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Preoperative Imaging of Abnormal Parathyroid Glands in Patients with Hyperparathyroid Disease Using Combination Tc-99m-Pertechnetate and Tc-99m-Sestamibi Radionuclide Scans

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Objective
To evaluate the efficacy of combined Tc-99m-pertechnetate and Tc-99m-sestamibi radionuclide scanning for imaging abnormal parathyroid glands in hyperparathyroid disease in a prospective study.

Summary Background Data
Established methods to localize abnormal parathyroid glands lack accuracy for routine use. Tc-99m-sestamibi used in conjunction with iodine-123 has excellent potential for preoperative imaging in patients with hyperparathyroid disease. An alternative method for parathyroid imaging was studied using Tc-99m-pertechnetate and Tc-99m-sestamibi.

Methods
Thirty patients with hyperparathyroid disease had Tc-99m-pertechnetate and Tc-99m-sestamibi subtraction radionuclide scanning to visualize abnormal parathyroid glands before surgery. The patients had surgery and pathologic confirmation of all parathyroid glands.

Results
In 23 patients with primary hyperparathyroidism, 12 of 13 solitary adenomas were visualized. Six of nine patients with diffuse hyperplasia had bilateral uptake consistent with diffuse hyperplasia. Three of nine patients had negative scans. One patient previously operated on for diffuse hyperplasia had only one gland scanned. Seven patients with renal failure-associated hyperparathyroid disease were scanned: five had bilateral uptake of Tc-99m-sestamibi consistent with hyperplasia, and two who had been previously operated on had localization of remaining abnormal parathyroid glands.

Conclusions
Tc-99m-pertechnetate combined with Tc-99m-sestamibi subtraction radionuclide scanning is less cumbersome to implement than iodine-123 combined with Tc-99m-sestamibi scanning. It has a high sensitivity for imaging solitary parathyroid adenomas or persistent solitary hyperplastic

glands. However it does not have the resolution necessary to delineate all parathyroid glands in diffuse hyperplasia.

The surgical treatment of hyperparathyroidism is successful in most patients.[1] Surgical failure occurs primarily because the solitary parathyroid adenoma is located outside the area of exploration or, in multiple glandular hyperplasia, hyperplastic parathyroid glands are unidentified. Most surgeons do not use preoperative radiologic localization studies routinely because the technology is limited.[2] Recent studies with Technetium (Tc)-99m-sestamibi, a new radionuclide, showed its ability to visualize abnormal parathyroid glands reliably. One method uses a subtraction technique with an iodine-123 scan of the thyroid gland. After oral administration of iodine-123, a 4-hour delay is required before thyroid imaging.[3] The second method uses Tc-99m-sestamibi alone with imaging of the neck for 2 to 3 hours.[4] This procedure is more sensitive in detecting adenomas than hyperplastic glands. We prospectively investigated combining Tc-99m-pertechnetate and Tc-99m-sestamibi to determine if this combination of radionuclides results in a more rapid, less cumbersome method for preoperative localization of abnormal parathyroid glands.

MATERIALS AND METHODS

Clinical Data

Using a study protocol approved by our institutional review board, 30 patients with primary, secondary, or tertiary hyperparathyroid disease were evaluated between June 1992 and July 1993. Twenty-two women and eight men were included in the group, with a mean age of 53 years (range, 28 to 88 years). All patients had serologic values of total and ionized calcium and intact parathyroid hormone levels that confirmed the diagnosis. Twenty-three of the thirty patients had primary hyperparathyroid disease. Seven patients had hyperparathyroid disease associated with renal failure; three were recieving hemodialysis and four had functioning renal transplants. Of these seven patients, three had secondary hyperparathyroid disease and four had tertiary hyperparathyroid disease. The clinical symptoms included bone pain in 24 (80%), muscular aches in 16 (53%), generalized systemic symptoms in 15 (50%), severe neurologic changes in 11 (37%), gastrointestinal complaints in 9 (30%), and renal calculi in 6 (20%).

