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^{201}Tl SPECT for evaluating head and neck cancer

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Background: Thallium-201 (^{201}Tl) has come to be widely used in the diagnosis of several kinds of malignant tumor, but its usefulness in diagnosing head and neck cancer has not been established. Purpose: This study investigated the usefulness of ^{201}Tl SPECT imaging in patients with head and neck cancer histologically confirmed. Methods: Eighteen patients with histologically proven head and neck cancer were studied. ^{201}Tl SPECT images were obtained both 15 min and 4 hours after intravenous injection of 148 MBq of ^{201}Tl-chloride. ^{201}Tl-indices were calculated semiquantitatively to assess the tracer uptake in relation to tumor size and histological type. Results: High ^{201}Tl uptake was noted in all primary tumors and metastatic lymph nodes on the both early and delayed images, but^{201}Tl-indices did not show any correlation with tumor size or histological type. Conclusion: Primary head and neck cancer and lymph node metastasis can be effectively visualized with ^{201}Tl SPECT. It may provide information in addition to morphological changes and may be a supplemental method to use in the evaluation of head and neck cancer.

Key words: ^{201}Tl SPECT, head and neck cancer, lymph node metastasis

INTRODUCTION

COMPUTED TOMOGRAPHY (CT) and magnetic resonance imaging (MRI) have significantly advanced the diagnostic ability to detect and delineate extracranial head and neck cancer,[1,2] but there are diagnostic difficulties in the detection of residual tumors in post surgical and post-radiotherapy fields because of the distortion of normal architecture.[2]

Positron emission tomography (PET) seems comparable to, or may better than, CT or MR in the study of head and neck cancers,[3–9] but there remain many practical problems in the clinical application of this technique.

Recently, thallium-201 (^{201}Tl) has come to be widely used in the diagnosis of several kinds of malignant tumor, such as lung cancer and brain tumor,[10–13] but there have been few reports referring to detection of head and neck cancer.[14–16] The aim of the present study is to investigate the usefulness of ^{201}Tl SPECT in the identification of primary tumor and cervical lymph node metastasis of head and neck cancer as compared with CT and histopathological findings.

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MATERIALS AND METHODS

Eighteen consecutive patients with head and neck cancer were studied. Fifteen patients were the initial cases with no prior therapy. The remaining three patients were recurrent cases without primary lesions owing to previous effective radiotherapy. Therefore only metastatic lymph nodes were evaluated in these three patients. The patient and tumor characteristics are given in Tables 1 and 2. All primary tumors were histologically verified by a biopsy. Clinical staging of tumors followed the UICC TNM-classification (1987), and it includes careful physical examination, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) when feasible.

Each patient was injected with 148 MBq of ^{201}Tl-chloride, and SPECT imaging was performed by means of a three-detector gamma camera (PRISM 3000, Picker International Inc.) equipped with a low-energy, high resolution parallel-hole collimator. Acquisition parameters were matrix 64 × 64 pixels, 30 sec per stop, 6 degrees steps, 20 stops. A one-peak energy window (80 KeV) was used. After preprocessing the data by nine-point weighted smoothing, the reconstructed images were

Table 1 Patients and tumor characteristics (primary)

Case	Age/Sex	Sites	Size (cm)	Histology	Grade	Stage	EI	DI	RI
1	57/M	Hypopharynx	3.0 × 1.2	SCC	III	T3N2M0	1.8	1.3	−0.29
2	64/M	Hypopharynx	2.0 × 1.5	SCC	II	T2N2M0	3.6	4.3	0.21
3	65/M	Hypopharynx	4.0 × 2.1	SCC	II	T3N2M0	4.1	2.5	−0.40
4	60/M	Hypopharynx	4.9 × 4.5	SCC	II	T3N2M0	4.0	3.0	−0.25
5	67/M	Oropharynx	4.2 × 2.8	SCC	II	T3N2M0	3.2	3.8	0.18
6	81/M	Oropharynx	4.5 × 3.1	SCC	I	T3N2M0	1.6	2.7	0.64
7	72/M	Gyngiva	5.0 × 2.5	SCC	II	T4N2M0	7.6	2.9	−0.53
8	62/M	Oropharynx	3.0 × 2.7	SCC	III	T3N2M0	3.3	3.0	−0.11
9	74/M	Oropharynx	4.8 × 3.5	SCC	III	T3N2M0	7.7	6.3	−0.18
10	56/M	Gyngiva	3.5 × 3.2	SCC	I	T3N1M0	4.9	2.8	−0.42
11	48/F	Oropharynx	3.0 × 2.1	SCC	I	T3N1M0	3.5	3.0	−0.15
12	67/M	Oropharynx	5.5 × 2.1	SCC	III	T4N2M0	3.8	2.6	−0.30
13	69/M	Hypopharynx	3.5 × 2.1	SCC	II	T2N1M0	3.4	1.9	−0.45
14	63/M	Tongue	2.7 × 2.5	SCC	I	T2N1M0	2.9	2.5	−0.14
15	58/M	Tongue	3.9 × 3.5	SCC	II	T3N2M0	3.6	2.5	−0.30

