Annals of Nuclear Medicine Vol. 17, No. 6, 475–480, 2003

Does supplementation of CT and MRI with gallium-67 SPECT improve the differentiation between benign and malignant tumors of the head and neck?

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The objective of our study is to determine whether ^{67}Ga SPECT can supplement CT and/or MRI diagnostic information by visual comparison of the two separate data sets in patients with head and neck tumors. ***Methods:*** A total of 50 patients with head and neck tumors (benign: 19, malignant: 31) were entered in the study. Three board-certified radiologists who had practical experience in interpreting both head and neck CT/MRI and ^{67}Ga SPECT images, participated as readers. All of the CT and/or MR images of each patient were shown to each reader first, who after they had finished interpreting them were shown the ^{67}Ga SPECT images. They were asked to score each image on a 7-point scale for the likelihood of the presence or absence of malignancy. Histological or cytological evaluation was done in all cases, and the radiologic studies were correlated with these findings. ***Results:*** Improvement of all three readers' performance was from 70.7% to 83.3% in the mean accuracy and from 0.790 to 0.921 in the mean Az value (p = 0.033, 0.163, 0.105 in the Az values) after they were shown the ^{67}Ga SPECT images. ***Conclusions:*** ^{67}Ga SPECT should substantially increase confidence in the diagnosis of head and neck tumors when CT and/or MRI do not permit differentiation between benign and malignant disease.

Key words: ^{67}Ga SPECT, head and neck neoplasm, magnetic resonance imaging, computed tomography

INTRODUCTION

HIGH-RESOLUTION computed tomography (CT) and magnetic resonance imaging (MRI) have become crucial tools for evaluating head and neck neoplasms, because they show precise anatomical details that cannot be visualized with other diagnostic modalities. Although many imaging modalities, such as radiography, ultrasonography (US), angiography, and radionuclide imaging are available, CT and MRI have been established as reliable standards for the diagnosis of head and neck tumors. CT and MRI frequently allow the characterization of vascularity and internal structures of neck masses, but they do not always permit precise diagnosis of neck masses or differentiation between benign and malignant neoplasms.

^{67}Ga citrate has been widely used to detect various malignant neoplasms,[1] and ^{67}Ga scintigraphy, in particular, now plays an important role in the staging and detection of primary and recurrent lymphomas.[2–4] Several investigators have reported that gallium whole-body scintigraphy and single-photon emission tomography (SPECT) are effective techniques for evaluating squamous cell carcinoma of the head and neck.[5,6] Although ^{67}Ga SPECT has poorer spatial resolution than CT or MRI, it often provides information on head and neck tumors different from that obtained by CT or MRI. Because of this, it seems that ^{67}Ga SPECT improves the diagnosis of head and neck tumors, if simultaneously

Received March 3, 2003, revision accepted June 10, 2003.
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Table 1 The final diagnoses of a total of 50 patients with head and neck tumors

Squamous cell carcinoma		21
tongue	9	
larynx	4	
maxillary sinus	2	
hypopharynx	2	
lymph node metastasis from tongue	2	
mouth floor	1	
ear skin	1	
Lymph node		12
non-Hodgkin's lymphoma	6	
class 2 cytology adenopathy	5	
granulomatous inflammation of the neck	1	
Parotid gland tumor		9
Warthin's tumor	4	
adenocarcinoma	2	
pleomorphic adenoma	2	
lymphangioma	1	
Submandibular gland tumor		3
adenoid cystic carcinoma	1	
adenocarcinoma	1	
mucous cyst	1	
Necrotic tissue after chemo-radiotherapy for tongue cancer		2
Radicular cyst of the mandibula		1
Odondogenic keratocyst of the maxillary sinus		1
Sublingual cyst (ranula)		1
Total		50

Table 2 Sensitivity, specificity, and accuracy for the diagnosis of head and neck malignant neoplasms by the two strategies: CT and/or MRI versus CT and/or MRI plus ^{67}Ga SPECT

