

Comparison of ^{201}Tl -chloride SPECT with $^{99\text{m}}\text{Tc}$ -MIBI SPECT in the depiction of malignant head and neck tumors

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Objective: Comparison of ^{201}Tl chloride SPECT (TI-SPECT) with $^{99\text{m}}\text{Tc}$ -MIBI SPECT (MIBI-SPECT) in the depiction of malignant head and neck tumors was prospectively studied. **Methods:** Forty-one patients with various tumors of the head and neck were included in this prospective study. Histologically, 36 patients had squamous cell carcinomas, 3 undifferentiated carcinomas, 1 transitional cell carcinoma, and 1 MALT lymphoma. All patients underwent a simultaneous dual-isotope SPECT of the head and neck with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -MIBI. Dual-isotope SPECT for early ($n = 41$) and delayed acquisition ($n = 21$) was performed. Qualitatively, 3 observers evaluated both TI-SPECT and MIBI-SPECT individually. The interpretation criteria were graded as grade 1 (no abnormal increased uptake) to 5 (definitely increased uptake of a degree equal to or greater than that of normal salivary gland). Statistical analysis of the comparison of TI-SPECT and MIBI-SPECT was performed. The interobserver difference was evaluated using the κ -coefficient. Quantitatively, T/N ratio (the ratio of the counts in the tumor divided by that in the normal nuchal muscles) and retention index were compared between TI-SPECT and MIBI-SPECT. **Results:** On both the early and delayed images, the grades of uptake of the tumor in TI-SPECT were significantly higher than those in MIBI-SPECT by three observers. The grade of TI-uptake of the tumor on the delayed images was 5 for all observers (κ -coefficient = 1); however, the κ -coefficient varied from 0.39 to 0.84 in early TI-SPECT, and in early and delayed MIBI-SPECT. Statistical differences in T/N ratio were noted between early TI-SPECT (2.87 ± 1.19) and MIBI-SPECT (2.48 ± 1.06), and between delayed TI-SPECT (2.11 ± 0.70) and MIBI-SPECT (1.20 ± 0.48). The retention index of TI-SPECT (0.81 ± 0.24) was significantly higher than that of MIBI-SPECT (0.52 ± 0.15). **Conclusions:** The present study qualitatively and quantitatively showed that ^{201}Tl had higher accumulation in the tumor than $^{99\text{m}}\text{Tc}$ -MIBI in both early and delayed images.

Key words: head and neck neoplasms, ^{201}Tl chloride, $^{99\text{m}}\text{Tc}$ MIBI, SPECT

INTRODUCTION

MAGNETIC RESONANCE IMAGING (MRI) and CT have been the main radiological diagnostic tools to detect malignant tumors in the head and neck, such as pharyngeal, oral, nasal and paranasal carcinomas. However, these modalities

have low sensitivity in detecting recurrent or residual tumors, as well as in distinguishing them from post-treatment changes. It is well known that thallium-201 (^{201}Tl) chloride has an affinity for various malignant tumors such as brain tumors,^{1,2} head and neck tumors,^{2–5} breast carcinomas,¹ lung carcinomas,^{1,2} thyroid carcinomas,^{1,2} and so forth. Furthermore, ^{201}Tl is more specific than gallium-67 (^{67}Ga) for differentiating tumors from benign or inflammatory pathologies.² Previous studies have also reported that ^{201}Tl single-photon emission tomography (TI-SPECT) is useful in evaluating treatment response and prognosis in tumors in the brain, head and neck, and other tumors.² $^{99\text{m}}\text{Tc}$ hexakis-2-methoxy-

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isobutylisonitrile (^{99m}Tc -MIBI), developed as a tracer for myocardial perfusion imaging, has also been shown to have an affinity for various tumors.^{1,6-10} Previous studies have assessed ^{99m}Tc -MIBI with regard to treatment response for radiotherapy and chemotherapy.^{11,12}

To our knowledge, few previous reports have compared TI-SPECT with ^{99m}Tc -MIBI SPECT (MIBI-SPECT) in the depiction of tumors of the head and neck. Evaluation of the degree of tracer uptake on pretreatment imaging is essential to assess the utility of these tracers for treatment response or prediction of prognosis. We performed a prospective study that compared TI-SPECT with MIBI-SPECT in the depiction of tumors of the head and neck.

