Limits to Parathyroid Imaging with Thallium-201 Confirmed by Tissue Uptake and Phantom Studies

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Correct location by ^{201}Tl imaging of 48 parathyroids in 35 patients was related to size; 25 out of 26 parathyroids of mass >1.0 g were correctly located, none of ten parathyroids <0.3 g was correctly located. In seven patients previously imaged, 108 μCi (4.0 MBq) of ^{201}Tl was injected when the thyroid was first exposed surgically. Subsequently weighed and histologically confirmed samples of parathyroid, thyroid, and skeletal muscle were counted against a standard in a well counter. Thallium-201 uptake, as %/g, did not differ between hyperplastic and adenomatous parathyroids. Mean parathyroid uptake was 0.018 %/g, thyroid 0.01 %/g, muscle 0.0026 %/g of administered dose. Lower limits for correct location lay between 0.006–0.0149% of administered dose and between 0.25–0.8 g. Studies using a ^{201}Tl phantom containing small aliquots of ^{201}Tl at higher concentrations suggested ~0.0075% of the usual patient imaging dose as a lower limit for correct location.

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Parathyroid imaging by the thallium-201 (^{201}Tl) thallous chloride and technetium-99m (^{99m}Tc) pertechnetate subtraction technique (*1,2*) has become a widely accepted procedure and is generally agreed to be an improvement on previous radioisotopic methods. A number of groups, however, have reported that the sensitivity of the technique is limited by its inability to locate correctly small parathyroid lesions (*3-6*). While some groups have reported quite high success rates with parathyroids in the range of 0.3–0.5 g, (*7-9*), and two correct locations of 0.06 g parathyroids have been reported (*7,9*), it is generally appreciated that the small size of some clinically important parathyroid lesions is likely to defy their correct location. The present study was undertaken further to examine, by estimation of ^{201}Tl uptake in parathyroids removed at operation, and by a simple study using a phantom, the limitations imposed upon successful locations by the size and ^{201}Tl uptake of parathyroids.

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PATIENTS AND METHODS

Patient Imaging

Thirty-five patients with biochemically established hyperparathyroidism were studied preoperatively by the ^{201}Tl and ^{99m}Tc subtraction technique. The imaging procedure previously described (*3*) was followed; 2.2 mCi (80 MBq) [^{99m}Tc]pertechnetate and 2.2 mCi (80 MBq) ^{201}Tl thallous chloride were given. A gamma camera* with a converging collimator was coupled to a computer† with acquisition in zoom mode for 10–15 min after ^{201}Tl injection. The resolution full width at half maximum of the collimator was 6.5 mm at 75 mm distance from surface.

Studies at Operation

Seven patients were studied with a further dose of ^{201}Tl thallous chloride at the time of operation. One hundred and eight-microcurie (4 MBq) doses were injected intravenously at the stage when the thyroid gland was first exposed and before any dissection or interference with blood supply had taken place. All samples of parathyroid removed, after weighing and histologic examination by frozen section (subsequently confirmed by examination of fixed tissue), were counted in a well counter against a 1/1K standard of the administered dose. Samples of thyroid gland and of skeletal muscle from the sterno-mastoid, weighing ~0.25 g, were likewise studied. The samples were not blotted or rinsed and the parathyroids were not reported to include any extraneous tissue such as thyroid gland or muscle. The samples were removed at times between 5 and 180 min after injection as dictated by the operative procedure.

Studies Using a Phantom

A 1-l plastic container, approximately cubical, was used to simulate the neck. This was filled with water containing 80 μCi (3 MBq) ^{201}Tl yielding an image on the gamma camera with approximately the same area and count rate as that of the field-of-view of the patient's neck obtained during in vivo imaging (300K in 5 min). Small quantities of ^{201}Tl at 10× higher concentration [0.8 μCi/ml (0.03 MBq)] in a small syringe were introduced, using varying volumes at varying depths in the container, which was placed 6 cm from the collimator face, and imaged for 10-min periods in the same way as the patients. No ^{99m}Tc was introduced into the container.