Radiologist A	Sensitivity	Specificity	Accuracy
CT/MRI	20/31 (64%)	12/19 (63%)	32/50 (64%)
CT/MRI plus SPECT	25/31 (81%)	13/19 (68%)	38/50 (76%)
Radiologist B	**Sensitivity**	**Specificity**	**Accuracy**
CT/MRI	26/31 (84%)	9/19 (47%)	35/50 (70%)
CT/MRI plus SPECT	29/31 (94%)	13/19 (68%)	42/50 (84%)
Radiologist C	**Specificity**	**Sensitivity**	**Accuracy**
CT/MRI	26/31 (84%)	13/19 (68%)	39/50 (78%)
CT/MRI plus SPECT	29/31 (94%)	16/19 (84%)	45/50 (90%)

interpreted and carefully correlated with the CT and/or MRI images. No investigators, however, have documented the diagnostic impact of ^{67}Ga SPECT by visual comparison of the two separate data sets in patients with head and neck tumors.

The objective of this study was to assess whether ^{67}Ga SPECT can provide more diagnostic information than CT and/or MRI alone in patients with head and neck tumors. We evaluated the differences between interpretation of CT and/or MRI images and CT and/or MRI plus ^{67}Ga SPECT images by board-certified radiologists in the diagnosis of head and neck malignant tumors.

PATIENTS AND METHODS

Patient selection

A total of 50 patients with head and neck tumors (benign: 19, malignant: 31) between August 2001 and May 2002 were entered in the study. They consisted of 17 females and 33 males who ranged in age from 18 to 92 years (mean 60.7 years). All patients underwent ^{67}Ga scintigraphy, including head and neck planar and SPECT imaging, within 1 week of plain and contrast-enhanced CT and/or MRI. All primary tumors and lymphadenopathy were histologically (n = 45) or cytologically (n = 5) confirmed after the imaging examinations. The range of pathologies was diverse. The final diagnoses are shown on Table 1.

Twenty-three head and neck malignant tumors were classified in accordance with the classification of the American Joint Committee on Cancer.[7] pT1, pT2, pT3, and pT4 were found in 12, 7, 2, and 2 patients respectively, and pN0, pN1, pN2 in 10, 2, and 11 patients respectively. A 55-year-old man with an 8 cm × 6 cm Warthin's tumor had the largest tumor in the series. The smallest lesion was a lymph node metastasis, 1 cm × 1 cm in size, in a 65-year-old man who had undergone surgery for tongue cancer.

CT and MRI

The CT images with contrast consisted of contiguous sections (5-mm thick, 16-cm field of view, and 512 × 512 matrix) obtained from the skull base to the thoracic inlet with a Siemens Somatom plus-s CT scanner (Erlangen, Germany).

The MR images (T1- and T2-weighted pulse sequences with transaxial and coronal slices of 3- to 5-mm thick, field of view 200–250 cm, 256 × 256 matrix) were obtained with a 1.5-T scanner (GE Signa Advantage Version 4.7, Milwaukee, Wis) before and after intravenous (iv) administration of gadolinium diethylenetriaminepentaacetic acid. Additional coronal images with fat suppression were obtained in cases in which the abnormality could not be reliably assessed by the conventional method.

^{67}Ga imaging

Head and neck planar and SPECT scans were obtained in all patients 48 hours after iv injection of 111 MBq (3 mCi) ^{67}Ga citrate. All images were obtained with a two-headed camera (GCA-72000 A/DI, Toshiba, Tokyo), equipped with middle-energy collimators. Three energy analyzers were used for acquisition, with settings of 93 keV, 184