MATERIALS AND METHODS

Patients

From April, 2001 to July 2004, 41 patients (mean age; 60.7 ± 11.5 years, males; 36, females; 5) with various tumors of the head and neck were included in this prospective study. All patients were histologically diagnosed by biopsy or surgery before or after SPECT studies. None of the patients had undergone any treatments such as radiotherapy, chemotherapy, and surgery when SPECT was performed. The tumors consisted of carcinoma of the nasopharynx ($n = 3$), oropharynx ($n = 10$), hypopharynx ($n = 7$), oral cavity ($n = 10$), nasal cavity ($n = 1$), maxillary sinus ($n = 1$), larynx ($n = 6$), cervical esophagus ($n = 1$), salivary gland ($n = 1$), and lacrimal gland ($n = 1$). Histologically, 36 patients had squamous cell carcinomas, 3 undifferentiated carcinomas, 1 transitional cell carcinoma, and 1 low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT). The T stage in the UICC classification¹³ was T1 in 1 patient, T2 in 9, T3 in 8, and T4 in 23. All patients underwent a simultaneous dual-isotope SPECT of the head and neck with ^{201}Tl and ^{99m}Tc -MIBI. All patients gave their informed consent prior to their participation to the study.

Table 1 The kappa coefficient of TI-201 SPECT

Observer	Early scan	Delayed scan
A vs. B	0.49	1
B vs. C	0.39	1
A vs. C	0.84	1

Table 2 The kappa coefficient of Tc-99m MIBI SPECT

Observer	Early scan	Delayed scan
A vs. B	0.49	0.64
B vs. C	0.39	0.47
A vs. C	0.62	0.52

Simultaneous dual-isotope SPECT

Dual-isotope SPECT for early acquisition was performed 15 min after the injection of 111 MBq ^{201}Tl and 600 MBq ^{99m}Tc -MIBI, whereas delayed acquisition was performed 3 h after injection. The early images were acquired in all

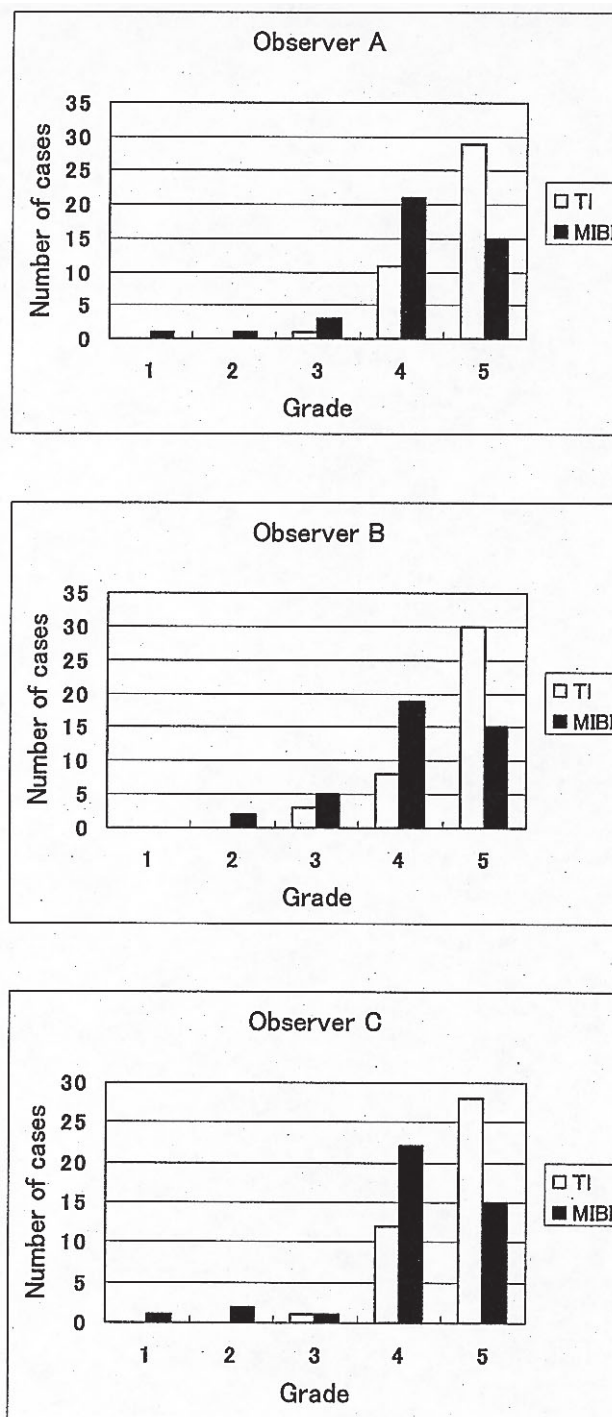


Fig. 1 Visual interpretation of early images of ^{201}Tl -SPECT and ^{99m}Tc -MIBI-SPECT by each observer. The grades of uptake of the tumor in ^{201}Tl -SPECT were significantly higher than those in ^{99m}Tc -MIBI-SPECT for each observer. TI: ^{201}Tl -SPECT, MIBI: ^{99m}Tc -MIBI-SPECT.

