ORIGINAL ARTICLE

UTILITY OF TL-201 SPECT IN CLARIFYING FALSE-POSITIVE FDG-PET FINDINGS DUE TO OSTEORADIONECROSIS IN HEAD AND NECK CANCER

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Accepted 29 December 2009
Published online 26 March 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21377

Abstract: *Background.* This study aimed to determine whether Tl-201 single photon emission CT (SPECT) is potentially useful in differentiating false-positive fluorodeoxyglucose positron emission tomography (FDG-PET) findings caused by osteoradionecrosis (ORN) from recurrent head and neck cancer after radiotherapy.

Methods. Five patients were recruited. Dual-phase FDG-PET and dual-phase Tl-201 SPECT were performed for each patient.

Results. All 5 patients proved to have ORN without recurrent cancer. By visual interpretation, the results were 4 positive versus 1 negative for PET, and 4 negative versus 1 positive for Tl-201 SPECT. The Tl-201 SPECT clarified 3 of the 4 false-positive PETs to be ORN. Dual-phase semiquantitative studies showed decreased standardized uptake value (SUV) over time in 3 of the 4 false-positive PETs and decreased lesion/background ratio over time in the false-positive Tl-201 SPECT.

Conclusion. The Tl-201 SPECT may help clarify suspected false-positive FDG uptake caused by ORN. Dual-phase FDG-PET and dual-phase Tl-201 SPECT may also have some value. © 2010 Wiley Periodicals, Inc. *Head Neck* **32:** 1648–1654, 2010

Keywords: Tl-201; SPECT; FDG-PET; osteoradionecrosis; head and neck cancer

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Contract grant sponsor: (DMR-96-065 and DMR-96-066) in China Medical University Hospital.

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Head and neck carcinomas are frequently occurring tumors, with more than 600,000 new cases each year worldwide.[1] The 5-year survival rates are between 30% and 40% in locally advanced disease.[2,3] Radiotherapy with or without chemotherapy/surgery is a primary treatment modality.[4]

Osteoradionecrosis (ORN) is a serious complication of head and neck radiotherapy with an incidence as high as 37% and is frequently refractory to treatment.[5] Early detection of local recurrence and its differentiation from ORN

after radiotherapy in patients with head and neck cancer are critically important, because management is different for these 2 conditions and delayed diagnosis may deprive patients of the opportunity for cure.[6,7] However, the differentiation between these 2 conditions is clinically difficult. The symptoms of ORN (foul odor, bleeding, exposed necrotic bone, and pain) may mimic those of recurrent tumor at the primary site.[8] Postirradiation changes on CT/MRI scan, eg, edema, fibrosis, or loss of tissue planes, may present a dilemma in differentiating between viable cancer and radiation effects.[9]

Although F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) is effective for the detection of residual/recurrent tumor after radiotherapy in patients with head and neck cancers,[10] false-positive scans caused by ORN have been reported.[11,12] In such cases, an additional scan with a different tumor imaging agent may help differentiate these 2 conditions.[13] The Tl-201 single photon emission CT (SPECT) has been suggested to be effective in detecting recurrent or residual head and neck cancers after radiotherapy in patients with indeterminate CT/MRI findings.[14–16] The aim of this study was to determine whether Tl-201 SPECT is potentially useful in clarifying false-positive FDG-PET findings caused by postirradiation ORN in head and neck cancers.

PATIENTS AND METHODS

Patients. The patients recruited consisted of 2 Taiwanese women and 3 Taiwanese men (age range, 43–54 years; mean age, 49.2 ± 4.9 years). Two patients had nasopharyngeal carcinomas (NPCs), 1 patient had right-side tongue cancer, 1 patient had right-side gum cancer, and 1 patient had left buccal cancer. They were treated in China Medical University Hospital, Taichung, Taiwan. These patients were treated with radiotherapy and were suspected to have recurrent tumor or ORN during clinical follow-up. FDG-PET and Tl-201 SPECT were performed, within a limited time frame, for each patient at 1.2 to 10 years (mean, 5.8 ± 3.6 years) after radiotherapy. Each patient's profile is listed in Table 1.