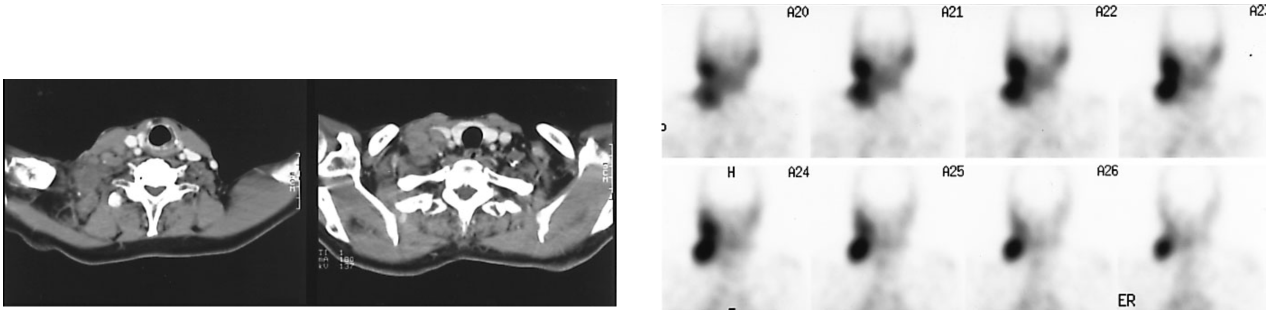

Fig. 1 A 76-year-old male with non-Hodgkin's lymphoma. Axial contrast-enhanced CT image at the level of the thyroid gland showing multiple adenopathy in the right neck (*left, middle*). Intense tracer uptake in the right neck is seen in this coronal ^{67}Ga SPECT image (*right*). Confidence in the diagnosis of malignancy by all three readers was improved by adding ^{67}Ga SPECT (from probably malignant to definitely malignant, indeterminate to probably malignant, and possibly malignant to definitely malignant).

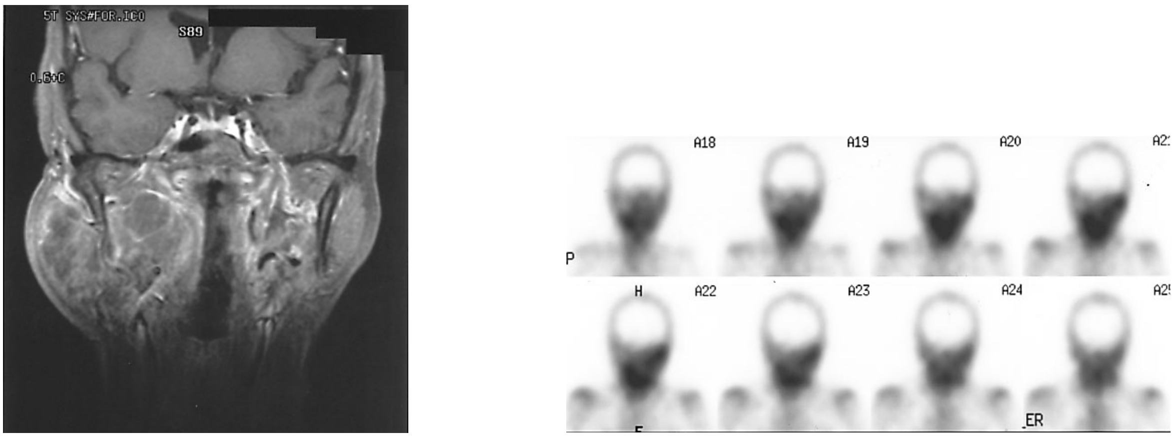

Fig. 2 A 54-year-old female who had lymphangioma with no evidence of malignancy on pathological report. This coronal contrast-enhanced, fat-suppression MR image through the parotids shows a heterogeneously enhanced large mass in the right neck (*left*). Coronal ^{67}Ga SPECT reveals little or no uptake by the lesion (*right*). Confidence in the diagnosis of malignancy by two of the three readers was improved by adding ^{67}Ga SPECT (possibly benign to probably benign, probably malignant to possibly benign).

keV, and 296 keV, with a 20% window. Sixty views (2 × 30; 6°/step), each registered over 30 s, were recorded using a 128 × 128 matrix corresponding to a pixel dimension of 3.4 × 3.4 mm. Transaxial and coronal tomograms were reconstructed using filtered back projection (Butterworth filter; order 8, cutoff 0.12 cycles/pixel). Slice thickness was approximately 3.4 mm.

