The need for parathyroid imaging in cases of persistent or recurrent postoperative hyperparathyroidism, however, is generally accepted, because the morbidity associated with neck exploration is increased by at least a factor of 10 and the surgical success rate is greatly reduced (*26,27*). Not only is it technically more difficult to perform subsequent operations because of the presence of scarring and obscuration of normal tissue planes, but residual abnormal parathyroid tissue is more likely to be in an aberrant or ectopic location (*28*).

Although postoperative hyperparathyroid patients were not evaluated in our present series, the results of this preliminary study are encouraging, and the use of both regional body FDG-PET and double-phase ^{99m}Tc-sestamibi-SPECT in patients with recurrent or persistent postoperative hyperparathyroidism deserves investigation.

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Four- to Twenty-four-Hour Uptake Ratio: An Index of Rapid Iodine-131 Turnover in Hyperthyroidism

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Rapid thyroidal iodine turnover may contribute to ^{131}I therapy failure in patients with hyperthyroidism. The utility of a 4- to 24-hr ^{131}I uptake ratio was evaluated as an index of thyroidal iodide retention in hyperthyroid patients. **Methods:** In 433 hyperthyroid patients, the success of ^{131}I therapy was correlated with the following factors: gender, pretreatment with antithyroid drugs, clinical diagnosis, magnitude of early and late thyroidal ^{131}I uptake values, and the 4- to 24-hr ^{131}I uptake ratio. **Results:** Of the 433 patients, 362 patients (84%) had a successful outcome after a single therapeutic dose of ^{131}I while 71 (16%) did not. Multiple linear regression analysis revealed that the highest statistically significant predictor of outcome was the 4- to 24-hr ^{131}I uptake ratio (p-value < 0.001); all other factors showed a weaker association. An ^{131}I uptake ratio of > 1 was found in 67 (15%) patients. Thirty-two of these 67 patients (48%) failed ^{131}I therapy, whereas those patients with uptake ratios of < 1.0, only 39/366 (11%) failed ^{131}I therapy. **Conclusion:** The 4- to 24-hr ^{131}I thyroidal uptake ratio is a practical substitute for exact determination of the effective half-life. It identifies patients who are likely to have a rapid ^{131}I turnover without the need for extended thyroid uptake measurements. An ^{131}I uptake ratio of ≥ 1 was found in 15% of hyperthyroid patients and was associated with a near 50% ^{131}I therapy failure rate.

Key Words: hyperthyroidism; rapid thyroidal iodine-131 turnover; Graves' disease

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Radioactive iodine (^{131}I) therapy is the most common modality for treatment of hyperthyroidism in the United States (*1*). Between 80% and 95% of patients with Graves' disease are controlled after one therapeutic dose of ^{131}I, which is a relatively safe, simple and effective form of therapy (*2–4*). The success rate of ^{131}I therapy has a high correlation with the ^{131}I

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dose administered (*2,4–9*). Other factors, including thyroid size, gland uniformity and pretreatment with antithyroid drugs, also affect therapeutic outcome (*2,5–11*).

The radiation dose delivered to the thyroid gland depends on the concentration of ^{131}I per gram of thyroid tissue as well as the residence time of ^{131}I in the thyroid gland. The latter is generally not measured. The mean biologic half-life is variable and is often assumed to be 24 days, which is equivalent to an effective half-life of 6 days (*2,9*). A significant number of hyperthyroid patients, however, may have rapid thyroidal ^{131}I turnover resulting in a shortened residence time of ^{131}I in the thyroid gland (*2,9–11*). Rapid thyroidal ^{131}I turnover is clinically significant in two respects: (a) it decreases the radiation dose delivered to the gland, which is a potential cause for therapeutic failure; and (b) it increases the whole-body radiation dose secondary to the additional release of protein-bound ^{131}I into the vascular system (*2,10*).

The effective half-life of ^{131}I can be measured by sequential thyroid uptake determinations over a period of 5–7 days (*2,9,10*). This approach, however, is time-consuming and not extremely practical in most clinical settings. We have utilized an alternative approach to obtain an index of thyroidal ^{13}I turnover in hyperthyroid patients by comparing the pretherapy 4–6 hr ^{131}I uptake values to 20–25 hr ^{131}I uptake values and correlating this uptake ratio to therapeutic outcome.