F-18 Fluorodeoxyglucose-Positron Emission Tomography Imaging. Dual-phase FDG-PET was performed with a PET scanner (Advance Nxi; GE Medical Systems) or a PET/CT scanner (Discovery STE; GE Medical Systems). Each patient was injected intravenously with 370 MBq (10 mCi) of F-18 FDG after fasting for 4 or more hours. The scan was performed twice: an early whole-body scan at 60 minutes after the injection, followed by a delayed scan of the head and neck region at 90 minutes.[17,18]

When using the PET scanner, images were acquired with an axial field of view of 15 cm (35 slices per field of view with a slice thickness of 4.30 mm), in the 2-dimensional mode, 3 minutes per bed position, followed by 1-minute transmission scans at selected bed positions. Images were reconstructed using vendor-provided software and formatted into transaxial, coronal, and sagittal image sets.[17] When using the PET/CT scanner, a non–contrast-enhanced low-dose x-ray CT transmission scan was acquired with the following parameters: 120 kVp, 80 mA; pitch: 1.375; slice thickness: 3.75 mm, before emission data were collected. From the collected emission and transmission data, images were reconstructed using the accelerated maximum likelihood reconstruction and ordered subset expectation maximization method with attenuation correction. Image pixel size was 3.0 mm in a 128 × 128 array.

Tl-201 Single Photon Emission Computed Tomography Imaging. The patient was positioned supine on the imaging table. Dual-phase Tl-201 head and neck SPECT images were acquired with a dual-head gamma camera (GE, Millennium, MG) equipped with low-energy, general purpose collimator, at 10 to 20 minutes and 2 to 3 hours after 92.5 MBq (2.5 mCi) of Tl-201 were

Table 1. Patient profile.

Clinical characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Female	Male	Female	Male
Age, y	43	52	52	45	54
Primary cancer site	Nasopharynx	Nasopharynx	R tongue	R gum	L buccal
Duration after therapy, y	8.7	10	4.8	4.1	1.2

Abbreviations: R, right; L, left.

injected intravenously. Data were collected from 64 projections over 360° (180° for each head) in 64 × 64 matrices, with an acquisition time of 20 seconds per projection using a photon peak window of 70 Kev ± 10%. Reconstruction of the image was performed with attenuation correction using a Butterworth filter, and with a cutoff frequency of 0.35 per centimeter and an order of 5. Then images of 1 pixel thickness were obtained in the sagittal, coronal, and transverse planes.

Image Interpretation. All PET or PET/CT and SPECT images were reviewed by 2 experienced nuclear medicine physicians who had no previous knowledge of the patient's clinical data. Each patient's FDG-PET and Tl-201 SPECT images were examined on the manufacturer's review station (Xeleris; GE Medical System). CT information was only utilized for improved lesion localization. To obtain more accurate localization for PET images, we imported the latest diagnostic CT of individual patients into Xeleris station and produced fusion images using the optional image registration program. For SPECT images, we also used the CT information of PET/CT or the imported latest diagnostic CT of individual patients to produce fusion images in the Xeleris station by using the image registration program.

To facilitate the visual interpretation of both PET or PET/CT and SPECT images, a 4-point visual scale was used: (1) no abnormal uptake; (2) diffuse uptake with intensity slightly higher than that of the surrounding tissue; (3) focal uptake with intensity greater than that of background tissue; and (4) intense uptake with intensity significantly greater than that of background tissue. The scan was considered negative if the visual scale was graded 1 or 2, and positive if it was graded 3 or 4. Disagreement on the imaging results, according to the visual scale, by the reviewers for each area in question was resolved by consensus. For each suspected lesion, the lesion's standardized uptake value (SUV) on FDG-PET and the lesion/background ratio on Tl-201 SPECT were recorded.

The reference standard was the subsequent results of histopathology or at least 6 months of clinical follow-up.

Semiquantitative Analysis. For FDG-PET, the dual-phase maximum SUV (SUVmax) within the region of interest (ROI) was used in the analysis. The retention index was defined as follows:

$$\frac{\text{Maximal SUV on delayed images} - \text{Maximal SUV on early images}}{\text{Maximal SUV on early images}}\ \%$$

For Tl-201 SPECT, the radioactivity count for a lesion was obtained by placing the ROI around the lesion identified from visual analysis. The background count was obtained by placing the ROI in a homogenous region adjacent to the lesion of interest in the same axial image slice. To minimize partial volume effects, the maximum count within an ROI was used. The lesion/background ratio was defined as the radioactivity count of the lesion divided by that of its background.

Statistical Analysis. All results are expressed as mean ± SD.