RESULTS

Patient Imaging

The results are summarized in Table 1. Forty-eight parathyroids were removed from 35 patients; all were in the neck except one deep to the medial end of the right clavicle. Twenty-nine of thirty-five (83%) parathyroids of mass over 0.5 g were correctly located and 24/25 of mass over 1.0 g, but only 1/13 (8%) of mass <0.5 g and none out of 10 of mass 0.30 g or less. Five patients had tertiary hyperparathyroidism, but only 4/13 (31%) of enlarged and removed glands were correctly located, and this is related to the smaller size of the parathyroids in these patients (Table 1). Thirty patients had primary hyperparathyroidism and 26/35 enlarged parathyroids (74%) were correctly located. There were four false-positive locations in three of the 35 patients. One patient had two false-positive locations (and one true-positive); these were attributable to patient movement in one of the earliest studies before a matrix shift program was instituted. The second had a nodular goiter; in addition to a false-positive location, a 3.4 g adenoma was correctly located. The third also had a nodular goiter and a 1.0-g adenoma was not correctly located. All the false-positive locations were within the thyroid bed. One other patient had an obviously nodular goiter and an enlarged parathyroid was correctly located. Three patients were previously explored. One had a negative imaging study and hyperplastic glands of 0.2 and 0.1 g were removed. The second had a correctly located 2.6-g adenoma removed. The third (not included among the 35) had a negative image and a fruitless second exploration, the only such of the patients imaged.

TABLE 1
Findings in 35 Patients with Primary and Tertiary Hyperparathyroidism*

Patients		Parathyroids	Correctly located >0.5 g	Correctly located <0.5 g	Not located >0.5 g	Not located <0.5 g
Primary	30	35	25	1	3	6
Tertiary	5	13	4	0	3	6
All	35	48	29	1	6	12

* Glands correctly located and not located separated by size >0.5 g and <0.5 g.

Studies at Operation

The results in the seven patients studied at operation are shown in Table 2. In the first two patients with tertiary hyperparathyroidism, four large and two small (though enlarged) hyperplastic parathyroids of mass 0.14–0.25 g were removed and none of them had been correctly located by imaging. In the third patient, two larger hyperplastic and correctly located parathyroids were removed. In Patients 4–7, with primary hyperparathyroidism, parathyroid adenomas of varying size, 0.8–5.2 g, all correctly located, were removed.

The smallest parathyroid correctly located weighed 0.8 g and contained 0.0149% of the administered dose (Patient 6) and the largest not located weighed 0.25 g and contained 0.006% of the administered dose (Patient 1). Percentage of administered dose per g, 0.011–0.033%, mean 0.018%/g, was not related to the histologic diagnosis of hyperplasia or adenoma (Table 2), or time of excision (Patients 1–3).

Table 3 shows activities in other tissues compared

TABLE 2
Findings in Parathyroids Removed at Operation in Seven Patients

Patient no.	Parathyroid	Scan	Mass (g)	Uptake %‡	%/g
1	Hyperplasia	—*	0.16	0.0053	0.033
		—	0.14	0.0015	0.011
		—	0.23	0.0030	0.013
		—	0.25	0.0060	0.017
2	Hyperplasia	—	0.14	0.0021	0.015
		—	0.15	0.0021	0.014
3	Hyperplasia	+†	1.70	0.0373	0.022
		+	2.50	0.0450	0.018
4	Adenoma	+	5.20	0.0730	0.014
5	Adenoma	+	3.35	0.0703	0.021
6	Adenoma	+	0.80	0.0149	0.019
7	Adenoma	+	1.32	0.0494	0.029

* Not located.
† Located correctly.
‡ Uptake as percent of administered dose and percent of administered dose per g.