Analysis

Three board-certified radiologists with practical experience in interpreting CT/MRI and ^{67}Ga SPECT head and neck images, participated as readers. All CT and/or MR images of each patient were shown to each reader first, and when interpretation of the CT and/or MR images had been completed they were shown the ^{67}Ga planar and SPECT images. The 50 sets of CT and/or MR images presented to the readers were as follows: CT images only were 28 sets, MR images only 10 sets, and both CT and MRI images 12 sets. No clinical information except the patients' age and sex was supplied, and the readers were not informed of the proportion of malignant cases. The images were read under similar light intensity, dim enough to facilitate interpretation.

The images were scored on a 7-point scale according to the likelihood of the tumor being malignant, ranging from "definitely benign" to "definitely malignant" on the basis of the readers' confidence in determining the benignancy or malignancy of the tumors imaged (1 = definitely benign lesion, 2 = probably benign lesion, 3 = possibly benign lesion, 4 = equivocal or indeterminate lesion, 5 = possibly malignant lesion, 6 = probably malignant lesion, 7 = definitely malignant lesion). The time allowed for interpretation was unrestricted. Diagnosis of malignancy was made when the readers marked a point scale of 5 or

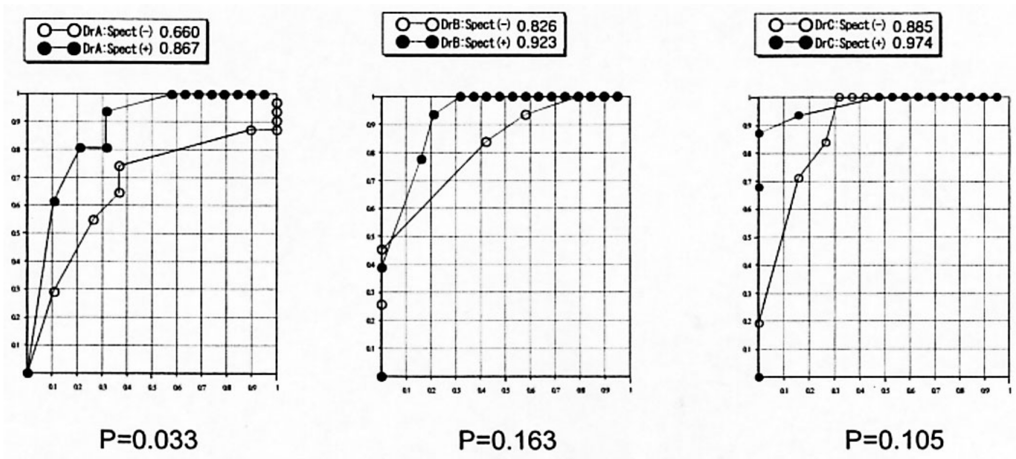

Fig. 3 ROC curves (areas under the ROC curves) of the three readers (Radiologists A: *left*, B: *middle*, C: *right*) for the two strategies: CT and/or MRI (○) and CT and/or MRI plus ^{67}Ga SPECT (●).

greater, and that of benignancy a point scale of 3 or less.

The readers' diagnostic performance was assessed for sensitivity, specificity, and accuracy. Receiver operating characteristic (ROC) analysis of the diagnosis of malignancy was performed for the three readers to compare CT and/or MRI with the CT and/or MRI plus ^{67}Ga SPECT readings, and the Az values (areas under ROC curves) were calculated for the three readers' performances using the Hanley's method.[8] Diagnostic criteria for benignancy or malignancy were left to the readers' discretion. As a rule, however, a focal uptake less than that of the salivary gland is probably benign, while a focal uptake greater than that of the salivary gland is probably a malignant or acute inflammatory disease.