RESULTS

Patients. The 5 patients with suspicious recurrent tumors or ORN in this study were followed up after their FDG-PET and Tl-201 SPECT scans for at least 6 months. Histopathologic results were available in 3 of them. According to the results of histopathology or more than 6-month clinical follow-up, all of these 5 patients proved to have ORN without recurrent cancer.

Visual Interpretation for Fluorodeoxyglucose-Positron Emission Tomography and Tl-201 Single Photon Emission Computed Tomography. The results of FDG-PET and Tl-201 SPECT analyses for the 5 patients with suspicious recurrent tumors or ORN are listed in Table 2. Only 1 (20%) FDG-PET scan was negative. In contrast, 4 (80%) of the 5 Tl-201 SPECT scans were negative. One patient had negative scans on both FDG-PET and Tl-201 SPECT (Figure 1); another patient had positive scans on both FDG-PET and Tl-201 SPECT (Figure 2). Note that the 3 discordant pairs were all negative by Tl-201 SPECT but positive by FDG-PET.

All 5 patients suspected clinically to have ORN or recurrent cancer proved to have ORN without recurrent cancer. There were 4 patients who had positive FDG-PET scans. None of them developed recurrent tumors. Three of the 4 patients with false-positive FDG-PET findings had negative Tl-201 SPECT scans (Figure 3).

Table 2. Results.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Clinical outcome	ORN by patho	ORN by F/U	ORN by F/U	ORN by patho	ORN by patho
Image results					
FDG-PET					
Visual scale (E→D)	4→4	3→3	1→1	3→3	4→4
Visual result	+	+	−	+	+
Dual-phase SUVs (E→D)	10.4→8.7	3.3→2.9		3.4→3.2	5.7→5.8
Retention index	−16.24%	−10.63%		−5.94%	2.65%
Tl-201 SPECT					
Visual scale (E→D)	2→2	1→1	1→1	3→3	1→1
Visual result	−	−	−	+	−
Dual-phase L/B ratio (E→D)				1.4→1.2	

Abbreviations: ORN, osteoradionecrosis; patho, pathology; F/U, follow-up; FDG-PET, fluorodeoxyglucose-positron emission tomography; E, early phase; D, delay phase; SUVs, standardized uptake values; SPECT, single photon emission computed tomography; L/B, lesion/background.

Dual-phase Standardized Uptake Value Maximum for Fluorodeoxyglucose-Positron Emission Tomography Uptake. Further semiquantitative analysis by dual-phase SUVmax was performed for the 4 false-positive FDG-PET scans. The average early phase SUVmax was 5.7 ± 1.7 and delayed phase SUVmax was 5.2 ± 1.4. The average retention index was −7.5% ± 8.0%. Three of the 4 false-positive FDG-PET scans showed decreased FDG uptake over time.

Dual-phase Lesion/Background Ratios for Tl-201 Single Photon Emission Computed Tomography Uptake. Semiquatitation of dual-phase lesion/background ratio showed decreased lesion/background ratio in the solo false-positive Tl-201 SPECT scan. The early phase lesion/background ratio was 1.2 and the delayed phase lesion/background ratio was 1.1.

DISCUSSION

ORN is one of the severe complications of radiotherapy. Now it is thought that the primary causes include radiation, trauma, and inflammation. The hypovascular-hypoxic-hypocellular condition after radiation causes breakdown of local tissue, formation of sequestra, and bone exposure. The symptoms of ORN and recurrent tumor are similar. It has been reported that 7 of

