Gallium-67 Scintigraphy in Differential Diagnosis of Malignant Tumours from Non-Tumorous Lesions of the Maxilla

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Objective: *To assess the gallium-67 (67Ga) scintigraphy in differential diagnosis of malignant tumours from non-tumorous lesions of the maxilla.*
Methods: *Nineteen patients with malignant tumours (six cases of squamous cell carcinoma and one case of malignant melanoma) and non-tumorous lesions (seven cases of maxillary sinusitis and five cases of postoperative maxillary changes) in the maxilla underwent 67Ga and bone scintigraphy with CT and MRI. The statistical analysis with respect to comparison between imaging features of 67Ga and bone scintigraphy and maxillary lesions was performed with the Pearson's chi-squared test.*
Results: *67Ga scintigraphy for six of the seven patients with malignant tumours in the maxilla was positive (85.7%), 0 of 12 patients with non-tumorous lesions were positive (0%) (P = 0.000). Bone scintigraphy for six out of seven patients with malignant tumours was positive (85.7%), 10 of 12 patients with non-tumorous lesions were positive (83.3%) (P = 0.891).*
Conclusion: *67Ga scintigraphy was useful for detection of malignant tumours in the maxilla. However, bone scintigraphy was not an effective technique for interpretation of malignant tumours, maxillary sinusitis and postoperative change in the maxilla.*
Key words: *carcinoma, gallium radioisotopes, gamma cameras, maxilla*
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Gallium-67 (67Ga) scintigraphy is a useful adjunct tool for differentiation of malignant tumours from benign tumours or inflammatory disease in the oral and maxillofacial region[1]. 67Ga scintigraphy is an effective technique for the evaluation of head and neck squamous cell carcinoma, especially tumour recurrence and distant metastases[2]. Furthermore, 67Ga single-photon emission tomography (SPECT) substantially increases confidence in the diagnosis of head and neck tumours when CT and/or MRI do not permit differentiation between benign and malignant disease[3].

Apart for squamous cell carcinoma, some authors have reported that 67Ga scintigraphy is useful in the differentiation of malignant lymphoma[4], malignant melanoma[5], sarcoidosis[6-8] and other inflammatory diseases[9,10]. However, to the best of our knowledge, 67Ga scintigraphy with multimodal imaging, such as bone scintigraphy, CT and MRI, compared with maxillary malignant tumours and non-tumorous lesions have not been reported in the literature. This study aimed to assess the value of 67Ga scintigraphy in differentiation between malignant tumours and non-tumorous lesions of the maxilla.

Materials and methods

Patient population

The ethics committee of the Nippon Dental University School of Life Dentistry at Niigata approved this retrospective study (ECNG-R-318). After providing written informed consent, 19 patients (12 male, seven female; age range 61 to 88 years, mean age 72.5 years) with maxillary malignant tumours (six squamous cell carcinoma

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and one malignant melanoma) and non-tumorous lesions (seven maxillary sinusitis and five postoperative maxillary change) underwent 67Ga and bone scintigraphy with CT and MRI at our university hospital from August 2013 to February 2017. The histopathological diagnoses of malignant tumours in the maxilla were obtained by surgery or biopsy in all cases.