RESULTS

The sensitivity, specificity, and accuracy of diagnosis of malignant neoplasms by the two strategies of CT and/or MRI and CT and/or MRI plus ^{67}Ga SPECT are shown in Table 2. Both sensitivity and specificity of all of the three readers' diagnostic performance were improved when the ^{67}Ga SPECT images were added to the CT and/or MR images (Figs. 1, 2). The accuracy of radiologist A's interpretation improved from 64% to 76%, the accuracy of radiologist B's interpretation from 70% to 84%, and the accuracy of radiologist C's interpretation from 78% to 90%. False positive rates were unchanged or improved from 32% to 32% in radiologist A, from 42% to 21% in radiologist B, and from 26% to 16% in radiologist C. There were three false positive new cases (5.3%, 3/57) when ^{67}Ga SPECT readings were added in the overall three readers' performance. The three false positive new cases were as follows: necrotic tissue after chemo-radiotherapy for tongue cancer, granulomatous inflammation of the neck, and pleomorphic adenoma in one patient each. False negative rates were improved or declined from 23% to 6.5% in radiologist A, from 6.5% to 0% in radiologist B, and from 0% to 6.5% in radiologist C. There were four false negative new cases (4.3%, 4/93) when ^{67}Ga SPECT readings were added in the overall three readers' performance. The four false negative new cases were small foci less than 1.8 cm in diameter, such as hypopharynx cancers, primary tongue cancer, and lymph node metastasis from tongue cancer in one patient each.

The Az values of the CT and/or MRI readings of the three readers were 0.660, 0.826, 0.885 (mean Az value: 0.790), as opposed to 0.867, 0.923, 0.974 (mean Az value: 0.921) for the CT and/or MRI plus ^{67}Ga SPECT readings. The Az values of all 3 readers' performances improved (from a mean Az of 0.790 to 0.921) when ^{67}Ga SPECT images were added to the CT and/or MR images (Fig. 3). The statistical difference was as follows: $p = 0.033$ in radiologist A, $p = 0.163$ in radiologist B, $p = 0.105$ in radiologist C.

DISCUSSION

The clinical use of CT and MRI has had a great positive impact on the management of head and neck patients, and many head and neck tumor patients have been saved as a result of the prompt and accurate diagnosis provided by CT or MRI. MRI or CT is currently indispensable for planning initial management and treatment as well as for monitoring patients.[9–11]

However, these morphological modalities are limited in terms of the precise tissue diagnosis of head and neck tumors, their viability, and estimation of therapeutic effect. The objective of MRI or CT is not to attempt to make a tissue diagnosis, but to delineate tumor margins and the extent of lesions, and to stage the tumor by the TNM system. Images of the head and neck region often exhibit direct artifacts produced by prosthetic appliances, such as dental alloys, amalgam, and swallowing movements, which degrade the image quality of MRI and CT.

Positron emission tomography (PET) with 2-[^{18}F]fluoro-

2-deoxy-D-glucose (FDG PET), on the other hand, has the advantage of detecting tumor viability.[12] FDG PET images are superior to ^{67}Ga SPECT images principally because the former have a lower background and higher activity in head and neck tumors than the latter. In addition to improved contrast resolution PET offers better spatial resolution. There have been reports that FDG PET is more accurate in the diagnosis of recurrent squamous cell cancer of the head and neck than CT or MRI,[13] but FDG PET is not widely available.

The key issue in ^{67}Ga head and neck SPECT lies mostly in the differentiation between benign and malignant disease, including primary, residual, and recurrent malignant neoplasms, in the head and neck region. Benign disease includes inflammatory lesions, post-treatment changes in malignant tumors, and benign tumors, such as pleomorphic adenoma, Warthin's tumor.

