patient. Further studies are needed to optimize ¹³¹I therapy in hyperthyroid patients with rapid thyroidal ¹³¹I turnover.

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Will Thallium-201 Replace Gallium-67 in Salivary Gland Scintigraphy?

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We investigated and compared findings on combined ^{99m}Tc pertechnetate-²⁰¹Tl with those of [^{99m}Tc]pertechnetate-⁶⁷Ga scintiscans to elucidate the advantages of ²⁰¹Tl in detecting various salivary glands disorders. **Methods:** We studied 23 patients: 6 had sialadenitis, 12 had benign tumors and 5 had malignant tumors. All but four patients had undergone [^{99m}Tc]pertechnetate (before and after lemon stimulation), ²⁰¹Tl (early and delayed) and ⁶⁷Ga imaging. **Results:** Five of six sialadenitis patients showed various degrees of diffuse uptake of ^{99m}Tc. All six except one showed early uptake without retention of ²⁰¹Tl on delayed imaging. The ⁶⁷Ga scan showed uptake in all patients except one. Nine of 12 benign tumors showed a cold defect on ^{99m}Tc scans. Patients with Warthin's tumors and plasmacytoma showed increased ^{99m}Tc uptake at the tumor with retention. The ²⁰¹Tl scan showed early uptake without retention in benign tumors. Five of the benign tumors, however, were positive on ⁶⁷Ga scan. None of the malignant tumors showed any uptake of ^{99m}Tc. The ²⁰¹Tl scan showed uptake with tumor retention on delayed images in three patients; three other patients also had positive ⁶⁷Ga scans. Overall, sensitivity and specificity of ²⁰¹Tl in detecting malignant tumors were 60% and 73%, respectively, with a negative predictive value of 85%. Sensitivity and specificity for ⁶⁷Ga were 60% and 47%, respectively, with a negative predictive value of 80%. **Conclusion:** In view of sensitivity, specificity and convenience of ²⁰¹Tl as well as future prospects for dual-isotope acquisition, ⁶⁷Ga may be replaced by ²⁰¹Tl in detecting salivary gland disorder.

Key Words: salivary glands; technetium-99m; thallium-201; gallium-67

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The usefulness of [99m Tc]pertechnetate to image the major salivary glands is well-established and the introduction of 67 Ga-citrate imaging has opened a new way of differentiating various pathological entities involving the salivary glands (*1-6*). Gallium-67, however, has shown some limitations in differentiating malignant from benign tumors (4, 7). Thallium-201-chloride has already shown its potential for detecting

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malignant tumors in various organs, and retention of 201 Tl in the delayed phase indicates possibile malignancy (8–10), although 201 Tl has not previously been applied in detecting the salivary gland disorders.

In this study, we compared 201 Tl and 67 Ga scan results to elucidate the advantage of 201 Tl in detecting various salivary gland disorders and determine the possibility of replacing 67 Ga with 201 Tl.

MATERIALS AND METHODS

Patient Population

Twenty-three patients (13 men, 10 women; age 20-84 yr) with major salivary gland swelling, were studied. All but four patients underwent ^{99m}Tc, ²⁰¹Tl and ⁶⁷Ga scintigraphy. Three of these four only had ^{99m}Tc and ⁶⁷Ga scans and the remaining patient only had ^{99m}Tc and ²⁰¹Tl scans. Six patients had sialadenitis, 12 had benign tumors (8 adenoma, 2 Warthin's tumor, 1 lipoma and 1 extramedullary plasmacytoma) and 5 had malignant tumors of various types. All tumors were diagnosed histopathologically after surgery, and sialadenitis are diagnosed either histologically after surgery or by clinical response to antibiotics indicated by decreased swelling and/or pain.

Technetium-99m Scans

Five to 10 min after intravenous injection of 185-370 MBq ^{99m}Tc, static spot images in the anterior and both anterior lateral oblique positions were taken by a gamma camera mounted with a LEAP collimator. Usually 500K counts/frame were acquired for the first frame and then settings were switched to the time required to obtain the first frame. After static images were acquired, the salivary glands were stimulated by 100% lemon juice (5-10 ml) and images after stimulation were obtained in the same three positions. Interpretations of scintigraphic findings have been described in details elsewhere (7). Briefly, nodular lesions were interpreted as decreased, increased or equal. The images after stimulation were interpreted as retention positive (+) or negative (-).