Image acquisition

CT imaging was performed with a 16-multidetector CT scanner (Aquilion TSX-101A; Toshiba Medical Systems, Otawara, Japan) using the maxillofacial protocol at our hospital: tube voltage, 120 kV; tube current, 150 mAs; field of view, 240 × 240 mm; and rotation time, 0.5 s. The protocol consisted of axial acquisition (0.50 mm) with axial, coronal, and sagittal multiplanar reformation (MPR) images. The patients received contrast enhanced CT (CECT) with non-ionic iodine for head and neck lesions. One non-ionic contrast media was used: Iohexol 300 mgI/mL (Omunipaque 300 Syringe, Daiichi-Sankyo, Tokyo, Japan). Contrast medium was administered as an injection of 100 mL at a rate of 2.0 mL/s (Autoenhance A-250, Nemoto-Kyorindo, Tokyo, Japan). The MR images (1.5 Tesla MR unit; EXCELART Vantage MRT-2003; Toshiba Medical Systems, Otawara, Japan) with a head coil included unenhanced axial T1-[repetition time (TR) 660 ms, echo time (TE) 12 ms], T2-weighted imaging (TR 4000 ms, TE 120 ms). After an injection of contrast medium (gadobutrol; Gadovist 1.0mol/L Syringe, Bayer, Osaka, Japan; 0.1 mL/kg), axial T1-weighted images (TR 660 ms, TE 12 ms) were acquired. 67Ga scintigraphy was obtained with an SNC-5100R (Shimadzu, Kyoto, Japan) and a Scintipack 24000 (Shimadzu) with a 512 × 512 matrix at 72 h after the injection, images were recorded on the computer at 6 min per frame. The radiopharmaceutical used in this study was 67Ga-citrate (Gallium Citrate-Ga67 Injection, FUJIFILM RI Pharma, Tokyo, Japan). Each patient was administered the agent at 185 MBq with a rapid intravenous injection. The stored data were displayed on a screen for analysis. Bone scintigraphy was obtained with an SNC-5100R (Shimadzu) and a Scintipack 24000 (Shimadzu) with a 512 × 512 matrix at 4 h after the injection, images were recorded on the computer at 5 min/frame. The radiopharmaceutical used in this study was 99mTc-labeled hydroxymethylene diphosphonate (99mTc HMDP) (Clear Bone Injection, Nihon Medi-Physics, Tokyo, Japan). Each patient was administered the agent at 740 MBq with a rapid intravenous injection. The stored data were displayed on a screen for analysis.

Image analysis

For patients with maxillary malignant tumours and non-tumorous lesions, imaging features of 67Ga and bone scintigraphy, CT and MRI were independently analysed by two oral and maxillofacial radiologists with more than 20 years of experience. Regarding 67Ga and bone scintigraphy, images of the lesions were classified into two groups[1]: positive – where the intensity of 67Ga and 99mTc HMDP in the lesion area was higher than that in the surrounding normal area – and negative, where the intensity of 67Ga and 99mTc HMDP in the lesion area was the same as in the surrounding normal area. Any discrepancies of the imaging evaluation were resolved by consensus of the two oral and maxillofacial radiologists.

Statistical analysis

The statistical analysis with respect to comparison between imaging features of 67Ga and bone scintigraphy and maxillary lesions was performed with the Pearson's chi-squared test. These analyses were performed with the statistical package IBM SPSS Statistics, version 24 (IBM Japan, Tokyo, Japan). A *P*-value lower than 0.05 was considered as statistically significant.

Results

The imaging features of malignant tumours in the maxilla with 67Ga and bone scintigraphy, CT and MRI are shown in Table 1. Regarding malignant melanoma (Fig 1), axial soft tissue algorithm CT showed mass lesion, and bone tissue algorithm CT indicated an osteolytic lesion with the destruction in the maxilla. 67Ga and bone scintigraphy showed increased uptake. On MRI, axial T1-weighted image (T1WI) revealed homogeneous, low-signal intensity. T2-weighted image (T2WI) revealed heterogeneous, low-signal intensity. Regarding squamous cell carcinoma (Fig 2), axial soft tissue algorithm CT showed mass lesion, and bone tissue algorithm CT indicated an osteolytic lesion with the destruction in the maxilla. 67Ga and bone scintigraphy showed increased uptake. On MRI, axial T1-weighted image (T1WI) revealed homogeneous, low-signal intensity. Post-contrast T1WI showed heterogeneous enhancement.

Table 2 shows the 67Ga and bone scintigraphy of malignant tumours and non-tumorous lesions in the maxilla. 67Ga scintigraphy for six out of seven patients with malignant tumours were positive (85.7%), none out of 12 patients with non-tumorous lesions were positive (0%) ($P = 0.000$). Bone scintigraphy for six out of

Table 1 Imaging features of malignant tumours in the maxilla with gallium-67 and bone scintigraphy, CT and MRI.