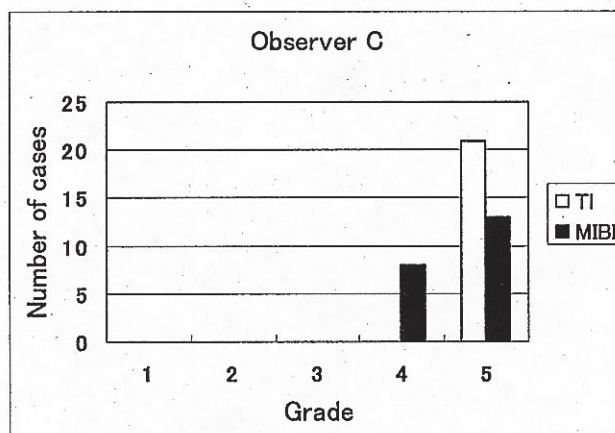
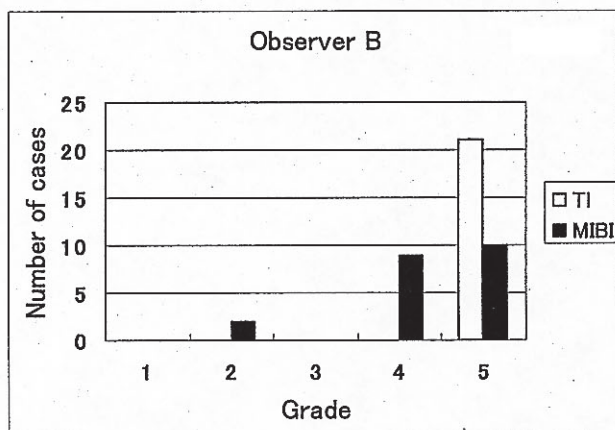
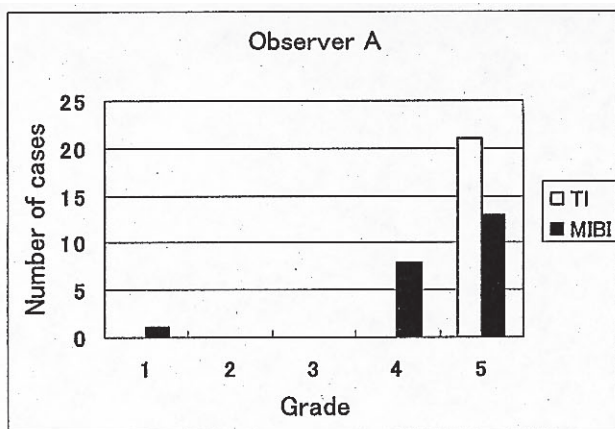
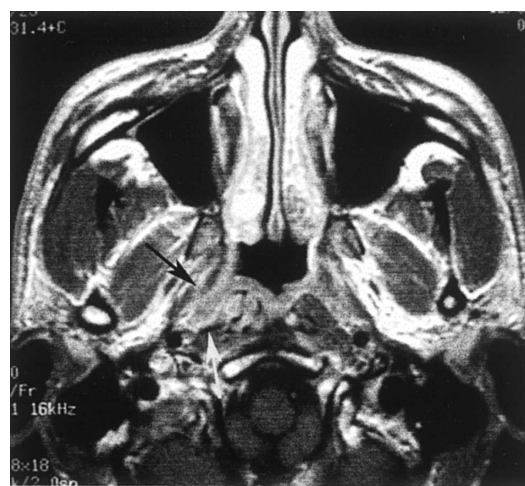
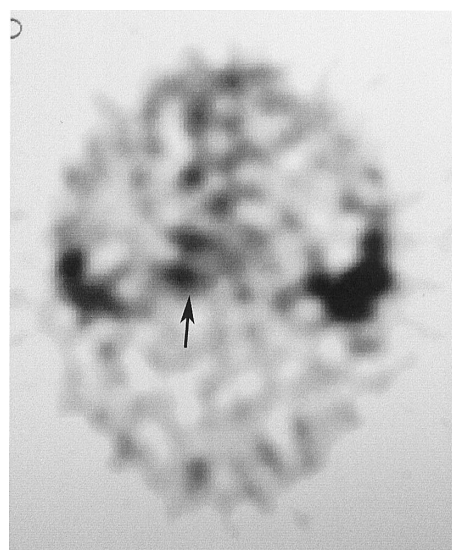