In our series, the ^{67}Ga SPECT image analysis was binary, cataloging positive versus negative. The accuracy and Az values for discrimination between benign and malignant disease improved after adding ^{67}Ga head and neck SPECT images to CT and/or MR images, and the Az values of all three readers increased. Thus, correlative reading of ^{67}Ga SPECT with CT and/or MR appears to be an accurate method for discriminating between benign and malignant disease, while ^{67}Ga SPECT is not sufficiently sensitive to be employed as an independent tool for differential diagnosis.

Interpretation of SPECT functional images is improved when they are co-registered with anatomic images.[14,15] Fusion images, such as SPECT/CT, SPECT/MRI, PET/CT, PET/MRI, are expected to provide additional diagnostic information as compared to the sum of their individual contributions. Fusion images, however, have several drawbacks in clinical settings. It is difficult to routinely obtain them. Either manually or automatically, visual co-registration may be time-consuming or unreliable. Other technical problems of fusion images can be numerated including position differences, respiratory movement, and anatomical changes induced by surgery or radiotherapy.

Recently developed gamma camera-mounted anatomical X-ray tomography provides high-resolution, high-contrast, cross-sectional X-ray transmission images that facilitate the anatomical location of radionuclide accumulation.[16] This brand-new machine has just been developed and is also associated with some problems such as dual-trained technologists, low throughput CT, ownership, and elastic deformation to partly account for change in body shape.

^{67}Ga SPECT is not a new or state-of-art imaging modality, nor a cancer-specific test. Acute inflammatory foci and granulomas such as sarcoidosis, avidly incorporate ^{67}Ga.[16] The exact mechanism of ^{67}Ga uptake by malignant tumors is unknown. Some investigators believe that there are tumor cell-associated transferrin receptors that bind the circulating ^{67}Ga transferrin complexes to the tumor cell.[1] Close correlation of ^{67}Ga SPECT images with the CT and/or MRI images, however, seems to improve the diagnostic confidence of readers who have ample experience with diagnostic radiology and full knowledge of ^{67}Ga imaging characteristics. Thus, if ^{67}Ga SPECT were integrated with anatomic imaging it would probably improve the diagnosis of head and neck tumors, which are difficult to diagnose by anatomical imaging modalities alone. This study focused on the differential diagnosis between benign and malignant lesions, and so ^{67}Ga SPECT may not be indicated for TNM staging.

It might be possible to replace other diagnostic modalities with ^{67}Ga SPECT or use it to eliminate unnecessary biopsies. This would be very important in the management of patients with salivary gland tumors, because open biopsy is contraindicated in such patients due to the risk of spillage and local implantation of tumor cells.[18] Most surgeons will perform fine-needle aspiration (FNA) biopsy on a palpable mass, although FNA has a low level of accuracy.[19] Therefore, the great utility of a functional study is that it can be done on patients who have had prior surgery and/or radiotherapy, which have made their necks difficult to evaluate clinically.

In our series, ^{67}Ga SPECT was chosen over ^{201}Tl or FDG SPECT. Approximately 90% of head and neck malignancies are squamous cell carcinomas, which incorporate ^{67}Ga more avidly than ^{201}Tl.[20,21] Some investigators state that ^{201}Tl is useful in the evaluation of malignant tumors in the head and neck region.[6,22–24] FDG is not routinely available and is costly in Japan, although FDG PET is currently the best functional test we have for evaluating possible head and neck malignancies. We believe that ^{67}Ga remains useful as a head and neck SPECT imaging agent in the clinical setting.

CONCLUSIONS

Closely correlated interpretation of ^{67}Ga SPECT and CT and/or MRI images of head and neck tumors substantially increases diagnostic confidence of the degree of malignancy. ^{67}Ga SPECT may have a continuing clinical role in the age of metabolic imaging, such as by FDG PET, or even in the coming molecular imaging age. ^{67}Ga SPECT can potentially serve as a low cost alternative to positron emission imaging.

ACKNOWLEDGMENTS

We thank Ms. Kimiko Namekawa, Mr. Yoshio Hohshito, and Mr. Tadaharu Kojima for their invaluable help in the preparation of the manuscript.

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