MATERIALS AND METHODS

Patients

There were 370 women and 90 men (mean age 40 ± 17 yr) included in this study. The medical records of all hyperthyroid patients referred to the nuclear medicine division at our institution for ^{131}I therapy between July 1980 and August 1993 were reviewed. A complete set of early (4 to 6 hr) and late (20 to 25 hr) ^{131}I uptake measurements was available in 460 of 525 patients, who subsequently received ^{131}I therapy for hyperthyroidism. A total of 402 patients had the clinical diagnosis of Graves' disease, and 58 patients had other etiologies for hyperthyroidism. The diagnosis of Graves' disease was primarily based on the finding of a uniformly enlarged thyroid gland in conjunction with a suppressed serum thyroid stimulating hormone (TSH) level (<0.1). The non-Graves' group included 37 patients with multinodular goiter, 12 with superimposed Graves' disease, 4 with Hashimoto's thyroiditis, 2 with Plummer's disease and 3 with autonomous hyperfunctional nodules.

All patients were evaluated by an endocrinologist and had thyroid function tests, including TSH, free thyroxine and total thyroxine levels. Serum triiodothyronine levels, thyroid-stimulating immunoglobulin assay and thyroid scans were also obtained in several patients. All medications that could interfere with thyroidal ^{131}I uptake were stopped 4 to 6 days before ^{131}I uptake measurements and/or ^{131}I therapy. Iodine-131 uptake measurements were obtained 4–6 and 20–25 hr after oral administration of 3–9 μCi of sodium iodide (^{131}I) using a single-channel analyzer spectrometer. All measurements were obtained with the uptake probe centered on the thyroid cartilage at a distance of 25 cm. A standard ^{131}I source was also counted in a Picker nuclear neck phantom at the same distance. Thyroidal uptake was calculated according to the following equation: percent ^{131}I uptake = (neck counts − thigh counts) × 100/(standard counts − background counts).

Each patient was evaluated by an experienced nuclear medicine physician who estimated the gland weight by thyroid palpation. The estimated thyroid gland weight was recorded in the chart at the time of therapy in 320 patients; it was not recorded in the remaining cases. The therapeutic dose of ^{131}I was based on the targeted dose of 0.1–0.15 mCi/g of thyroid. A dose of 0.15 mCi of ^{131}I per gram of tissue was used for patients over 50 yr of age as well as those with nodular and/or very large thyroid glands.

Iodine-131 therapy outcome was assessed from the patient's clinical follow-up and was classified as successful if at least one of the following criteria was met: (a) development of clinical symptoms of hypothyroidism or (b) elevation of serum TSH to normal or above normal levels. The ^{131}I therapeutic outcome was classified as unsuccessful if the patient had: (a) persistent clinical or biochemical hyperthyroidism and needed antithyroid medication or (b) required additional ^{131}I therapy or surgical treatment for persistent hyperthyroidism lasting an average of 5.2 mo after an initial therapeutic dose of ^{131}I. Twenty-seven patients were lost to follow-up after the initial ^{131}I therapy. Therefore, outcome data were available for 433 patients. The mean follow-up period was 26 mo (range 6–141 mo). Early peaking of ^{131}I uptake in the thyroid gland was defined as an early (4 to 6 hr)/late (20 to 25 hr) ^{131}I uptake ratio of ≥1.0.

Statistical Analysis

Parameters in the two groups of patients with successful and unsuccessful ^{131}I therapeutic outcomes were compared using two-tailed Student's t-test and z-test. A p-value of < 0.05 or z-values of > 1.96 or < -1.96 were considered significant. Multiple linear regression analysis was performed to test if the outcome of ^{131}I therapy correlated with the following independent factors; age, sex, estimated weight of the gland, therapy dose, magnitude of early and late ^{131}I uptake values, clinical diagnosis, T4 and FT4 levels, early-to-late ^{131}I uptake ratio and pretreatment with antithyroid medications. Binary values were assigned to nonparametric variables, including sex, diagnosis and therapy outcome.