Case	Age (years)	Gender	Lesion	Scintigraphy		CT		MRI findings		
				Gallium-67	Bone	Size of tumour	CT findings	T1WI	T2WI	Post-contrast T1WI
1	81	Female	MM	Positive	Positive	40.7 × 17.5 mm	Osteolytic lesion with the destruction did not undergo enhancement examination	Low	Low	Did not undergo
2	62	Male	SCC	Positive	Positive	48.3 × 46.7 mm	Osteolytic lesion with the destruction heterogeneous enhancement	Low	High	Enhancement
3	65	Male	SCC	Positive	Positive	31.5 × 23.8 mm	Osteolytic lesion with the destruction heterogeneous enhancement	Low	High	Enhancement
4	68	Female	SCC	Negative	Negative	9.2 × 6.9 mm	Heterogeneous enhancement without bone destruction	Low	High	Enhancement
5	70	Male	SCC	Positive	Positive	45.5 × 33.9 mm	Osteolytic lesion with the destruction heterogeneous enhancement	Low	High	Enhancement
6	82	Female	SCC	Positive	Positive	39.0 × 31.3 mm	Osteolytic lesion with the destruction heterogeneous enhancement	Low	High	Enhancement
7	88	Female	SCC	Positive	Positive	21.5 x 21.3 mm	osteolytic lesion with the destructive heterogeneous enhancement	Low	High	Did not undergo

MM, malignant melanoma; SCC, squamous cell carcinoma; T1WI, T1-weighted image; T2WI, T2-weighted image.

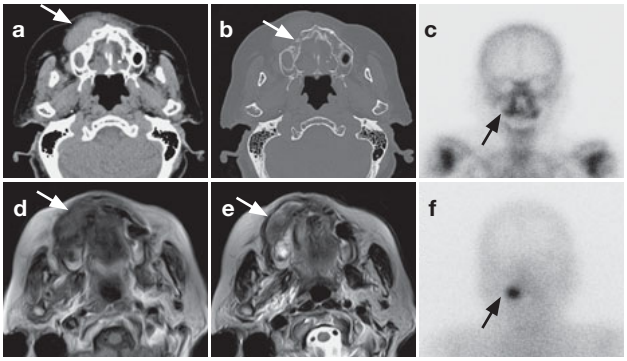

Fig 1 Malignant melanoma of the right side of the maxilla in an 81-year-old female. Axial soft tissue algorithm CT (a) and bone tissue algorithm CT (b) show a mass lesion with the destruction of buccal cortex in the right maxilla (arrow). Bone scintigraphy shows increased uptake (arrow) (d). On MRI, axial T1-weighted image (T1WI) revealed homogeneous, low-signal intensity (arrow) (d). T2-weighted image (T2WI) revealed heterogeneous, low-signal intensity (arrow) (e). 67Ga scintigraphy shows increased uptake in the maxilla (arrow) (f).

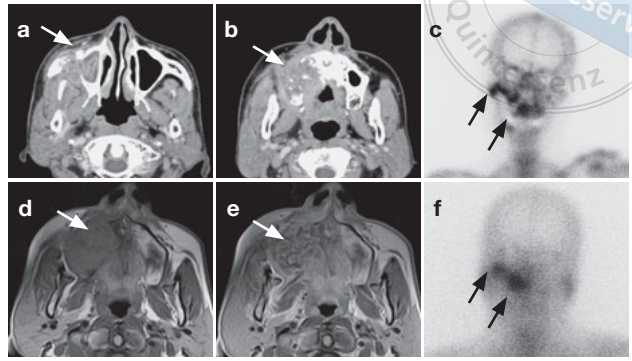

Fig 2 Squamous cell carcinoma of the right side of the maxilla in a 62-year-old male. Post-contrast axial soft tissue algorithm CT (a, b) show a mass lesion with the destruction of the right maxilla (arrow). Bone scintigraphy shows increased uptake (arrows) (c). On MRI, axial T1-weighted image (T1WI) revealed homogeneous, low-signal intensity (arrow) (d). Post-contrast T1WI showed heterogeneous enhancement (arrow) (e). 67Ga scintigraphy shows increased uptake (arrows) (f).

seven patients with malignant tumours was positive (85.7%), 10 of 12 patients with non-tumorous lesions were positive (83.3%) ($P = 0.891$).