SCC: squamous cell carcinoma; EI: early index; DI: delayed index; RI: retention index; Grades I, II and III: well, moderately and poorly differentiated, respectively.

Table 2 Patients and tumor characteristics (lymph nodes)

Case	Age/Sex	Metastasis	Primary	Size (cm)	EI	DI	RI
1	57/M	Neck (right)	Hypopharynx	3.5 × 2.4	1.9	1.6	−0.19
		Neck (left)		2.2 × 1.1	2.3	2.1	−0.19
2	64/M	Neck (right)	Hypopharynx	2.5 × 2.2	4.2	4.6	0.10
3	65/M	Neck (right)	Hypopharynx	2.8 × 2.0	2.4	2.2	−0.09
		Neck (left)		1.4 × 1.2	2.9	2.4	−0.19
4	60/M	Neck (right)	Hypopharynx	3.5 × 2.5	2.4	2.2	−0.09
5	67/M	Neck (right)	Oropharynx	4.5 × 4.2	3.1	2.5	−0.17
6	81/M	Neck (right)	Oropharynx	2.5 × 2.4	1.5	2.4	0.35
		Neck (left)		2.5 × 1.0	1.4	2.1	0.56
7	72/M	Neck (right)	Gyngiva	1.3 × 1.3	2.7	2.2	−0.19
8	62/M	Neck (right)	Oropharynx	1.6 × 1.4	3.1	2.6	−0.16
9	74/M	Neck (right)	Oropharynx	2.1 × 1.2	7.7	6.5	−0.15
		Neck (left)		1.3 × 1.1	3.6	4.0	0.10
10	56/M	Neck (right)	Oropharynx	2.1 × 1.8	5.6	2.4	−0.58
11	48/F	Neck (left)	Oropharynx	1.7 × 1.5	4.6	5.8	0.26
12	67/M	Neck (left)	Oropharynx	2.1 × 1.9	2.9	2.5	−0.15
13	69/M	Neck (right)	Hypopharynx	1.6 × 1.3	3.7	4.4	0.16
14	63/M	Neck (right)	Tongue	1.8 × 1.5	4.8	3.8	−0.26
15	58/M	Neck (left)	Tongue	2.0 × 1.8	3.6	4.5	0.25
16	78/M	Neck (left)	Hypopharynx	5.6 × 3.1	3.2	2.3	−0.29
17	85/M	Neck (right)	Tongue	2.8 × 1.5	1.7	1.6	−0.03
18	57/M	Neck (left)	Oropharynx	4.1 × 2.2	3.8	4.3	0.13

SCC: squamous cell carcinoma; EI: early index; DI: delayed index; RI: retention index.

obtained with a Ramp filter following back-projection with a Butterworth filter. The slice thickness was 4.6 mm. Attenuation correction was not performed.

All primary tumor uptake of ^{201}Tl was evaluated visually and diagnosed as positive when the activity was higher than or equal to parotid gland uptake. Any visually positive hot spot in accordance with lymph node seen on CT was diagnosed as a metastatic lymph node.