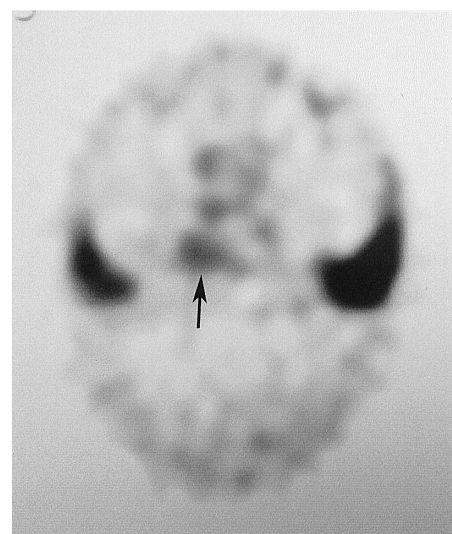
Fig. 2 Visual interpretation of delayed images of ^{201}Tl -SPECT and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT by each observer. The grades of uptake of the tumor in ^{201}Tl -SPECT were significantly higher than those in $^{99\text{m}}\text{Tc}$ -MIBI-SPECT for each observer. TI: ^{201}Tl -SPECT, MIBI: $^{99\text{m}}\text{Tc}$ -MIBI-SPECT.



A



B

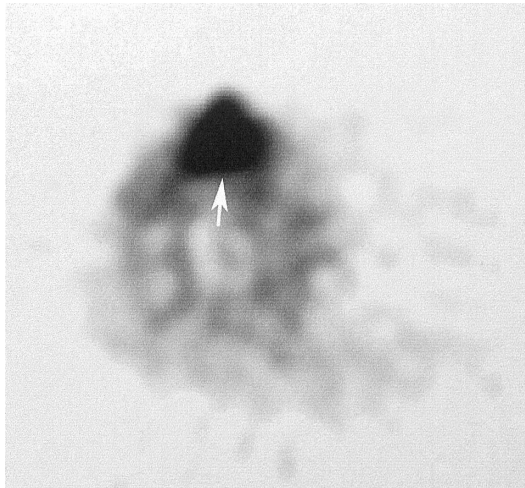


C

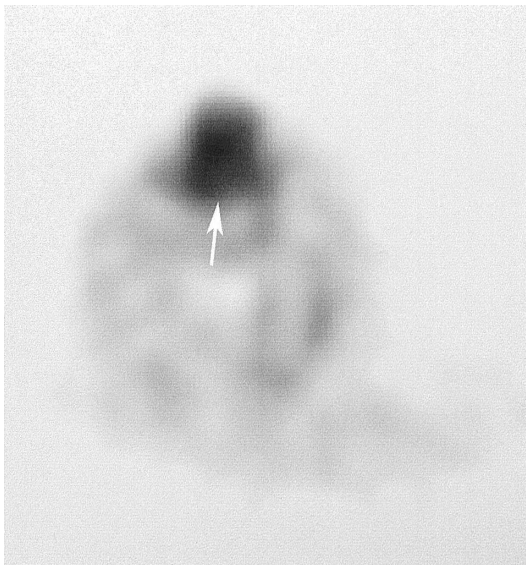
Fig. 3 A 42-year-old man with nasopharyngeal carcinoma. Contrast enhanced T1-weighted MR image shows a tumor (A, arrows) in the posterolateral wall of the nasopharynx. The degree of ^{201}Tl uptake (B, arrow) in the tumor was greater than that of $^{99\text{m}}\text{Tc}$ -MIBI (C, arrow) uptake in the early images.