RESULTS

Of 433 evaluable patients, 362 (83.6%) had a successful outcome after one therapeutic dose of ^{131}I. Of these 362 patients, 322 had Graves' and 40 had non-Graves' disease. The administered treatment dose of ^{131}I was 145 ± 93 μCi per estimated gram of tissue. One-hundred thirty patients (36%) were treated with antithyroid medications before ^{131}I therapy; the remaining 232 patients received no antithyroid medications before ^{131}I therapy (Table 1). In our institution, antithyroid medications are routinely withheld during the immediate period before and after ^{131}I treatment. In 22 patients, however, the severity of the clinical symptoms warranted the institution of antithyroid medications 1–2 wk after ^{13}I therapy. This group of patients included 21 cases of Grave's disease and collectively accounted for only 5% of our patient population. Seventeen (77.3%) patients in this group responded favorably to ^{131}I therapy, as compared to 83.6% for the entire population. The difference was not statistically significant. Thus, antithyroid medication in the post-therapy period was not considered to be a significant factor in our subsequent analyses.

Seventy-one patients (16.4%) remained hyperthyroid for a mean of 5.2 mo after an initial therapeutic dose of ^{131}I; 57 had Graves' disease and 14 had non-Graves' disease (52 women, 19 men). Forty-two (59%) of the 71 patients who failed the initial ^{131}I therapy had received antithyroid medications before ^{131}I therapy (Table 1).

The parameters in the two groups are compared in Table 1. The magnitude of early ^{131}I uptake and the early-to-late ^{131}I uptake ratio was significantly greater in the patients who remained hyperthyroid. Male patients, those pretreated with antithyroid drugs, and those with non-Graves' disease also showed significant correlation with an unsuccessful ^{131}I therapy outcome. There were no statistically significant differences with respect to age, estimated weight of the gland, percent late

TABLE 1
Comparison of Variables in Groups Successfully and Unsuccessfully Treated with Iodine-131

Variable	Successful (n = 362)	Unsuccessful (n = 71)	p value
Sex (male) (%)	17	27	S*
Graves' disease (%)	89	80	S*
Pre-ATD Rx (%)	36	59	S*
Weight of gland (g)†	59 ± 26	58 ± 22	0.81
Total thyroxine (μg/dl)	16.7 ± 6	17.4 ± 8	0.54
Free thyroxine (ng/dl)	3.6 ± 1.9	3.6 ± 2.3	0.90
Early ^{131}I uptake (%)	50 ± 24	66 ± 26	<0.01
Late ^{131}I uptake (%)	69 ± 16	71 ± 17	0.28
4- to 24 hr ^{131}I uptake ratio	0.70 ± 0.22	0.91 ± 0.31	<0.01
Administered dose (μCi/g)	145 ± 93	155 ± 96	0.51

*Statistical significance of the difference was tested with z-test (value >1.86 significant).
†Obtained from 326 patients whose thyroid weight was recorded.
Pre-ATD Rx = pretreatment with antithyroid drugs.

uptake of ^{131}I, free and total thyroxine or therapeutic ^{131}I dose per estimated gram of tissue.

Regression Analysis

The correlation between the outcome of ^{131}I therapy and multiple independent variables, including age, sex, pretreatment with antithyroid drugs, clinical diagnosis and magnitude of the early and late ^{131}I uptake were obtained using multiple linear regression analysis. The analysis aimed at estimating the relative contribution of each factor and identifying those that showed the strongest correlation. Both the early and late uptake values as well as the clinical diagnosis showed a statistically significant correlation with the outcome (Table 2).

A clinical diagnosis of Graves' disease was associated with a favorable outcome after ^{131}I therapy, whereas a high 4-hr ^{131}I uptake value or a low 24-hr ^{131}I uptake value was a strong predictor of ^{131}I therapy failure. The early-to-late ^{131}I uptake ratio proved to be the strongest predictor of ^{131}I therapeutic failure (coefficient = 0.43 and $p < 0.01$). Figure 1 shows the relationship between the ^{131}I uptake ratio and the failure rate of ^{131}I therapy for the entire patient population. The failure rate is fairly constant for uptake ratios of less than 1.0, but there is a dramatic increase in the failure rate when the uptake ratio is equal to 1.0 or greater. Figure 2 shows the relationship between the 4-hr percent uptake value and ^{131}I therapy failure rate, and demonstrates that there was more variability in the 4-hr percent uptake value as a predictor of response to ^{131}I therapy than in the 4- to 24-hr ^{131}I uptake ratio.