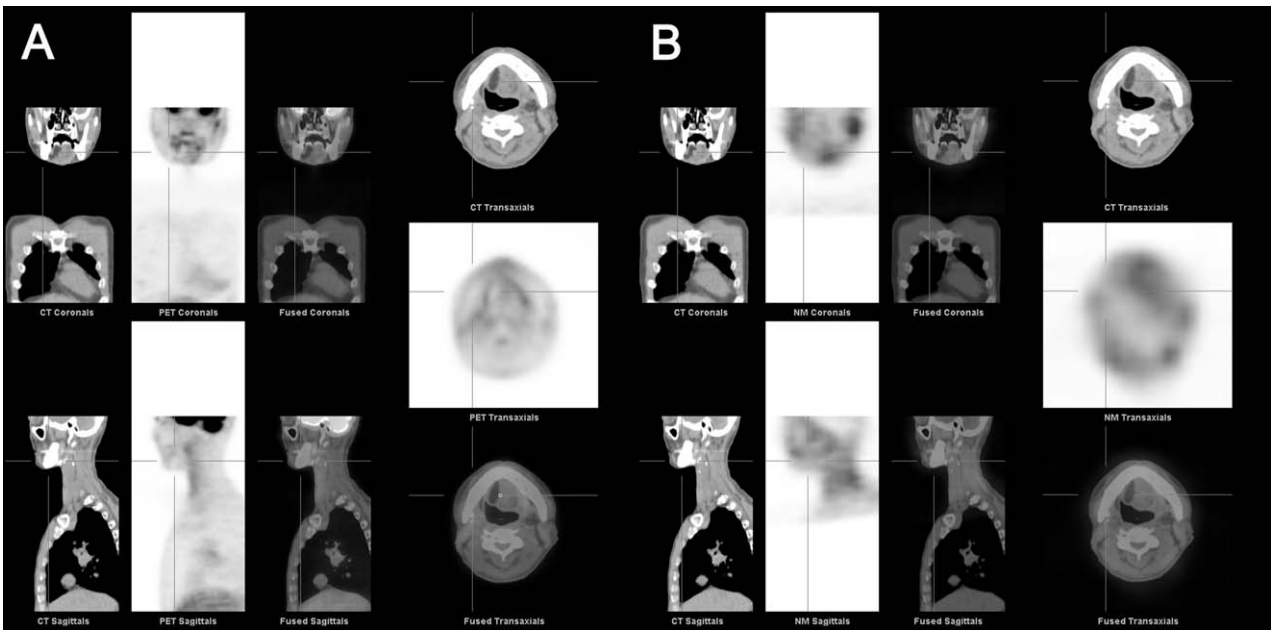

FIGURE 1. (**A**) FDG PET/CT for the right mandibular region. (**B**) Tl-201 SPECT and CT fused image for the right mandibular region. An example of negative scans in both FDG PET and Tl-201 SPECT scans in the right mandibular region.

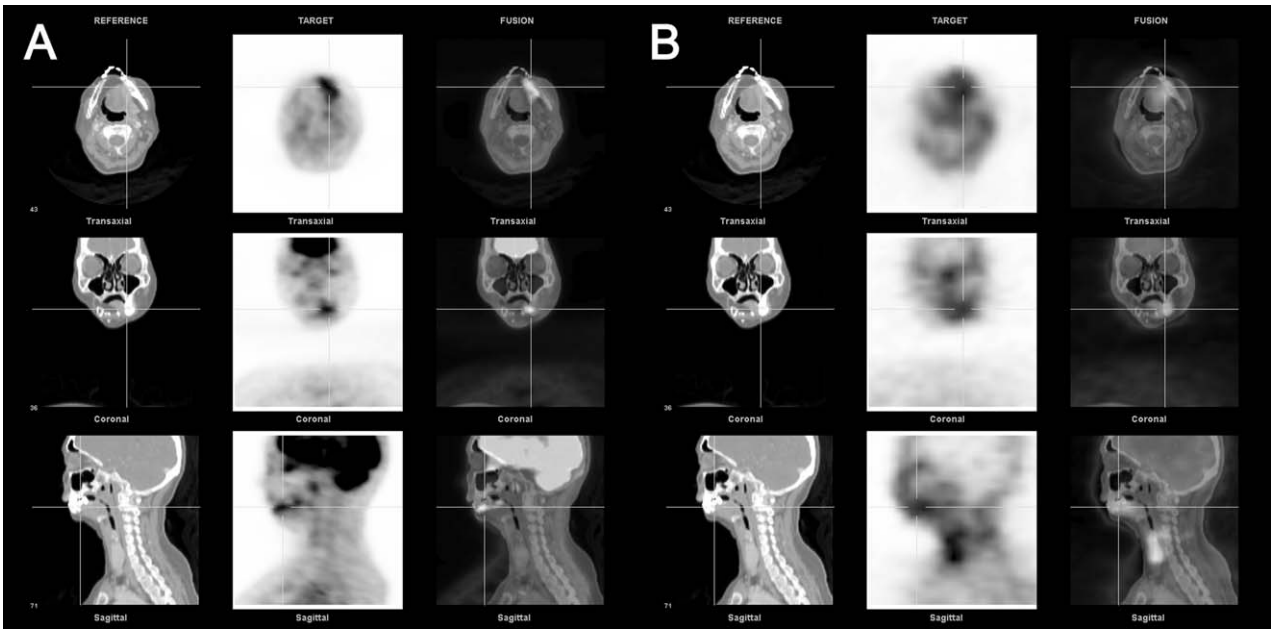

FIGURE 2. (**A**) CT (left), FDG PET (middle) and fused images (right) of the left mandibular region. (**B**) CT (left), Tl-201 SPECT (middle) and fused images (right) of the left mandibular region. An example of both FDG PET and Tl-201 SPECT false-positive scans in the left mandibular region.