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Radionuclide Studies

Before surgical exploration, all patients had radionuclide localization using a combined sequential Tc-99m-pertechnetate and Tc-99m-sestamibi scan. Tc-99m-pertechnetate is a radionuclide commonly used for thyroid imaging. Tc-99m-sestamibi is a cardiac imaging agent approved by the Federal Drug Administration that accumulates in the thyroid and parathyroid glands. Patients were initially given an intravenous dose of 148 megabecquerel (MBq) of Tc-99m-pertechnetate followed 30 minutes later by thyroid gland imaging using a computer-interfaced gamma camera with a high-resolution, parallel hole collimator. With the patient remaining in the supine position and immobilized, 148 MBq of Tc-99m-sestamibi was administered intravenously. The neck was immediately scanned for an additional 20 minutes, followed by a scan of the chest. The data were analyzed for motion, and the Tc-99m-sestamibi image was subtracted from the Tc-99m-pertechnetate image.

Surgical Procedures

Patients not previously operated on had bilateral neck exploration and identification of all parathyroid glands that could be located. The results of the radionuclide scans was used by the operating surgeon to confirm the radiologic images. The largest diameter of each gland was measured *in vivo*; small biopsies samples were also taken to establish the presence of parathyroid tissue. Only the adenoma was resected in those patients having a diagnosis of solitary adenoma. Those patients who had a diagnosis of diffuse hyperplasia had a more extensive dissection in the paratracheal, the paraesophageal, and the pericarotid sheath areas. The thymic remnant was extracted through the cervical exposure after a subtotal parathyroidectomy was performed. Routinely at least 3.5 parathyroid glands were resected; the viable remnant of approximately 35 mg of tissue was marked with a metallic clip. Those patients who had been previously operated on had limited neck exploration with attention directed to the area localized by the sestamibi scan; if frozen section histologic analysis confirmed the presence of parathyroid tissue, the exploration was completed. All patients had postoperative correction of their hyperparathyroid disease.

Data Analysis

In each patient, the radionuclide localization data were correlated with the surgical, anatomic, and patho-

Table 1. RESULTS OF OPERATION FOR HYPERPARATHYROIDISM

Disease	No. of Patients	Surgical/Pathologic Diagnosis
Primary	13	Solitary adenoma
	9	Diffuse hyperplasia
	1	Residual hyperplastic gland
Secondary and tertiary	5	Diffuse hyperplasia
	2	Residual hyperplastic gland and carcinoma

logic data to determine the sensitivity and specificity of the sestamibi scan. Statistical analysis of the difference of the means was performed using the unpaired Student's *t*-test. Sensitivity was defined as the ratio of true-positive results to the sum of true-positive plus false-negative results. Specificity was defined as the ratio of true-negative results to the sum of true-negative plus false-positive results. Positive predictive value was defined as the ratio of true-positive results to the sum of true-positive and false-positive results.

RESULTS

Surgical Findings

Thirteen of the 23 patients with primary hyperparathyroid disease had solitary parathyroid adenomas (Table 1). All 13 parathyroid adenomas were within the field of surgical exploration accessible from a neck incision. There were 6 right inferior, 1 right superior, 4 left inferior, and 2 left superior parathyroid gland adenomas. A total of 38 parathyroid glands were found in these 13 patients, with 13 adenomas and 25 normal parathyroid glands (Table 2). A mean of 2.9 ± 0.9 standard deviation (SD) total glands were found per patient. A mean of 1.9 ± 0.9 SD normal glands were found per patient with solitary adenomas. The mean weight of the solitary adenomas was 0.96 ± 0.8 g SD, with a range of 0.2 to 3.0 g. The mean largest diameter of the adenomas was a 20.9 ± 9.9 mm SD, with a range of 11 to 44 mm (Table 3). The mean largest diameter of the normal glands was 7.2 ± 2.7 mm SD, with a range of 4 to 16 mm. This difference was statistically significant ($p = 0.001$). Ten of the 23 patients with primary hyperparathyroid disease had diffuse hyperplasia. Three patients had primary hyperparathyroidism associated with the multiple endocrine neoplasia 1 syndrome. One patient had two previous operations in which three hyperplastic parathyroid glands were removed. The fourth hyperplastic gland was found at reoperation and resected. The other 9 patients had subtotal parathyroidectomy. Twenty-two hyperplastic glands