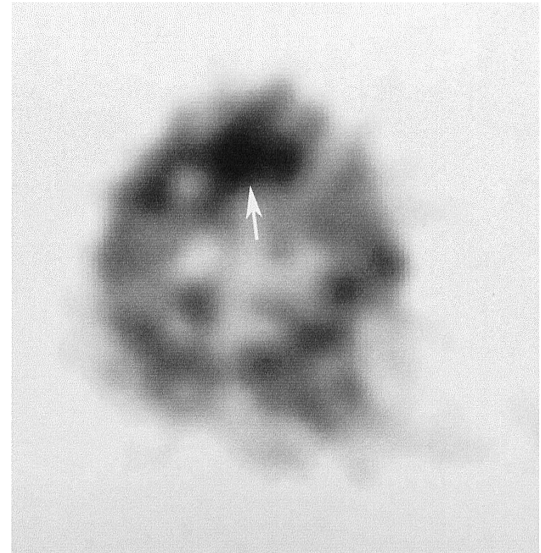
A



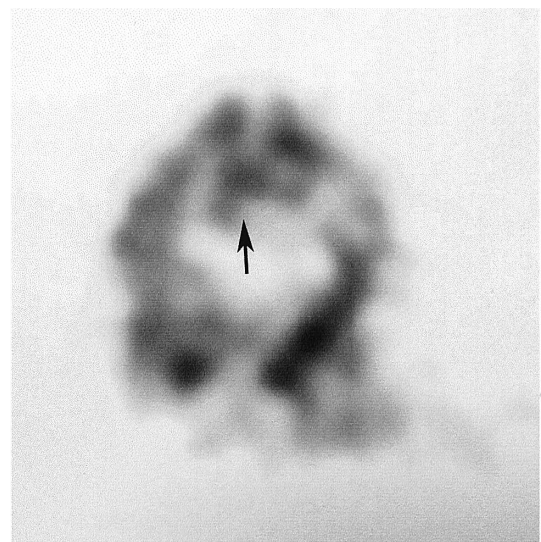
B



C



D



E

patients. Delayed images were acquired only in 21 patients, because double phase SPECT studies overloaded patients. The equipment consisted of a dual-head rotating gamma camera equipped with a low-energy, high-resolution collimator. Counts of seventy-two projections over 360-degree were obtained using a 128×128 matrix for 30 s per each projection. Total acquisition time was 36 min. The energy window was set at 71 keV with a 15% window for ^{201}Tl images, and 140 keV with a 15% window for $^{99\text{m}}\text{Tc}$ -MIBI images. The transaxial sections were reconstructed using a Ramp filter following filtered back-projection with a Butterworth filter (order 5, cutoff 0.68).

Fig. 4 A 67-year-old man with laryngeal carcinoma. Contrast-enhanced CT shows a tumor in the posterior aspect of the epiglottis (A, arrows). The degree of ^{201}Tl uptake (B, arrow) in the tumor was greater than that of $^{99\text{m}}\text{Tc}$ -MIBI (C, arrow) uptake in the early images. Retention of ^{201}Tl was seen in the delayed images (D, arrow), whereas $^{99\text{m}}\text{Tc}$ -MIBI had almost washed out (E, arrow).

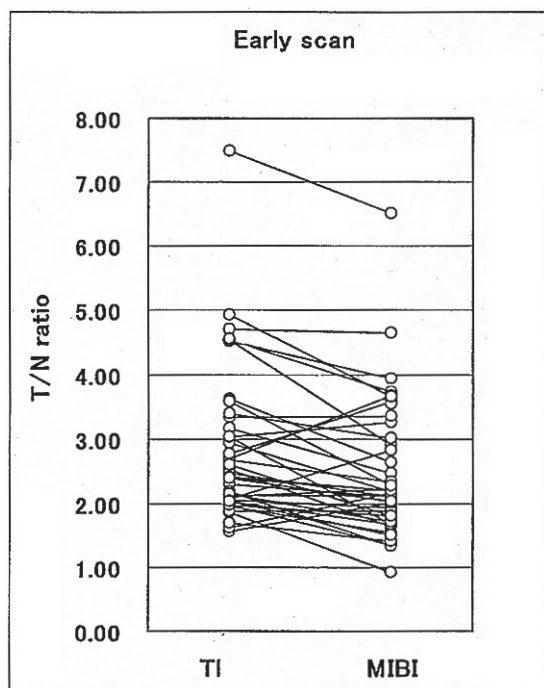


Fig. 5 Quantitative analysis (T/N ratio) in the early images. A statistical difference in the T/N ratio was observed between early ^{201}Tl -SPECT (2.87 ± 1.19) and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT (2.48 ± 1.06). TI: ^{201}Tl -SPECT, MIBI: $^{99\text{m}}\text{Tc}$ -MIBI-SPECT.

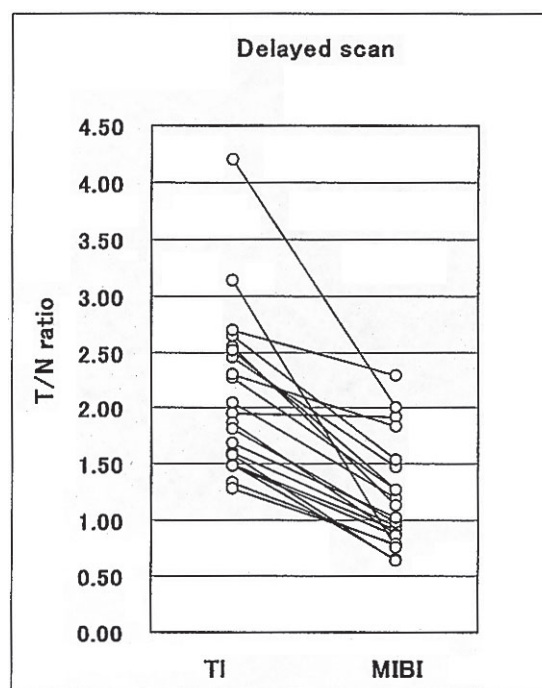


Fig. 6 Quantitative analysis (T/N ratio) of the delayed images. A statistical difference was observed in the T/N ratio between delayed ^{201}Tl -SPECT (2.11 ± 0.70) and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT (1.20 ± 0.48). TI: ^{201}Tl -SPECT, MIBI: $^{99\text{m}}\text{Tc}$ -MIBI-SPECT.