A similar analysis was performed on the 326 patients whose estimated thyroid weights had been actually recorded in the chart at the time of therapy. The failure rate correlated significantly with the ^{131}I uptake ratio as well as the clinical diagnosis, but not with the estimated weight of the thyroid gland. The regression model additionally included thyroxine and free thyroxine levels and administered dose per gram of thyroid, but the model did not show a significant association between these parameters and failure of ^{131}I treatment.

TABLE 2
Multiple Linear Regression Analysis on Failure of Iodine-131 Treatment

	Six variant analysis without 4–24-hr ^{131}I uptake ratio entered in the model*		Five variant analysis with 4–24-hr ^{131}I uptake ratio replacing 4- and 24-hr % uptake values†	
Variable	Coefficient	p-value	Coefficient	p-value
Age (yr)	−0.00022	0.84	−0.000006	0.99
Pre-ATD Rx	0.06	0.09	0.063	0.076
Sex (male)	−0.008	0.85	−0.013	0.75
Diagnosis (GD)	−0.18	<0.01	−0.19	<0.01
4-hr % uptake	0.007	<0.01		
24-hr % uptake	−0.006	0.01		
4- to 24-hr ^{131}I uptake ratio			0.43	<0.01

*F = 9.8; significance of $F < 0.00001$.
†F = 11.5; significance of $F < 0.00001$.
Pre-ATD Rx = pretreatment with antithyroid drugs; GD = Graves' disease.

DISCUSSION

The actual radiation dose delivered to thyroid tissue is the most important factor affecting outcome of ^{131}I therapy in hyperthyroid patients (*2,9–11*). Other factors such as gender, race, age and size and nodularity of the thyroid gland also show a correlation with therapeutic outcome (*2,9*). In our study, two methods that might indicate the rate of thyroidal ^{131}I turnover were evaluated as potential predictors of the outcome of ^{131}I therapy. The early (4 to 6 hr) ^{131}I uptake value and the 4- to 24-hr ^{131}I uptake ratio were evaluated. The early-to-late ^{131}I uptake ratio gave the best predictive index of ^{131}I therapeutic outcome.

Almost 50% of the patients failed to respond to ^{131}I therapy if the ^{131}I uptake ratio was one or greater. The relationship, however, between ^{131}I uptake ratios and therapeutic outcome was not linear. The likelihood of therapeutic failure for patients with a 4- to 24-hr ^{131}I uptake ratio of less than 1.0 was relatively constant, ranging between 10% and 12%, whereas for patients with a 4- to 24-hr ^{131}I uptake ratio equal to or greater than 1.0 the failure rate was 48% (Fig. 1).

There were three additional parameters identified that correlated with therapeutic outcome: prior treatment with antithyroid medications, gender and clinical type of hyperthyroidism. When a linear regression model was utilized to evaluate all parameters simultaneously, only the 4 to 24-hr ^{131}I uptake ratio and the clinical type of hyperthyroidism were dominant discriminators. Patients with Graves' disease are more likely to have a successful response to therapeutic doses of ^{131}I than those with non-Graves' disease (*2,9,10*).

The higher failure rate of ^{131}I therapy among patients with an uptake ratio of >1.0 might be explained by the rapid clearance or turnover of ^{131}I from the thyroid gland. This results in a shorter effective half-life of ^{131}I with less radiation subsequently delivered to the gland. If patients with rapid thyroidal ^{131}I turnover are treated with the usual dose of ^{131}I, they are more likely to fail the initial treatment. It has been shown that use of ^{131}I therapy doses of 3–10 mCi in patients with rapid ^{131}I thyroidal turnover results in a 60% less radiation dose to the thyroid gland compared with those with relatively stable ^{131}I uptake (*2*). A mean dose of about 28 mCi of ^{131}I was required to deliver an adequate radiation dose for successful treatment in such patients.