Thallium-201 Scans

For early images, 5-10 min after intravenous injection of 111 MBq ²⁰¹Tl, anterior and both lateral oblique views were obtained using the same gamma camera, collimator and acquisition methods as in the ^{99m}Tc study. For delayed images, the same views were obtained 3-4 hr after injection. The early images were interpreted as warm (activity in the tumor or involved gland was equal to the normal gland), hot (activity in the tumor or gland was more than the normal gland) and cold (activity in the tumor was less than the normal gland or surrounding normal glandular tissue). Delayed images were interpreted as retention-positive (+), when activity in the tumor or gland was more than the normal gland or surrounding glandular tissue, and retention-negative (-), when activity in the tumor or gland was equal to the normal gland or tissue.

Gallium-67 Scans

Seventy-two hours after intravenous injection of 111 MBq 67 Ga, static images in three positions (anterior and lateral) were taken by a gamma camera mounted with a medium-energy collimator. Scan findings were interpreted as negative (-) when activity in the tumor or gland was equal or less than the normal contralateral gland, positive (+) when activity was higher than that in the contralateral gland, but equal to or less than the normal nasal activity, and strongly positive (++) when activity was higher than the normal nasal activity.

RESULTS

Table 1 shows a summary of the patients and their scan findings. All patients with sialadenitis showed various degrees of diffuse ^{99m}Tc uptake except for one, who did not have any uptake in the glands due to Sjogren syndrome with multiple cystic changes. Only one patient demonstrated retained ^{99m}Tc activity after lemon stimulation. The early ²⁰¹Tl scan showed various degrees of diffuse activity in all patients except the patient with Sjogren syndrome who had multiple photopenic areas in both parotid glands. Tumoral retention of ²⁰¹Tl occurred in only in one patient who had sialadenitis with intraparotid lymphadenitis. Gallium-67 scans showed accumulation in all involved glands except for the patient of lymphadenitis.

The ^{99m}Tc scans for 9 of 12 patients with benign tumors demonstrated a cold area at the tumor site without tumor tracer retention after lemon stimulation. Two patients with Warthin's tumor had hot areas with retention on their ^{99m}Tc scan. Thallium-201 scans depicted various degrees of early accumulation without retention on the delayed scan except in three patients. Two of the patients had Warthin's tumor; tracer retention was depicted on their delayed ²⁰¹Tl images. Thallium scans also depicted central photopenia in two patients with cystic change. In contrast, 5 of 11 patients had positive ⁶⁷Ga scan results. Figure 1 depicts a patient with typical pleomorphic adenoma. Figure 2 shows a patient with Warthin's tumor. The ²⁰¹Tl, ⁶⁷Ga and ^{99m}Tc scans of the patient with lipoma depicted cold spots at the tumor site. The 99mTc scan results for the patient with plasmacytoma mimicked Warthin's tumor whereas the early ²⁰¹Tl scan depicted activity without tumor retention.

All patients with malignant tumors had cold areas without tumor retention on the ^{99m}Tc scans. The ²⁰¹Tl scans in three of five patients showed increased tracer accumulation with retention in all tumors and lymph nodes. One patient had a cystic cavity inside the tumor, which appeared as a photopenic area on the early ²⁰¹Tl images. There were also three positive⁶⁷Ga scan results, including lymph nodes. Figure 3 shows a case of lymphoma within the right submandibular gland with lymph node metastasis.

DISCUSSION

We previously reported the results of combined 99m Tc and 67 Ga scintiscans in various disorders of the major salivary glands, which showed its advantage in diagnosing sialadenitis and its high negative predictive value (NPV) for malignancy (7). The 67 Ga scans were nonspecific in differentiating benign from malignant lesions due to high uptake by inflammatory lesions; an observation also reported by others (4). Moreover, 67 Ga scanning is usually performed 72 hr after injection, which is inconvenient for both patients and technologists with regard to time and schedule. Thallium-201 has already shown its potential to differentiate benign from malignant tumors in various organs, and retention of 201 Tl in the tumor 2–4 hr after injection increases the probability of malignancy (8-10). Moreover, both 201 Tl and 99m Tc scintigraphy can be performed within a single day, eliminating the need to return for a second examination.

To date, various radiopharmaceuticals, including positron emitters, have been used to differentiate benign from malignant salivary gland disorders (11,12). In this study, 99m Tc, 201 Tl and 67 Ga scans were obtained to compare the scan results of combined 99m Tc/ 201 Tl with that of 99m Tc/ 67 Ga to determine the advantage of 201 Tl and the possibility of replacement of 67 Ga for the investigation of salivary gland disorders.

