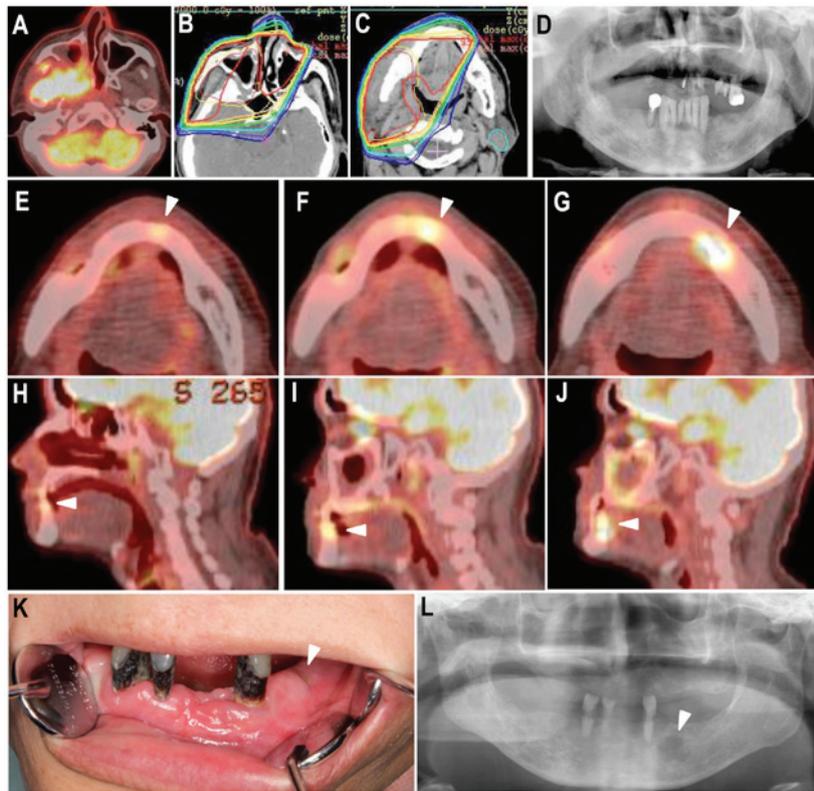


Figure 2. Representative case of increased FDG accumulation: Localized type increasing to extensive type. (A) Pre-treatment FDG-PET computed tomography (CT) shows a right maxillary carcinoma invading the middle cranial fossa. (B and C) Planning CT images. (D) Panoramic radiographic image for the oral examination before radiation therapy (RT). Note the slight uptake of FDG (arrowhead) in the axial view 2 years 2 months after RT (E). Localized type of FDG accumulation (arrowhead) in the axial view 3 years 1 month after RT (F). Extensive-type FDG accumulation (arrowhead) in the axial view 4 years after RT (G). Sequential increase of FDG accumulation (arrowhead) in sagittal views 2 years 2 months after RT (H), 3 years 1 month after RT (I), and 4 years after RT (J). (K) A small fistula with pus discharge (arrowhead) in the left mandibular molar region detected 4 years 5 months after RT. (L) Panoramic radiography shows bone resorption (arrowhead) in the distal area of the left mandibular canine 4 years 5 months after RT.