For semiquantitative assessment, regions of interest (ROIs) were sited both in the lesions and in the normal soft tissues. In settings of ROIs of normal tissues, we chose the perivertebral space. Accordingly, the lesion/normal uptake ratio of ^{201}Tl activity was measured from mean counts-per-voxel obtained on both the early and delayed scans, representing the early index (EI) and delayed index (DI) respectively. Subsequently, the retention index (RI) was calculated as follows:

(Delayed index − Early index)/(Early index)

Only three of eighteen lymph nodes (cases 16–18) were

Table 3 Detectability of head and neck cancer on Tl-201 SPECT

	Early	Delay
Primary (n = 15)	15 (100%)	15 (100%)
Lymph node (n = 22)	22 (100%)	22 (100%)

histologically proven as metastasis by biopsy. For diagnosing other cervical lymph node metastasis, computed tomographic images were reviewed by two head and neck radiologists, and the diagnosis was reached by using the following previously established criteria[6]: 1) Lymph nodes greater than 1.0 cm. 2) Nodes with central necrosis regardless of size. 3) Pericapsular extension. 4) Obliteration of fat or perivascular tissue planes.

Statistical analysis

The correlation between the ^{201}Tl indices and tumor size was calculated by linear regression. Probability values less than 0.05 were considered to be statistically significant.

RESULTS

Primary lesion

^{201}Tl-SPECT showed an increase in tracer uptake in all 15 primary lesions on both early and delayed images (Table 3), but the degree of tracer uptake varied considerably between individuals and some cases showed poor contrast on the delayed images because of high ^{201}Tl uptake in surrounding soft tissues such as mandible and splenius capitis muscle.

In the quantitative analysis, there was no significant correlation between the ^{201}Tl uptake indices and tumor size or histopathological grade.

Lymph nodes

All metastatic neck lymph nodes detected by CT were visualized clearly on ^{201}Tl SPECT (Table 3). There were no lymph nodes with central necrosis, pericapsular extension nor obliteration of perivascular tissue planes smaller than 10 mm on CT. The smallest metastatic lymph node detected was therefore, 13 × 11 mm in size. No significant correlation was found between ^{201}Tl uptake indices and lymph node size.

Representative cases

Case 1 (Patient No. 7): A 72-year-old-man with gingival cancer. The histological grade was moderate. CT scan showed an irregular soft tissue density mass with central necrosis destroying left mandible (Fig. 1a). ^{201}Tl SPECT demonstrated marked increased activity corresponding to the tumor on the both early and delayed images (Fig. 1b, c). Increased activities of surrounding soft tissues were noted on the delayed images (Fig. 1c). The early index (EI) was 7.6, delayed index (DI) was 2.9 and retention index (RI) was –0.6.

Case 2 (Patient No.16): A 78-year-old man with left cervical lymph node metastasis from hypopharyngeal cancer. The primary lesion was healed after radiotherapy 9 months ago. CT showed a left sided enlarged cervical lymph node (Fig. 2a). High ^{201}Tl uptake was noted in the left neck lymph node on both early and delayed images (Fig. 2b, c). Compared with the early image, the delayed image showed poor contrast between the tumor and surrounding tissues including bones. The ^{201}Tl indices were EI: 3.1, DI: 2.3 and RI: –2.9, respectively.

DISCUSSION

Primary lesion

Thallium-201 uptake is considered to reflect the regional blood flow and viability of tumor cells related to proliferative activity.[10,11] This technique has been shown to be useful for detecting malignant tumors such as lung cancer or brain tumor.[10–13] Regarding the mechanism of ^{201}Tl accumulation in tumors, a relationship to Na-K ATPase has been reported.[17] In studies of head and neck cancer, there have been a few report showing the value of ^{201}Tl-scintigraphy in the delineation of tumors as a hot spot.[14–16] In the current study, we could corroborate the results of these previous studies by ^{201}Tl-SPECT with a triple head gamma camera.

While head and neck cancer can be visualized as tracer accumulation, the degree differed considerably among patients and there were no significant correlations between ^{201}Tl indices and tumor size. Moreover no association was found between ^{201}Tl uptake indices and the histological grade of cancer.

Although blood flow usually depends on tumor size,[18] it is heterogeneous and variation could occur in the calculated blood flow of the tumor with necrosis.[18] Human studies in patients with head and neck cancer also found great variation in both absolute blood flow and the ratio of flow distribution in the tumor and non-tumor.[18] Variation in tumor blood flow may be one of the reasons for the non-correlation between tumor size and ^{201}Tl uptake indices.