TABLE 3
Findings in Parathyroids (Mean Values in Patients 1–3)

Patient no.	Parathyroid %/g	Thyroid* %/g	Thyroid %	Muscle* %/g
1	0.019 (4)	0.013	0.26	0.0012
2	0.015 (2)	0.011	0.22	0.0047
3	0.020 (2)	0.010	0.20	0.0030
4	0.014	0.004	0.07	0.0013
5	0.021	0.010	0.21	0.0016
6	0.019	0.013	0.26	0.0037
7	0.029	0.014	0.07†	0.0030
Mean	0.018	0.010	0.20	0.0026

* Thyroid and muscle as in Table 2.
† Patient on 1-thyroxine replacement.

with parathyroids. Percentage of administered dose per g in thyroid (0.004–0.014, mean 0.010%/g) was approximately half that found in parathyroid. With the exception of Patient 7 who was on 1-thyroxine replacement, these patients had grossly normal thyroids of estimated mass 20 g, and the mean thyroid activity, 0.2% of administered dose, is in agreement with other published studies using ^{201}Tl (*10,11*). Percent of administered dose in muscle was 0.0012–0.0047, mean 0.0026%/g; this mean was approximately one-seventh of the mean activity in parathyroids. Blood samples taken only in the first two patients showed activity %/g at 20 and 30 min approximately half that in muscle samples taken a few minutes later.

Activity in the various tissues as percent of administered dose/g as a function of time after injection is illustrated in Fig. 1 and shows some downward trend in activity with time, but there is considerable scatter. Muscle and thyroid samples (only one from each patient) were usually removed shortly after the parathyroid (or the last parathyroid) was removed. When more than one parathyroid was removed there was no consistent change in the activity %/g with time (Patients 1–3). Activity in parathyroids as percent of administered dose as a function of parathyroid mass (Fig. 2) shows an approximately linear relationship.

Studies with the Phantom

A syringe containing 1 ml of ^{201}Tl solution at a concentration of 0.8 μCi/ml (0.03 MBq/ml) representing 0.037% of the usual 2.2 mCi (80 MBq) patient imaging dose was readily located when imaged at any depth within the phantom containing 80 μCi (3 MBq) ^{201}Tl. A syringe containing 0.2 ml of ^{201}Tl solution representing 0.0075% of the usual patient imaging dose was able to be located correctly only when imaged at a depth of 2 cm in the phantom but not at a depth of 4 cm. This is the activity that would be present in a 0.4-g parathyroid, assuming the mean activity found at operation of 0.018%/g. A syringe containing 0.1 ml of solution (0.0037%/1) could not be located when imaged in any position in the phantom.

DISCUSSION

The results of parathyroid imaging reported in this study show a relatively low sensitivity of 62.5% (in terms of 48 parathyroids found at operation). However, 21% of these parathyroids weighed less than 0.3 g, and there were only four false-positive locations, so these results are probably typical of those obtained by current methods of ^{201}Tl and ^{99m}Tc subtraction imaging, and illustrate the limitations of the technique in practice.

The studies at operation, though limited in numbers, indicate that correct location of the larger parathyroids of mass ≥0.8 g and activity ≥0.0149% of the adminis-

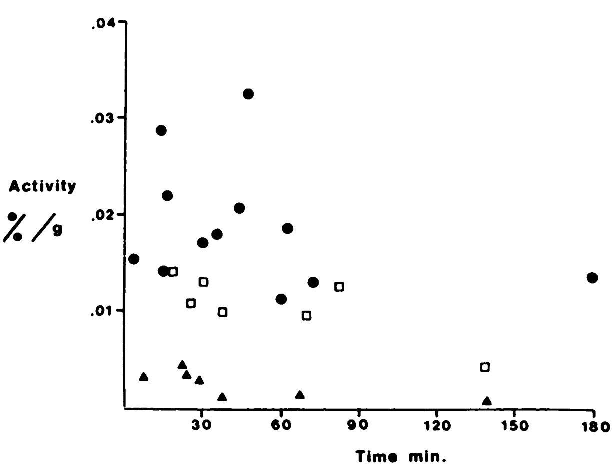

FIGURE 1
Activity in parathyroid, thyroid, and muscle, percent of administered dose per g as function of time (min) after injection. (●) Parathyroid, (□) Thyroid, (▲) Muscle