Attenuation correction was not performed. Transaxial images were displayed with a slice thickness of 6.6 mm.

Visual interpretation

Three experienced nuclear medicine physicians with knowledge of the patients' clinical information including pathological diagnoses evaluated both TI-SPECT and MIBI-SPECT individually referring to MRI or CT. The qualitative interpretation criteria used were as follows: Grade 1; no abnormal increased uptake, Grade 2; questionable increased uptake, Grade 3; definitely increased uptake, but of a degree less than that of normal mucosa, Grade 4; definitely increased uptake of a degree equal to or more than that of normal mucosa, but less than that of normal salivary gland, and Grade 5; definitely increased uptake of a degree equal to or greater than that of normal salivary gland. For statistical analysis of the comparison of TI-SPECT and MIBI-SPECT, Wilcoxon signed-ranks tests were performed using the StatView software (SAS Institute Inc., version 5.0). Results were considered significant at $p < 0.01$. The interobserver difference was evaluated using the κ -coefficient (<http://lang.nagoya-u.ac.jp/tech/stat/kappa.html>).

Quantitative analysis

Regions of interest (ROIs) were set both on the tumor uptake and the normal uptake of the nuchal muscles. The ROI on the tumor uptake included the highest tracer

uptake by the tumor. The ROI placement was made referring to MR images. The ratio of the average counts of the ROI in the tumor and in the normal nuchal muscles (T/N ratio) was then calculated. T/N ratios of the early images and the delayed images were compared between TI-SPECT and MIBI-SPECT. To evaluate the degree of retention in the delayed images, the retention index was calculated as the T/N ratio of the delayed image divided by the T/N ratio of the early image. For the statistical analysis, paired-t tests were performed using the StatView software (SAS Institute Inc., version 5.0). Results were considered significant at $p < 0.01$.

RESULTS

The visual interpretation of each observer is shown in Figures 1 and 2. On both the early and delayed images, the grades of uptake of the tumor in TI-SPECT were significantly higher than those in MIBI-SPECT by every observer (Figs. 3 and 4). The κ -coefficient for interobserver difference is shown in Tables 1 and 2. The grade of ^{201}Tl -uptake of the tumor on delayed images was 5 by all observers; however, the κ -coefficient varied from 0.39 to 0.84 in the early TI-SPECT, and in early and delayed MIBI-SPECT. Figures 5 and 6 show a quantitative analysis (T/N ratio) of the early and delayed images. Statistically significant differences in T/N ratio were observed between early TI-SPECT (2.87 ± 1.19) and MIBI-SPECT

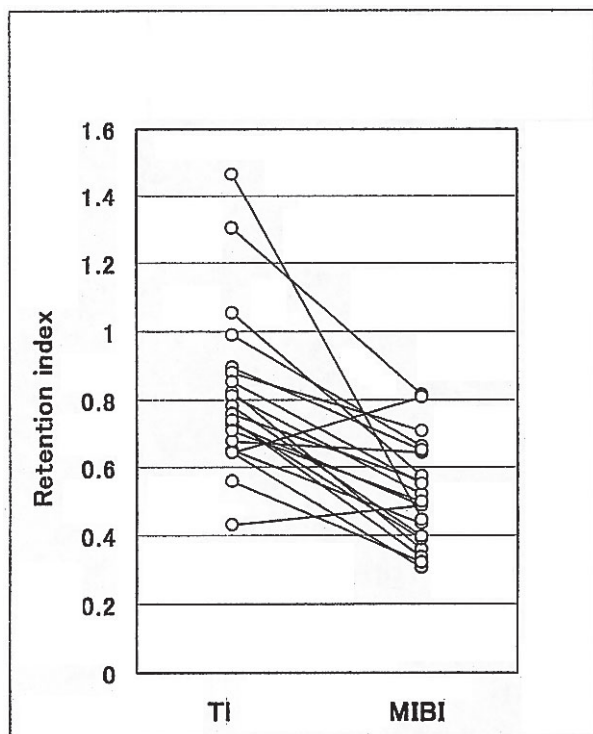


Fig. 7 Retention index of ^{201}Tl and $^{99\text{m}}\text{Tc}$ -MIBI. The retention index of ^{201}Tl -SPECT (0.81 ± 0.24) was significantly higher than that of $^{99\text{m}}\text{Tc}$ -MIBI-SPECT (0.52 ± 0.15). TI: ^{201}Tl -SPECT, MIBI: $^{99\text{m}}\text{Tc}$ -MIBI-SPECT.