A previous study on other tumors showed that ^{201}Tl uptake reflects tumor proliferative activity, while it does not correlate with the size of the tumor.[10] Our results corroborated this finding indicating that proliferative activity is different in each tumor independent of the size.

Although poorly differentiated neoplasm is supposed to show higher uptake than well-differentiated cancer if the ^{201}Tl uptake reflects tumor proliferative activity, no relation was found with the histologic grade in the current study. Similar results have been obtained in FDG-PET studies.[4,7] The reason is uncertain, one possibility is that the tumor sometimes changes from slowly growing and well-differentiated to rapidly growing and poorly differentiated neoplasm.[8] Moreover, viable tumor cells are not always distributed homogeneously in neoplastic tissues.[10] Such instability of cell cycles and the heterogeneity of

a

b

c

Fig. 1 Case 1 (Patient No. 7), a 72-year-old man with gingival cancer. Irregular soft tissue density mass destructing left mandible is noted on CT (a). Marked increased activity corresponding to the tumor were shown on the both early (b) and delayed (c) ^{201}Tl SPECT images.

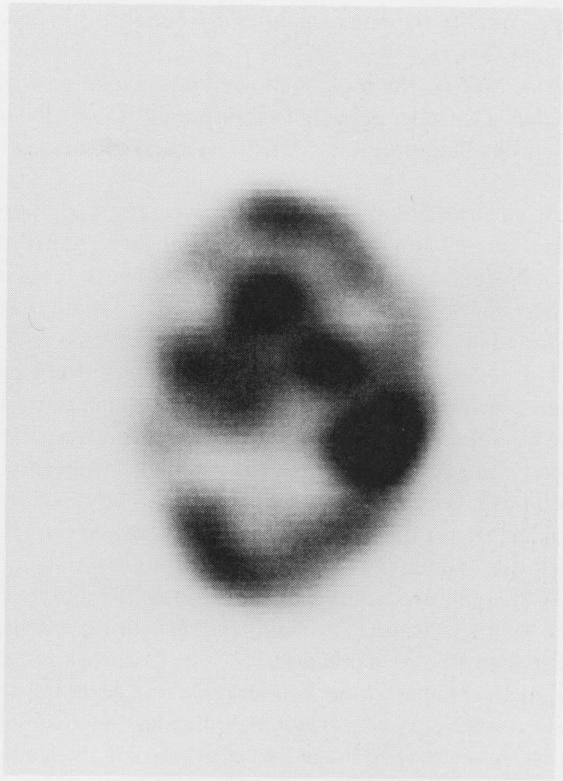
tumor tissues may explain our results.

According to previous studies on various tumors, prolonged ^{201}Tl retention suggests malignancy and a high retention index is considered to be a useful index for differential diagnosis.[10,12,13] In the current study, although prolonged ^{201}Tl retention was noted, the retention index in most patients tended to be a minus value because of high tracer washout between the early and delayed studies. In such cases, tumor activity tended to become hard to interpret, being affected by surrounding soft-tissue activities including muscles and bones on the delayed images. On the other hand, benign head and neck lesions such as granulomatous inflammatory diseases sometimes show prolonged ^{201}Tl retention,[19] so that the ^{201}Tl retention index may not be so useful in differentiating head and neck cancer from a benign disease as compared with its usefulness in other regions. And early images only may be enough to detect head and neck cancer.

Traditionally, ^{67}Ga-citrate has been used to diagnose head and neck cancer,[14] but ^{67}Ga-citrate shows high accumulation in inflammatory lesions such as sinusitis and it is sometimes difficult to distinguish cancer tissue from surrounding inflammatory tissues. From this point of view, ^{201}Tl-SPECT may be suitable for the evaluation of tumor extension.