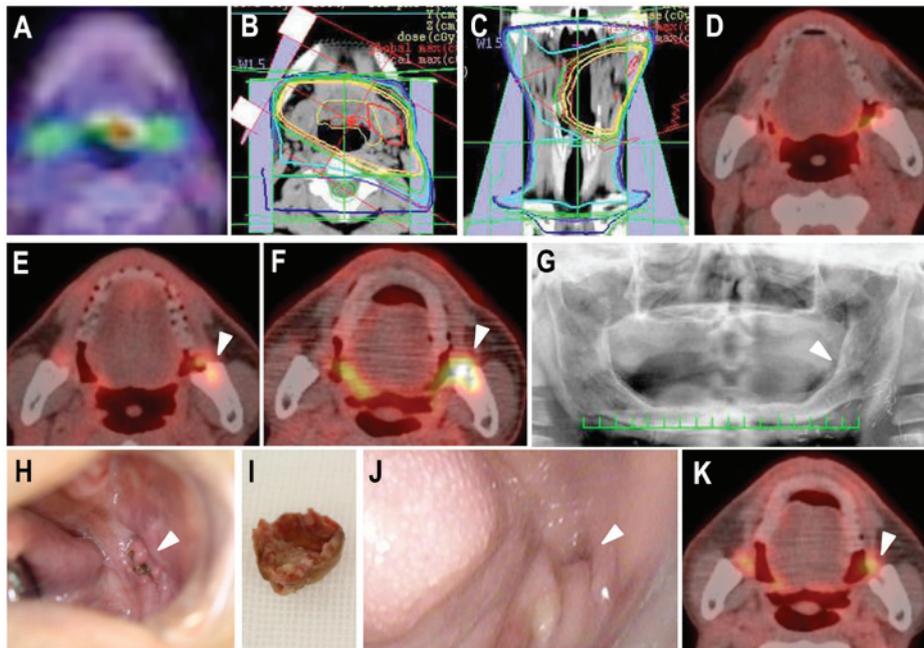


Figure 3. Representative case of increased FDG accumulation: Spot type changing to localized type. (A) Pre-treatment FDG-PET CT shows a left oropharyngeal carcinoma. (B and C) Planning CT images. Note the slight uptake of FDG in the axial view (D) 3 years 7 months after RT and the spot type of FDG accumulation (arrowhead) in the axial view (E) 4 years 8 months after RT. (F) Localized type of FDG accumulation (arrowhead) in the axial view 5 years 8 months after RT. (G) Panoramic radiography shows no obvious bone resorption (arrowhead) in the anterior edge of the left mandibular ramus 5 years 10 months after RT. (H) Bone exposure with a mucosal defect (arrowhead) in the left retromolar region 5 years 10 months after RT. (I) Removed sequestrum after repeated conservative treatment. (J) Epithelialization (arrowhead) was achieved after sequestrectomy. (K) Disappearance of FDG accumulation after healing of mandibular osteoradionecrosis.

Table II. Fluorodeoxyglucose accumulation.

Parameter	Values ^a (n=14)	SUV _{mean} median (range)	SUV _{max} median (range)
PET classification ^b at second visit			
Extensive	6 (43)	4.94 (3.36-6.94)	9.1 (4.83-13.48)
Localized	5 (36)	4.19 (3.54-4.64)	6.16 (5.62-8.47)
Spot	3 (21)	2.96 (2.78-3.27)	4.42 (3.84-6.29)
P-value ^c		0.022	0.075
Increased FDG accumulation before the second visit ^d			
Total	7 (50)		
'Spot' to 'localized'	5 (36)		
'Localized' to 'extensive'	2 (14)		

PET, positron emission tomography; FDG, fluorodeoxyglucose; CT, computed tomography; SUV, standard uptake value. ^aData are reported as the number (percentage) of study patients. ^bDescribed in detail in the 'Patients and methods' section. ^cKruskal-Wallis rank sum test. Comparison of SUV among extensive, localized, and spot types at second visit. ^dFDG accumulation before second visit to our department was evaluated retrospectively on post-treatment PET-CT during the observation period.

irrigation, with antibiotic administration only when absolutely necessary.

A 64-year-old man was re-referred for evaluation of left lower jaw pain. He previously underwent CCRT for left oropharyngeal carcinoma in our hospital (Fig. 3) and an oral examination before CCRT initiation in our department. The patient had pain and swelling in the left mandibular molar region at 5 years 10 months after completion of CCRT. Retrospective evaluation of the post-treatment follow-up PET CT revealed sequential FDG uptake (Fig. 3). The FDG accumulation was not found on PET CT at 3 years 7 months after CCRT completion (Fig. 3). However, on PET CT at 4 years 8 months after CCRT, spot accumulation of FDG at the anterior edge of the left mandibular ramus was found (Fig. 3). On PET CT at 5 years 8 months after CCRT, an area of bone resorption was found along the left ramus, changing the type of PET classification to localized accumulation of FDG (Fig. 3). Although the panoramic radiographic image at the second visit did not show obvious bone resorption at the left mandibular ramus (Fig. 3), a fistula with exposure of necrotic bone was found in the left retromolar region (Fig. 3). He was treated conservatively with repeated local irrigation and sequestrectomy under local anesthesia (Fig. 3), which resulted in epithelialization of the area with necrotic bone exposure (Fig. 3). Recent PET CT showed no FDG accumulation in the mandible (Fig. 3).

Discussion

We had hypothesized that post-treatment follow-up with FDG-PET CT to monitor head and neck carcinoma would be useful for detecting ORN. This retrospective case series study shows the sequential increase in FDG uptake in patients with mandibular ORN, indicating that post-treatment follow-up with FDG-PET CT has the potential not only to evaluate cancer recurrence and metastasis but also to detect and help us understand the disease conditions of ORN.

We introduced a novel classification of ORN based on the range of FDG accumulation in relevant tissues. In the PET clas-

Table III. Association between fluorodeoxyglucose accumulation and type of treatment for 14 patients.

PET classification at second visit	No. of patients ^a (n=14)	P-value ^b
Conservative treatment		
Extensive accumulation	1 (7)	0.026
Localized accumulation	4 (29)	
Spot accumulation	3 (21)	
Surgical treatment		
Extensive accumulation	5 (36)	
Localized accumulation	1 (7)	

^aData are reported as the number (percentage) of study patients.

^bFisher's exact test. Comparison of extensive type, conservative vs. surgical group.

sification of ORN, the spot type probably reflects inflammation due to marginal or apical periodontitis. ORN can develop in odontogenic foci (e.g., periodontal and apical disease) or in cases of failure to heal after dental extraction (10). As shown in Fig. 2, ORN sequentially progressed from local odontogenic foci that exhibited spot accumulation of FDG. The spot accumulation of FDG in the mandible on post-treatment follow-up FDG-PET CT indicates a latent lesion that could cause ORN. Early detection of such latent lesions based on spot accumulation of FDG allows prompt initiation of conservative treatment, such as local irrigation and dental treatment. Importantly, ORN can also occur spontaneously (10). As shown in Fig. 3, ORN can occur in edentulous patients, so the lesion cannot be detected on plain radiography alone. Localized FDG accumulation reveals lesions that are at risk of being overlooked (or not appearing at all) on plain radiography.