All scan interpretations were determined by visual analysis. In our previous study (7), the criterion for diagnosis of sialadenitis was various degrees of diffuse ^{99m}Tc uptake with positive ⁶⁷Ga accumulation in the involved gland. All but one

TABLE 1Scintigraphic Findings

Patient no.	Age (yr)	Sex	Dx	^{99m} Tc-scan	Lemon stimulation	²⁰¹ TI		
						Earty	Delayed	67Ga
1†	54	М	LA		R (–)	W	+	_
2†	58	F	SA	I	R (-)	W	_	+
3†	68	F	SA	I	(R (-)	н	-	++
4†	44	м	SA	D	R (–)	н	-	++
5†	40	F	SA	ns	R (–)	W*	-	+
6†	48	м	SA	D	R (+)	W	_	+
7 [‡]	22	м	PA	С	R (-)	W		++
8 [‡]	62	м	PA	С	R (-)	н	-	-
9 [‡]	47	м	PA	С	R (-)	nd	nd	+
10 [‡]	60	F	PA	С	R (-)	W	_	+
11 [‡]	20	F	PA	С	(R (-)	nd	nd	
12 [‡]	84	F	PA	С	R (-)	н	+	++
13 [‡]	67	F	PA	С	R ()	nd	nd	+
14 [‡]	74	м	MA⁺	С	R (-)	С	_	_
15 [‡]	63	м	L	С	R (-)	С	_	С
16 [‡]	71	F	WT	н	R (+)	н	+	-
17 [‡]	71	F	WT⁺	н	R (+)	W.	+	-
18 [‡]	64	F	PC	н	R (+)	W	-	nd
19 [§]	76	м	MM	С	R (+)*	W*	-	-
20 [§]	69	м	AC	С	R (-)	W	_	+
21 [§]	65	М	AS	С	R (-)	H**	+	++*
22 [§]	61	м	ML	С	R (-)	H**	+	++*
23 [§]	59	м	SCC	С	R (-)	H**	+	_

* Tumor with cystic change.

[†] Patients with sialadentis.

[‡] Patients with benign tumors.

§ Patients with malignant tumors.

** Uptake to both primary tumors and lymphnodes.

LA = intraparotid lymphadenitis; SA = sialadenitis; PA = pleomorphic adenoma; MA = monomorphic adenoma; L = lipoma; WT = Warthin's tumor; PC = extramedullary plasmacytoma; MM = malignant myoepithelioma; AC = adenocarcinoma; AS = anaplastic small cell carcinoma; I = diffuse increased uptake; D = diffuse decreased uptake; ns = not seen due to Sjogren syndrome; C = cold; H = hot (activity more than normal gland); R = retention; R^* = retention to peripheral normal tissue; W = warm (activity equal to normal gland); W^* = warm with a cold area/areas; and nd = not done.

patient with sialadenitis in this study also fulfilled this criterion. The exception was a case of suspected intraparotid lymphadenitis that did not show any avidity for ⁶⁷Ga; the disease subsided after one course of antibiotics. If we consider various degrees of diffuse ^{99m}Tc uptake and early diffuse uptake without retention of ²⁰¹Tl as criteria for sialadenitis, five of six patients with sialadenitis fulfilled the criteria. In each study, the patient who did not fulfill the criteria had lymphadenitis, there was also retention of ²⁰¹Tl at the site of intraparotid lymph node swelling. The reason for the absence of ⁶⁷Ga uptake was not clear but might have been due to smaller (<1.5 cm) lymph node size, while ²⁰¹Tl retention might be due to an inflammatory process causing extracellular edema and delayed clearance. A comparison of the ⁶⁷Ga ²⁰¹Tl scan results show that both agents have similar sensitivity in detecting sialadenitis, but ²⁰¹Tl has the advantages of convenience and time-efficiency.



FIGURE 1. Typical pleomorphic adenoma (mixed tumor) in a 62 yr-old man. (A) Technetium-99m scan shows a cold defect at the mass in right parotid gland. (B) Delayed ²⁰¹TI scan shows no retention at the mass. (C) Gallium-67 scan shows negative (-) uptake by the tumor.



FIGURE 2. A 71-yr-old woman with Warthin's tumor. (A) Technetium-99m scan after lemon stimulation shows intense retention at the mass in the right parotid gland. (B) Delayed ²⁰¹TI scan also showed retention at the mass. (C) Gallium-67 scan showed no uptake in the mass.