Although CT scanning has long been the standard for evaluating this part of the body, beam hardening and dental material artifacts limit its role for evaluating soft-

a



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c

Fig. 2 Case 2 (Patient No. 16), a 78-year-old man with left cervical lymph node metastasis from hypopharyngeal cancer. Primary lesion was healed after radiotherapy 9 months ago. Left sided enlarged neck lymph node is noted on CT (a). High ^{201}Tl uptake were shown in the left neck lymph node on both early (b) and delayed (c) ^{201}Tl SPECT images.

tissue extension of head and neck cancer.[2] The detection of local recurrent tumor using CT in patients after surgical treatment is particularly difficult owing to anatomic distortion. Moreover, CT sometimes cannot differentiate a recurrent tumor from an operation scar or radiation fibrosis. MR imaging is superior to CT in assessing the extent of head and neck cancer because the contrast between tumor and surrounding tissues is superior in MR imaging,[2] but MR imaging is also affected by dental metallic artifacts and it is not available in the case of claustrophobia. ^{201}Tl-SPECT does not have limitations such as metallic artifacts and it also provides coronal and sagittal images which are helpful in identifying tumor extension precisely. It may also help to distinguish local recurrence from fibrosis or operation scar. Because of the low cost and ready availability of the gamma camera in most clinical centers, ^{201}Tl-SPECT may offer alternative or supplemental means for the evaluation of the extent of head and neck cancer. It may also be useful for the early detection of local recurrence.

Metastatic lymph node

The current study showed that we could identify metastatic lymph nodes as small as 1.0 cm in diameter by CT criteria, unlike the observations in a previous report stating that the detectable size lower limit is around 1.5 cm or 2.0 cm.[20] This may be owing to the improvement in

image quality by using the high resolution triple head gamma camera.[21]

But, ^{201}Tl-uptake indices showed no correlation with the size. Two other possible factors as well as variation in blood flow and proliferative activity, were also considered.

As all metastatic lymph nodes in the current study were diagnosed only on the basis of morphological criteria by CT, we should consider the interminglement of reactive lymph nodes which it is difficult to differentiate from metastatic lymph nodes.[8]

Moreover, metastatic lymph nodes are not always homogeneous and approximately 12% of all tumor-positive neck dissection specimens harbor only micrometastasis,[22,23] so there might have been such heterogeneous metastatic lymph nodes in the current study. Such a limitation may explain the non-correlation between lymph-node size and the ^{201}Tl-uptake indices.

Although there is little consensus about the most suitable technique to use in assessing lymph node metastasis,[2] US guided aspiration is considered to be the most accurate staging technique for neck metastasis,[2] but accuracy depends on the skill of ultrasonographers and cytopathologists. And it may be diagnosed as negative in the biopsy of lymph nodes with occult metastasis. In this respect, ^{201}Tl SPECT scan would be recommended both for screening and to determine the indication of the repeated US guided biopsy in patients with suspected neck lymph node metastasis.

Study limitations

This study has a number of limitations. First, we chose the perivertebral space as the most appropriate position to get control counts because other regions contain muscles or salivary glands in which there are remarkable individual differences in ^{201}Tl-uptake. Although the perivertebral space also contains many tissues such as vertebral bodies, prevertebral muscles and scalene muscles,[24] they showed few activities on visual inspection and made a striking contrast to tumor activities. However variation in soft tissue activities which depend on individual differences could not be eliminated.

Second, in blinded evaluation without CT and/or MRI imaging, the activity of lesions in relation to background is sometimes relatively lower and makes it difficult to distinguish the tracer uptake of primary tumor or metastatic lymph nodes from high tracer accumulation to the neck muscles, tongue and salivary glands. This is sometimes a limitation of ^{201}Tl as a head and neck tumor seeking agent. In the current study, correct image correlation between CT and ^{201}Tl SPECT images was sometimes necessary for detailed evaluation.

Third, we ignored lymph nodes smaller than 1 cm in diameter, but there were possibly both non-enlarged metastatic lymph nodes[8] and micrometastasis.[22,23] As such metastatic lymph nodes cannot be diagnosed only by the morphological changes,[6] small hot spots on ^{201}Tl-SPECT should be interpreted with caution in the detection of lymph node metastasis.

Fourth, we used CT images as a goldstandard. Although MRI is a more reliable imaging method for head and neck cancer staging, CT is preferred in evaluating osseous changes such as erosion of the mandible and sinus wall.[2] As most cases in current studies were advanced stage cancer with bone destruction, we chose CT as the basic imaging method.

CONCLUSIONS

In summary, all primary head and neck cancers and all cervical lymph node metastasis diagnosed by CT were visualized with ^{201}Tl SPECT. Our results suggested that ^{201}Tl SPECT could be a useful non-invasive method for detecting and evaluating the extent of head and neck cancer and its cervical lymph node metastasis.

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