Contrast-enhanced CT or magnetic resonance imaging (MRI) examination is routinely performed for cancer

follow-up, and in general, are taken more frequently than PET CT. However, CT for cancer follow-up is not thin-slice, therefore, it is often difficult to detect early ORN. It is probably difficult for attending doctors (i.e., otolaryngologists, radiation oncologists, and medical oncologists) and radiologists who are not used to diagnose jaw osteomyelitis to detect early ORN with MRI alone. In contrast, FDG accumulation is easy to be detected. Taken together, if attending doctors or radiologists detect spot or localized FDG accumulation in the mandible on routine follow-up PET CT, it would be better to consider the introduction to oral and maxillofacial surgeons or dental oncologists.

In the present study, we found a significantly higher rate of patients who required surgical interventions in the extensive-type group (PET classification). Interestingly, a recent study of MRONJ showed that the extent of FDG uptake predicted the surgical outcome (11). The authors showed that FDG uptake extending below the mandibular canal was more likely to require segmental resection, and they concluded that FDG-PET CT could provide additional treatment planning information that did not necessarily correlate with the clinical or CT findings (11). We think that the range of FDG accumulation in extensive-type ORN (PET classification) reflects the inflammation in surrounding soft tissues as the result of infection of necrotic bone. In this study, patients with extensive-type ORN mostly had pathologic fractures and orocutaneous fistulas with chronic pus drainage that caused severe pain and decreased quality of life. They therefore required surgical intervention. Another important point in extensive-type ORN is the differentiation from tumor recurrence. In extensive-type ORN, an incisional biopsy of surrounding soft tissues should be performed to exclude tumor recurrence before surgical intervention.

Thus, to avoid invasive procedures, early intervention before ORN progresses to such an extent that FDG accumulation spreads to the surrounding soft tissues is important. In this study, there was a 43% incidence of extensive-type ORN at the second visit. It is important that dental oncologists continue routine follow-up in patients who have undergone RT for head and neck malignancy. They must recognize, however, that oral examination and plain radiography alone are not enough to detect latent lesions in some patients. Therefore, we recommend that dental oncologists assess post-treatment follow-up FDG-PET CT for early detection of potential foci in the jaw that may portend ORN, similar to the manner in which radiation oncologists, medical oncologists, and head and neck surgeons evaluate the presence or absence of cancer recurrence or metastasis.

This study showed that the incidence of increased FDG accumulation areas on follow-up PET CT (i.e., 'spot' to 'localized' or 'localized' to 'extensive') was 50% in patients who developed mandibular ORN (Table II). The changes of the PET classification were from spot to localized type in 36% of the areas, and from localized to extensive type in 14%. If spot-type accumulation is detected on follow-up PET CT, conservative treatment should be performed. Localized-type accumulation (PET classification) may be equivalent to intermediate-stage ORN. Jacobson *et al* (3) noted that it is difficult to recommend a definitive treatment course for the intermediate stage of ORN. Importantly, the localized type has the potential to develop into the extensive type (i.e., advanced ORN), which mostly

requires surgical intervention. We have no recommended treatment criteria for localized-type accumulation. Although a randomized controlled trial concluded that HBO is no better than placebo (12), HBO or medication therapy which has been attracting attention (pentoxifylline-tocopherol-clodronate therapy) (13) may be necessary for localized-type accumulation. In this study, one patient with localized-type accumulation underwent surgery. Even though FDG accumulation does not protrude into the surrounding soft tissue, surgical intervention might be better to be selected for patients who have severe pain probably due to inferior alveolar nerve injury. In 50% of patients with ORN in this study, FDG accumulation did not increase (i.e., non-progressive cases). The pathogenetic difference between the progressive and the non-progressive cases still remains elusive. As shown in Fig. 3, FDG accumulation disappeared after healing of mandibular ORN. Follow-up PET CT may be useful not only for the detection of progression of ORN but also the evaluation of existence of stable disease or healing of disease.

There were limitations in this study. First, the study had a small sample size, and it was retrospective. Second, the cutoff value of the SUV could not be defined. A recent study that reported the value of FDG-PET CT for diagnosing implant-related infection of the tibia did not measure the SUV (14). Another study on differentiating between tumor recurrence and ORN concluded that the significant overlap of SUV values in patients with tumor recurrence and ORN renders SUV values relatively impractical in such cases (15). Although determining the cutoff value of SUV for the diagnosis of ORN may be difficult, a further study should be conducted that focuses on the SUV value of not only mandibular ORN and periodontal and apical diseases but also non-specific accumulation after RT for head and neck cancer.

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