We (7) and others (4) previously showed false-positive uptake of ⁶⁷Ga in pleomorphic adenoma due to the presence of ⁷Ga-avid protein and other factors (13–15). Except for Warthin's and oncocytoma (16,17), most tumors appear as cold defects on ^{99m}Tc scans. In the current study, the patient with benign extramedullary plasmacytoma also had increased tumoral ^{99m}Tc uptake. If we exclude these exceptional cases with hot ^{99m}Tc scan results, then it would be important to differentiate benign from malignant tumors from the cold lesions on the ^{99m}Tc scans. Of the nine benign cold lesions on the ^{99m}Tc scan, ⁶⁷Ga depicted five false-positive scans, whereas ²⁰¹Tl demonstrated various degrees of uptake without retention on delayed images for all patients except one. Moreover, ²⁰¹Tl detected cystic change as a photopenic area inside the tumor. The two patients with Warthin's tumors showed typical 99mTc scan patterns as well as retention of ²⁰¹Tl on delayed scans. The exact mechanism of ²⁰¹Tl retention could not be explained but may be due to the active metabolism in Warthin's tumor resulting in an increased Na⁺, K⁺ ATPase system because Warthin's tumor has marked mitochondrial density (18). Diagnosis of Warthin's tumor or oncocytoma, however, could be confirmed by 99m Tc imaging alone (16,17). The 99m Tc scan results of plasmacytoma were similar to that of Warthin's tumor but the uptake mechanism was not known and further clarification is needed. A comparison of ⁶⁷Ga and ²⁰¹Tl scan results in cold lesions with ^{99m}Tc shows that ²⁰¹Tl is more advantageous than ⁶⁷Ga with regard to specificity. Also, ²⁰¹Tl detected more tumors with cystic changes.

Of the five malignant cold lesions on ^{99m}Tc scans, both ⁶⁷Ga and delayed ²⁰¹Tl imaging had two false-negative results. Thallium-201 detected lymph node metastasis in all patients but ⁶⁷Ga failed to detect the tumor as well as lymph node metastasis in one patient. One negative ²⁰¹Tl scan depicted a malignant myoepithelioma with cystic change inside the tumor, which appeared as a photopenic area on the early images. Therefore, ²⁰¹Tl retention might not be prominent due to a lack of solid tissue, but the ⁶⁷Ga scan also showed absence of uptake. At surgery, the origin of the tumor on the other false-negative ²⁰¹Tl scan was unclear. The tumor (<1.5 cm) was believed to have originated from the skin. Nonretention of ²⁰¹Tl might be due to smaller tumor size, but the ⁶⁷Ga showed positive uptake. In detecting malignant tumors, both ²⁰¹Tl and ⁶⁷Ga had similar results, but ²⁰¹Tl detected cystic change in one patient .

If the results of delayed 201 Tl scans and 67 Ga scans are compared for all patients, the sensitivity and specificity for 201 Tl scans in detecting malignancy were 60% (3/5) and 73% (11/15), with positive (PPV) and negative predictive values (NPV) of 43% (3/7) and 85% (11/13), respectively. Sensitivity and specificity of the 67 Ga scans were 60% (3/5) and 47% (8/17), with PPV and NPV of 25% (3/12) and 80% (8/10),



FIGURE 3. Malignant lymphoma with lymph node metastasis in a 61-yr-old man. (A) Technetium-99m scan showed cold defect at the mass in the right submandibular gland. (B) Thallium-201 scan showed retention of activity by both the tumor and lymphnode (arrow) on delayed image. (C) Gallium-67 image showed strong uptake (++) in the tumor and lymph node.

respectively. Since sialadenitis could be differentiated by the diffuse nature of 99m Tc uptake and Warthin's tumor could be diagnosed by the 99m Tc scan alone due to their hot uptake (except for a few rare tumors), only cold lesions on 99m Tc scans would be potentially malignant tumors. A comparison of 201 Tl and 67 Ga scans of lesions that were cold on 99m Tc scans reveals that 201 Tl had a sensitivity of 60% (3/5) sensitivity, specificity of 83% (5/6), PPV pf 75% (3/4) and NPV of 71% (5/7), while the sensitivity and specificity of 67 Ga scans were 60% (3/5) and 55% (5/9), with a PPV and NPV of 43% (3/7) and 71% (5/7), respectively. Moreover, 201 Tl detected all cases of cystic changes and could be used for SPECT imaging with semiquantitative analysis to increase the detectability of the smaller mass. Dual-isotope acquisition (99m Tc and 201 Tl) with application of the triple-energy window (TEW) method will further decrease the total examination time.

CONCLUSION

Our preliminary experience indicates that ^{99m}Tc/²⁰¹Tl imaging of salivary gland disorders may be superior to ^{99m}Tc/⁶⁷Ga imaging due to their sensitivity and specificity in detecting malignant lesions, convenience for both patients and technologists and future prospects for dual-isotope acquisition with TEW.

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