33 patients (21%) who had ORN in the head and neck region had recurrent cancer, and that an average of 2.4 sequestrectomy procedures were carried out before reaching the final correct diagnosis of recurrent cancer.[19] Early differentiation between local recurrence and ORN is important, because management is different for these conditions. However, differentiation between these 2 conditions is difficult clinically.

The usefulness of FDG-PET in the detection of residual/recurrent tumor after radiotherapy in patients with head and neck cancer had been

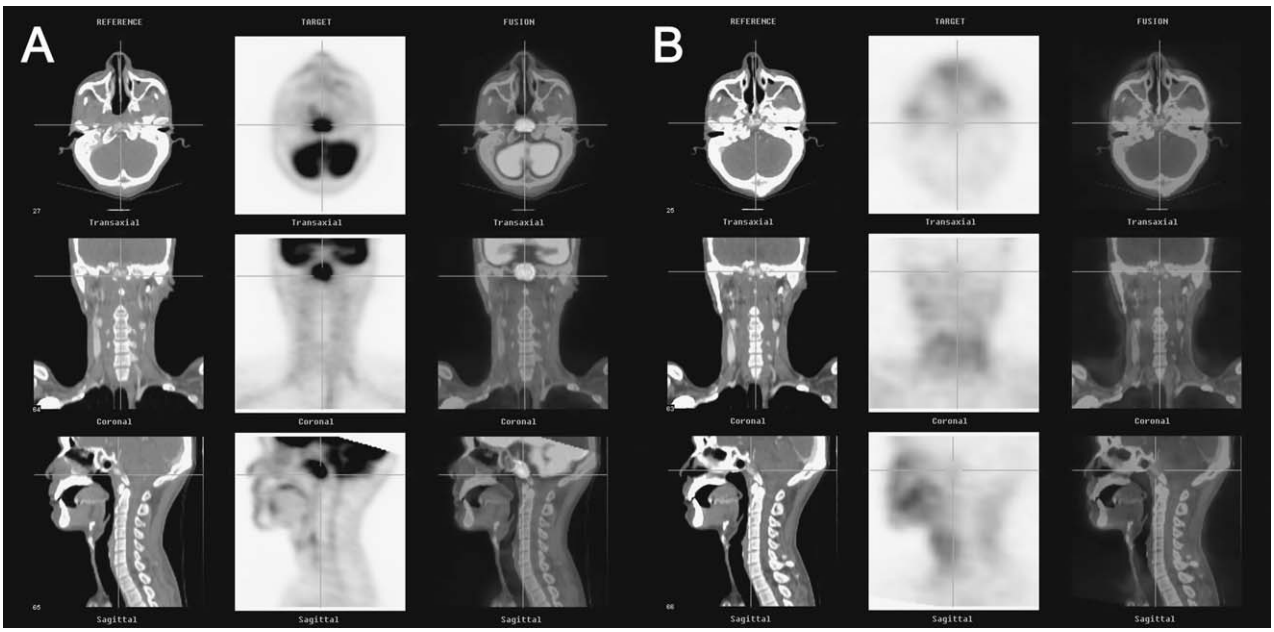

FIGURE 3. (**A**) CT (left), FDG PET (middle) and fused images (right) of the nasopharyngeal region. (**B**) CT (left), Tl-201 SPECT (middle) and fused images (right) of the nasopharyngeal region. An example of FDG PET false-positive but Tl-201 SPECT true-negative ORN at nasopharyngeal region.

established. FDG-PET can identify viable tumor on the basis of higher glycolytic rates in neoplasms than in necrotic or reactive tissues. It is regarded as a better tool in postirradiation follow-up, especially for those who have inconclusive CT/MRI findings.[20] However, false-positive FDG-PET results caused by ORN have been reported.[11,12]

Tl-201 is a potassium analog, and tumor uptake of Tl-201 is dependent on blood flow and on the sodium-potassium adenosine triphosphatase (ATPase) system. Other factors contributing to its uptake include tumor viability, ion cotransport system, calcium ion channel exchange, vascular immaturity with leakage, and increased cell membrane permeability.[21] Due to the different tumor uptake mechanisms, we examined the potential usefulness of Tl-201 SPECT in clarifying false-positive FDG-PET findings caused by ORN in patients with head and neck cancer.