Rapid ^{131}I turnover has been ascribed to the so-called "small iodine pool syndrome," which can be seen in patients pretreated with antithyroid drugs, those who have undergone a subtotal thyroidectomy or unsuccessful ^{131}I therapy, and those with T3 thyrotoxicosis (*2,9,12,13*). Becker and Hurley (*2*) reported that about 15% of their hyperthyroid patients had a very rapid ^{131}I

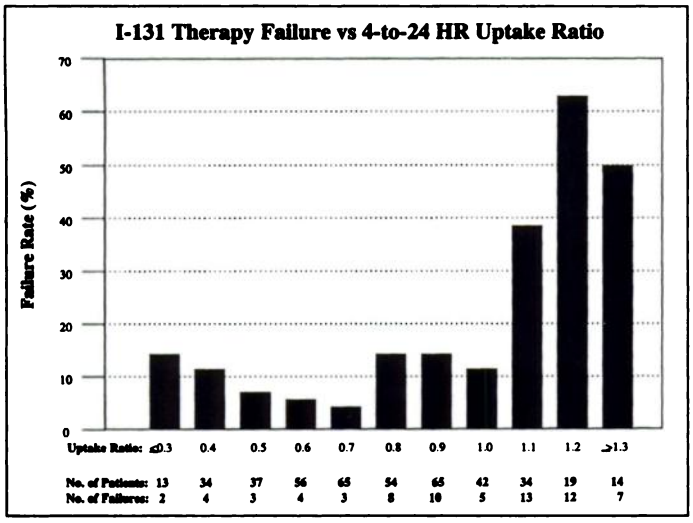

FIGURE 1. Failure of ^{131}I therapy in hyperthyroid patients is shown as a function of the ratio of thyroidal uptake at 4 hr to that at 24 hr. Bars represent percent failure rate. The actual number of patients included in each data range is shown under the graph.

turnover with an average biologic half-life of 2.8 days. Similarly, we observed that 15% of our patients had a ^{131}I uptake ratio of ≥ 1, which also appears to be indicative of rapid thyroidal uptake and ^{131}I turnover.

Rapid thyroidal ^{131}I turnover is of additional clinical importance because of the higher radiation dose delivered to all organs of the body. Radiolabeled thyroid hormone or protein-bound ^{131}I is the primary source of radiation to the bone marrow after ^{131}I therapy (*2,14–16*). If a therapeutic dose of ^{131}I sufficient to deliver an adequate radiation dose to the thyroid gland is given to patients with rapid ^{131}I thyroidal turnover, the radiation dose to the blood and, therefore, bone marrow is rather high (154 ± 34 rads) (*2,16*). The radiation dose delivered to bone marrow is not only related to the amount of thyroidal hormone released, but also to its specific activity, which is inversely related to the intrathyroidal exchangeable iodine pool (*17*). In patients with a diminished intrathyroidal iodine pool, there is a substantial increase in the specific activity of the

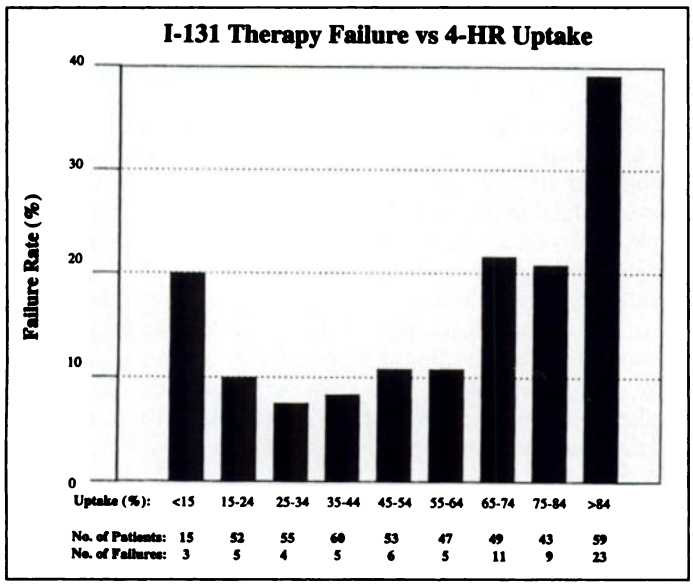

FIGURE 2. Failure of ^{131}I therapy is shown as a function of the thyroidal uptake of ^{131}I at 4 hr. Bars represent percent failure rate. The actual number of patients included in each data range is shown under the graph.

radiolabeled thyroid hormone secreted by the thyroid gland (*16,17*).

There have been conflicting published results about the effects of prior antithyroid drug therapy on the outcome of ^{131}I therapy. Some studies have reported no effect (*2,18–21*), whereas others have reported a decreased incidence of hypothyroidism after ^{131}I treatment (*5,11,22–25*). In our study, 62% of patients with an ^{131}I uptake ratio of ≥ 1.0 had received antithyroid medications, whereas only 38% of patients with an ^{131}I uptake ratio of less <1 had received antithyroid medications ($p < 0.01$). This implies that antithyroid agents may alter ^{131}I thyroidal kinetics by increasing ^{131}I turnover.