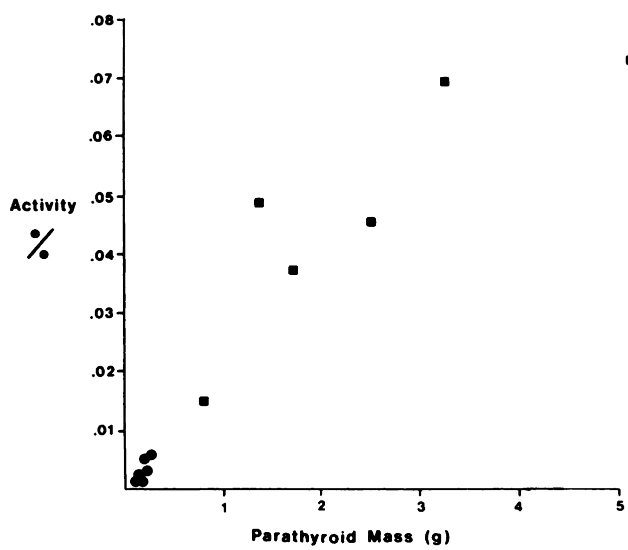

FIGURE 2
Activity, percent of administered dose, as function of parathyroid mass. (■) Correctly localized, (●) Not localized

tered dose had been achieved, and that location failed with parathyroids of mass ≤0.25 g and activity ≤0.006%. These studies also indicate that thyroid activity in percent of administered dose per g is about half that in parathyroid, and both are variable. The ratio between mean parathyroid and muscle activities is perhaps more important; this was only seven and inevitably tends to make it more difficult to locate a small parathyroid against a considerable bulk of other tissues in the neck. A somewhat higher parathyroid/muscle ratio of 17 has been quoted in a previous study (*12*).

Although most of the patients described had not previously been explored, there is no reason to think that the same constraints of size and uptake do not apply in patients imaged after a previous unsuccessful operation. The phantom experiments, where the situation in the neck was closely simulated using very small sources containing ten times background activity, suggested a lower limit of size for correct location of ~0.4 g, depending on depth.

The studies at operation also indicate that considerable biologic variation is to be expected and suggest that some considerably smaller glands, e.g., <0.4 g, might be located and some larger ones, e.g., a few >1.0 g, might not; this is confirmed by a number of reports (*3–9*). Generally, the main determinant for successful location is the size of the parathyroid which varies over 100-fold from >10 g to <0.1 g. Experience has shown that most glands >1 g will be correctly located and most <0.3 g will not; in this range of mass, the uptake per gram, which in our study ranged threefold from 0.033 to 0.011%/g becomes particularly important, but background activity is also important. In the presence of nodular goiter, failure to locate a parathyroid correctly, and the occurrence of false-positive images are difficult to avoid. There may be some decline in parathyroid uptake after the usual and probably optimal imaging time at ~5–10 min (*13,14*), so the values for activity as percent of administered dose obtained in some of the samples removed at operation are probably a little lower than the activity at the time of imaging. This would also help to account for the considerable success reported in locating glands of mass down to ~0.3 g despite the inherent difficulties. The studies here reported, however, reinforce the experience of a number of centers that correct location of parathyroids of mass less than ~0.3 g is unlikely to be regularly accomplished using currently available techniques of ^{201}Tl and ^{99m}Tc imaging (*3–9*). This is unfortunate since a number of significantly hyperfunctioning parathyroids are <0.3 g (21% in the present series) and these are inevitably less easy to find at operation. There is, therefore, still no substitute for skilled and meticulous surgery. The current imaging technique is of real value in a considerable proportion of cases, but a more sensitive method for parathyroid location is still needed.

FOOTNOTES

*General Electric Medical Systems, Milwaukee, WI (Maxicamera II).

†Nodecrest Medical Systems, UK.

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