Discussion

The 67Ga scintigraphy has been widely used to detect various malignant neoplasms, such as squamous cell carcinoma[1,3], malignant lymphoma[4] and malignant melanoma[5] of the head and neck. In our study, the 67Ga scintigraphy for six out of seven patients with malignant tumours was positive (85.7%), none out of 12 patients with non-tumorous lesions were positive (0%) ($P = 0.000$).

Regarding mechanism of gallium-67 accumulation in tumours, Tsan et al[11] showed that 67Ga was delivered to the tumour through capillaries with increased permeability, and 67Ga binding proteins might also contribute to the accumulation and retention of 67Ga in tumours. We showed that images for one out of six patients who had squamous cell carcinoma were negative (16.7%) in the 67Ga scintigraphy. This one case (Case 4) had small tumours with no bone destruction. We consider that the size of tumours is also a factor of the degree of 67Ga accumulation in lesions.

Regarding malignant melanoma, in our study, the 67Ga scintigraphy for the one patient with malignant melanoma was positive (100%). However, Murata et al[5] showed that the primary site detection rate was 25% using 67Ga scintigraphy of malignant melanoma.

In this study, the 67Ga scintigraphy for none of the 12 patients with non-tumorous lesions (maxillary sinusitis and postoperative maxillary change) in the maxilla was positive (0%). Li et al[1] indicated that 67Ga scintigraphy for two of the 11 patients with chronic inflammatory lesions (1/4 parotitis, 1/5 submaxillaritis and 0/2 lymphadenitis) was positive (18.2%). Tsan et al[11] showed that some tumours may be taken up by inflammatory cells when they are present. Furthermore, Keijsers et al[6] reported imaging the inflammatory activity of sarcoidosis, namely, overall sensitivity to detect active sarcoidosis was 88% for 67Ga imaging.

Ishii et al[7] reported that 67Ga scintigraphy was useful in differentiating between sarcoidosis and IgG4-related disease. Tsai et al[10] suggested that the kidney uptake index from the absolute quantitative renal 67Ga scintigraphy may be a useful parameter for evaluating the disease activity in lupus nephritis. However, the authors consider that 67Ga scintigraphy was more useful for malignant tumours than for inflammatory lesions in the maxilla. Furthermore, we recommend 67Ga and bone scintigraphy with multimodal imaging, such as CT and MRI, for detection of malignant tumours and inflammatory lesions.

The limitation of this study was that the sample was relatively small and not enough types of tumour or inflammatory lesions in the maxilla were included. Therefore, further research is necessary to validate these results.

In conclusion, 67Ga scintigraphy was useful for detection of malignant tumours in the maxilla. However, bone scintigraphy was not an effective technique for interpretation of malignant tumours, maxillary sinusitis and postoperative change in the maxilla.

Table 2 Gallium-67 and bone scintigraphy of malignant tumour and non-tumorous lesions in the maxilla.

Lesions	Number of cases	Gallium-67 scintigraphy (P = 0.000)		Bone scintigraphy (P = 0.891)	
		Positive	Negative	Positive	Negative
Malignant tumour	7	6 (85.7%)	1 (14.3%)	6 (85.7%)	1 (14.3%)
Squamous cell carcinoma	6	5 (83.3%)	1 (16.7%)	5 (83.3%)	1 (16.7%)
Malignant melanoma	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
Non-tumorous lesions	12	0 (0%)	12 (100%)	10 (83.3%)	2 (16.7%)
Maxillary sinusitis	7	0 (0%)	7 (100%)	5 (71.4%)	2 (28.6%)
Postoperative maxillary change	5	0 (0%)	5 (100%)	5 (100%)	0 (0%)

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Conflicts of interest

The authors reported no conflicts of interest related to this study,

Author contribution

Dr Ichiro OGURA designed the study, acquired the case data, and prepared the manuscript; Dr Takaaki ODA revised the manuscript; Dr Mikiko SUE analysed the radiological data; Dr Yoshihiko SASAKI interpreted the radiological data; Dr Kazuhide HAYAMA approved the final revised manuscript.

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