There were 5 patients included in our study. According to pathology and clinical follow-up, all 5 patients were diagnosed to have ORN without recurrent cancer. Using visual interpretation, the false-positive rate of FDG-PET is higher than Tl-201 SPECT (80% in FDG-PET and 20% in Tl-201 SPECT). Tl-201 SPECT was correctly negative in 3 of the 4 false-positives by FDG-PET.

ORN was defined as the slow-healing, radiation-induced ischemic necrosis of bone associated with soft tissue necrosis occurring in the absence of primary tumor necrosis, recurrence, or metastasis.[6] FDG accumulation is not specific to tumors. Increased uptake of FDG at suspected sites of inflammation and infection is used to detect a variety of inflammatory and infectious disorders.[22] Therefore, the possible mechanism for false-positive FDG-PET findings in cases of ORN may be due to inflammatory process. Tl-201 uptake is not directly related to cell glycolysis. Tl-201 accumulates predominately within viable tumor tissue, less within normal or inflammatory tissues and least in necrotic or nonactive tissues.[23] This may contribute to the potential usefulness of Tl-201 in clarifying false-positive FDG-PET scans caused by ORN in patients with head and neck cancer. However, severe inflammation/infection combined with ORN still has the possibility to cause moderately increased Tl-201 uptake in the region. This may be the possible reason for the false-positive Tl-201 SPECT in patient 4.

There is increased interest in using dual-phase studies of both FDG-PET and Tl-201 SPECT in differentiating malignant from benign processes. It seems that lesions with increased SUVs of FDG over time are likely to be caused by malignancy. In contrast, lesions with decreased SUVs over time are likely to have a benign etiology.[22] Similarly, in malignant lesions, Tl-201 SPECT shows slow washout or increased retention on the delayed scan. Indeed, decreased FDG uptake over time was observed in 3 of 4 false-positive FDG-PET scans in our study. Decreased lesion/background ratio was observed in the solo false-positive Tl-201 SPECT scan in our study. Our preliminary data show that dual time imaging seems to be useful in distinguishing recurrent tumor from ORN.

FDG-PET is still the preferred choice in clinically inconclusive cases suspected to have recurrent head and neck tumor or ORN after radiotherapy. Due to its much better spatial resolution than Tl-201 SPECT, FDG-PET can easily detect not only local recurrence but also distant metastases. Despite its seemingly lower positive predictive value, it was shown to have high negative predictive value in previous reports[24] and in our study. If a false-positive FDG-PET scan is suspected, dual-phase FDG-PET or an additional Tl-201 SPECT may be helpful.

The number of cases in this study was too small, and all of the included cases turned out to have ORN. There were no recurrent tumors in the patients included in this study. Further research with a larger number of cases and patients with recurrent tumors are needed to confirm the results of our study. However, according to previous reports, recurrent patients are both Tl-201 and FDG-PET positive. Combining previous reports with our preliminary study that ORN patients are more frequently true-negative with Tl-201 SPECT than FDG-PET, Tl-201 SPECT seems to have its clinical value in clarifying suspected false-positive FDG-PET caused by ORN in patients with head and neck cancer. The other limitation is the lack of the optimal cutoff value of retention index for dual-phase FDG-PET imaging, which needs to be determined in future studies.

CONCLUSION

Our results suggest that in clinically inconclusive cases of suspected recurrent head and neck tumor or ORN after radiotherapy, false-positive FDG uptake caused by ORN is not uncommon.

Adding a Tl-201 SPECT may help differentiate false-positive FDG uptake caused by ORN by visual interpretation. By semiquantitative analysis, dual-phase FDG-PET and dual-phase Tl-201 SPECT may also have some value in distinguishing recurrent tumor from ORN.

Acknowledgments. We want to thank the grant support of the study projects (DMR-96-065 and DMR-96-066) in China Medical University Hospital.

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