(2.48 ± 1.06), and between delayed TI-SPECT (2.11 ± 0.70) and MIBI-SPECT (1.20 ± 0.48). The retention index of TI-SPECT (0.81 ± 0.24) was significantly higher than that of MIBI-SPECT (0.52 ± 0.15) (Fig. 7).

DISCUSSION

Although CT and MR imaging, which have excellent spatial resolution, can detect small tumors in the head and neck region, nuclear medicine imaging has been reported to have better diagnostic value in detecting recurrent tumors after treatment^{3-7,9} as well as in evaluating treatment response.^{2,11,12,14} Tumors of the head and neck region can be imaged by TI-SPECT and positron emission tomography (PET) using 18-fluoro-2-deoxyglucose (^{18}F -FDG).^{1,2,15} ^{18}F -FDG-PET has excellent spatial resolution compared with SPECT, and has been reported to have excellent diagnostic accuracy. However, widespread clinical use of PET has not yet been achieved, because of economic and practical problems. On the other hand, SPECT is much more widely available. We previously reported the superiority of ^{201}Tl compared with ^{67}Ga to image tumors of the head and neck region.¹⁶

The mechanism of ^{201}Tl uptake by tumors, which is different from that of $^{99\text{m}}\text{Tc}$ -MIBI, is thought to be linked to the Na,K-ATPase pump in the cell membrane. Biologi-

cally, ^{201}Tl acts similarly to potassium for intracellular transport across the cell membrane via Na,K-ATPase.¹ The uptake of ^{201}Tl seems to correlate somewhat with tumor vascularity.¹ On the other hand, recently, MIBI-SPECT has also been reported to have an affinity for tumors such as breast cancer,¹⁰ brain tumor,^{12,17} nasopharyngeal tumor,^{6,7,9} and lung cancer.⁸ The exact mechanism of $^{99\text{m}}\text{Tc}$ -MIBI uptake by tumors is still unclear; however, the mitochondrial/plasma membrane potentials and cellular mitochondrial content of tumor cells can play a significant role in tumor uptake of $^{99\text{m}}\text{Tc}$ -MIBI.¹ Uptake may also be influenced by increased tumor blood flow or capillary permeability.¹

A few reports have compared ^{201}Tl with $^{99\text{m}}\text{Tc}$ -MIBI for imaging tumors.¹⁸⁻²¹ Nishiyama et al.¹⁸ reported that $^{99\text{m}}\text{Tc}$ -MIBI was not superior to ^{201}Tl in differentiation of the histological diagnosis of malignant brain tumors. Yamamoto et al.¹⁹ also compared ^{201}Tl and $^{99\text{m}}\text{Tc}$ -MIBI in the detection of recurrent brain tumors, and demonstrated the usefulness of $^{99\text{m}}\text{Tc}$ -MIBI in the detection of recurrent brain tumors after radiotherapy. To our knowledge, a comparison of ^{201}Tl with $^{99\text{m}}\text{Tc}$ -MIBI for tumors of the head and neck has been reported only by Wang et al.²¹ In the present study, visual interpretation showed a significantly higher uptake of ^{201}Tl than $^{99\text{m}}\text{Tc}$ -MIBI in the tumor; however, the value of the κ -coefficient among observers did not show good agreement (0.39–0.84), other than the delayed scans of ^{201}Tl . Decreased uptake in the salivary gland, thyroid, and normal mucosa may have resulted in the good agreement for the delayed ^{201}Tl images. Background uptake in the early ^{201}Tl and $^{99\text{m}}\text{Tc}$ -MIBI images, and in the delayed $^{99\text{m}}\text{Tc}$ -MIBI images may be one of the factors explaining the relatively low value of the κ -coefficient. This low κ -coefficient may be also due to some differences in the experience of the observers. There was actually a difference of 5-year training period among three observers. The qualitative interpretation criteria in the present study depend on uptakes to the tumor, normal mucosa, and salivary glands. When we evaluate the degree of tumor uptake, we visually compare the tumor uptake with the uptake of its surrounding tissues such as the normal mucosa and salivary glands on films or displays. In normal cases, the highest uptake of ^{201}Tl and $^{99\text{m}}\text{Tc}$ -MIBI is usually seen in the salivary glands.