Increased resistance to ^{131}I therapy after the administration of antithyroid drugs has also been attributed to the radioprotective effect of the sulfhydryl groups that are present in antithyroid medications (*25–28*). Recent studies indicate that pretreatment with carbimazole, which does not contain sulfhydryl groups, is also associated with a higher incidence of recurrent or persistent hyperthyroidism (*11,22*). Carbimazole has been shown to reduce the effective half-life of thyroidal ^{131}I (*22,29*). This change in intrathyroidal ^{131}I kinetics may actually account for the increased failure rate of ^{131}I therapy.

Thyroidal ^{131}I uptake measurements in post-therapy patients have revealed considerable variability in ^{131}I kinetics (*30–32*). In our patients, post-therapy ^{131}I uptake measurements were obtained only in those who failed initial ^{131}I therapy and had a second ^{131}I treatment. Seventeen of 24 patients (71%) with an initial ^{131}I uptake ratio of ≥ 1 converted their ^{131}I uptake ratio to <1 after the first therapeutic dose of ^{131}I. Furthermore, 82% of these patients had a successful outcome after the second therapeutic dose of ^{131}I.

There is currently no consensus among thyroidologists as to the best therapeutic approach to be used in patients with rapid thyroidal ^{131}I turnover to optimize the radiation dose delivered to the gland and to minimize the dose delivered to the bone marrow. It has not been clearly established if nonradioactive iodide, which induces a rapid decrease in circulating thyroxine and triiodothyronine (*2,9,33*), can be used routinely after ^{131}I therapy to reduce the rate of thyroidal ^{131}I turnover. Small doses of antithyroid medications taken after ^{131}I treatment have also been shown to control clinical hyperthyroidism and reduce whole body radiation exposure (*34*). In addition, the use of lithium therapy, which blocks the secretion of thyroid hormone (*35*), needs to be investigated.

As with most retrospective studies, this study has certain shortcomings. The weight of the thyroid gland was estimated by palpation. Among experienced clinicians, the interobserver variablity for estimates of thyroid gland size is 30% for small glands and greater for larger glands (*4,36*). The classification as to the type of hyperthyroidism was based primarily on clinical judgment. Thus, it is possible that there was some overlap between the groups of patients with Graves' disease and those with non-Graves' disease.

CONCLUSION

The 4- to 24-hr ^{131}I uptake ratio appears to be a practical index for predicting rapid ^{131}I turnover in hyperthyroid patients. An ^{131}I uptake ratio of >1.0, present in 15% of our patients, was associated with a near 50% initial ^{131}I failure rate, whereas a ratio of <1.0 was associated with only an 11% failure rate. In patients with rapid ^{131}I turnover, adjunctive measures such as iodide drops, low-dose antithyroid medications, or lithium after ^{131}I therapy may be used to reduce the therapeutic dose of ^{131}I. This would help minimize the whole-body radiation dose to the

patient. Further studies are needed to optimize ^{131}I therapy in hyperthyroid patients with rapid thyroidal ^{131}I 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-^{201}Tl with those of [^{99m}Tc]pertechnetate-^{67}Ga scintiscans to elucidate the advantages of ^{201}Tl 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), ^{201}Tl (early and delayed) and ^{67}Ga 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 ^{201}Tl on delayed imaging. The ^{67}Ga 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 ^{201}Tl scan showed early uptake without retention in benign tumors except in three patients, two of whom had Warthin's tumor. Five of the benign tumors, however, were positive on ^{67}Ga scan. None of the malignant tumors showed any uptake of ^{99m}Tc. The ^{201}Tl scan showed uptake with tumor retention on delayed images in three patients; three other patients also had positive ^{67}Ga scans. Overall, sensitivity and specificity of ^{201}Tl in detecting malignant tumors were 60% and 73%, respectively, with a negative predictive value of 85%. Sensitivity and specificity for ^{67}Ga were 60% and 47%, respectively, with a negative predictive value of 80%. **Conclusion:** In view of sensitivity, specificity and convenience of ^{201}Tl as well as future prospects for dual-isotope acquisition, ^{67}Ga may be replaced by ^{201}Tl 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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