Quantitatively, in both the early and delayed images, the T/N ratio was significantly higher in TI-SPECT than in MIBI-SPECT. This semi-quantitative measurement of T/N ratio is influenced by tumor uptake and background uptake by the salivary and thyroid glands, and normal or inflammatory mucosa. In the head and neck region, there have been some studies using $^{99\text{m}}\text{Tc}$ -MIBI in the detection of recurrent nasopharyngeal carcinomas after treatment. Kao et al.⁷ and Shiau et al.⁶ reported the effectiveness of combined use of CT and MIBI-SPECT to differentiate benign lesions from recurrent or residual tumors. However, they did not compare $^{99\text{m}}\text{Tc}$ -MIBI with ^{201}Tl . Wang

et al.²¹ performed a comparative study of these two agents in the detection of nasopharyngeal carcinomas, and suggested that sensitivity was slightly higher in Tl-SPECT than in MIBI-SPECT. Henze et al.²² also showed a low tumor detection rate with MIBI-SPECT in the pretreatment evaluation of carcinomas of the hypopharynx and larynx, and they noted that physiological ^{99m}Tc-MIBI uptake in the nasal and oral cavity, and the thyroid and salivary glands impaired the interpretation of ^{99m}Tc-MIBI uptake by the tumors. One possible solution may be the use of perchlorate to prevent the uptake of free ^{99m}Tc-perchnetate, as Kao et al.⁷ and Tsai et al.⁹ demonstrated in their studies.

On the other hand, a major advantage of ^{99m}Tc-MIBI is the ^{99m}Tc-labeled agent, as ^{99m}Tc is readily available and produced from a Molybdenum generator. Shorter physical half-life of ^{99m}Tc is also optimal for use. The mechanism of ^{99m}Tc-MIBI uptake in tumors of the head and neck may be one of the factors responsible for the decreasing T/N ratios. In squamous cell carcinomas, which were histologically found in most of the subjects in the present study, ultrastructural analysis has shown a very heterogeneous picture of mitochondria. This change in mitochondria may result in low accumulation of ^{99m}Tc-MIBI.²² However, the number of tumors with other kinds of histology was too small. Thyroid carcinomas and other adenocarcinomas were not included in the present study. Further studies including a greater number of tumors should be performed.

In the delayed images, all 3 observers in the present study interpreted higher uptake by the tumor in ²⁰¹Tl than ^{99m}Tc-MIBI for every tumor. This was semiquantitatively confirmed by the higher T/N ratio and retention index of Tl-SPECT. The use of delayed images of ²⁰¹Tl was also assessed, because ²⁰¹Tl tends to be retained in malignant tumors. On the other hand, few reports have assessed delayed images of ^{99m}Tc-MIBI in tumors. In a previous study²² evaluating carcinomas of the hypopharynx and larynx using ^{99m}Tc-MIBI, close correlation in radioactivity count ratio of tumor to nuchal muscle existed between the early and delayed ^{99m}Tc-MIBI images. Their study could not confirm the usefulness of delayed ^{99m}Tc-MIBI. With respect to delayed images of ^{99m}Tc-MIBI, previous studies have emphasized that washout of ^{99m}Tc-MIBI from tumors is related to the multi-drug-resistant energy dependent P-glycoprotein pump system.^{1,22} This system is not necessarily related to the differentiation between malignant and benign tumors, and this increased washout of ^{99m}Tc-MIBI may be seen in malignant tumors such as squamous cell carcinomas in the head and neck, like in the subjects in the present study.

We found that for malignant tumors in the head and neck before treatment, ²⁰¹Tl accumulated to a greater degree in the tumor than ^{99m}Tc-MIBI as evidenced in both the early and delayed images. Especially, delayed ²⁰¹Tl images seemed to be more feasible because of less

interobserver difference as well as higher T/N ratio. Early ²⁰¹Tl images might be possibly omitted to depict malignant tumors in the head and neck region. The result in the present study may indicate the superiority of ²⁰¹Tl to ^{99m}Tc-MIBI in evaluating the tumor response to treatment. However, evaluation of ²⁰¹Tl and ^{99m}Tc-MIBI in the assessment of the tumor response to treatment such as chemotherapy and radiotherapy should be further examined. Even if ²⁰¹Tl or ^{99m}Tc-MIBI is superior to CT or MRI in the assessment of tumor response to treatment, it could not be an alternative. Contrast or spatial resolution of CT or MRI is definitely superior to that of SPECT. Fusion images with these modalities would be desirable to depict tumors as well as to assess treatment response.

In conclusion, the present study qualitatively and quantitatively showed that in the malignant tumors in the head and neck, ²⁰¹Tl had higher accumulation than ^{99m}Tc-MIBI in both early and delayed images.

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