Table 2. DISTRIBUTION OF PARATHYROID GLANDS AT OPERATION

Disease	No. of Pathologic Glands	No. of Normal Glands	No. of Glands/Pt.
Primary			
adenoma	13	25	2.9 ± 0.9 SD
hyperplasia	21	0	2.6 ± 0.7 SD
residual hyperplasia	1	0	1
Secondary and tertiary			
hyperplasia	19	0	3.8 ± 0.4 SD
residual hyperplasia and carcinoma	6	0	3.0 ± 0 SD

were found in these patients, with a mean of 2.4 ± 0.9 SD hyperplastic glands per patient. The mean largest diameter of these hyperplastic glands was 12.3 ± 7.4 mm SD, with a range of 5 to 34 mm.

In the seven patients with renal failure-associated hyperparathyroidism (secondary and tertiary), two patients previously had surgery for the disease. One of these patients had a solitary parathyroid adenoma excised 5 years before coming to us; at reoperation, a subtotal parathyroidectomy for three hyperplastic glands was performed. In the other patient, a subtotal parathyroidectomy had been performed 10 years earlier; at reoperation, two hyperplastic nodules and a parathyroid carcinoma were resected. The remaining five patients had successful subtotal parathyroidectomy. Twenty-five hyperplastic glands were found in these seven patients, with a mean of 3.6 ± 0.5 SD hyperplastic glands per patient. The mean largest diameter of these hyperplastic glands was 15.6 ± 8.1 mm SD, with a range of 5 to 36 mm.

Radionuclide Data

Tc-99m-pertechnetate plus Tc-99m-sestamibi subtraction scanning localized 12 of 13 solitary parathyroid

Table 3. LARGEST DIAMETER (IN MM) OF PARATHYROID GLANDS AT OPERATION

Disease	Largest Diameter (mm) (mean ± SD)	Range (mm)
Primary		
Adenoma (N = 13)	20.9 ± 9.9	11–44
Normal Glands (N = 25)	7.2 ± 2.7	4–16
Hyperplastic Glands (N = 22)	12.3 ± 7.4	5–34
Secondary and tertiary		
Hyperplastic Glands and carcinoma (N = 25)	15.6 ± 8.1	5–36

Table 4. CORRELATION OF Tc-99m-SESTAMIBI LOCALIZATION OF PARATHYROID GLANDS WITH SURGICAL AND PATHOLOGIC FINDINGS

Histology	True (+)	True (−)	False (+)	False (−)
Adenomas	12	0	1	1
Normal	0	25	0	0
Hyperplastic	35	0	0	11
Carcinoma	1	0	0	0

adenomas in patients having primary hyperparathyroid disease (Table 4, Fig. 1). None of the normal parathyroid glands found at surgery were imaged using this method. The only solitary adenoma that was not localized weighed 0.2 g, with a diameter of 11 mm, compared with the mean weight of 1.02 ± 0.8 g SD and a mean largest diameter of 21.8 ± 9.8 mm SD for the 12 solitary adenomas that were localized. The sensitivity for detection of solitary adenomas was 92% and the specificity was 100%. The positive predictive value was 100%. Comparison of the mean largest diameter of the imaged solitary adenomas (21.8 ± 9.8 mm SD) with the mean largest diameter of the nonimaged normal parathyroid glands and solitary adenoma (7 ± 3 mm SD) showed a significant difference ($p = 0.001$).

The results of Tc-99m-pertechnetate plus Tc-99m-sestamibi subtraction scanning of those patients with diffuse hyperplasia from primary, secondary, and tertiary hyperparathyroid disease were analyzed together (Fig. 2). In three patients who had previous surgery, the remaining abnormal parathyroid glands were localized. Thirty-seven of 47 abnormal parathyroid glands (46 hyperplastic and 1 carcinoma) found at surgery correlated with preoperative radionuclide imaging. The mean largest diameter of the imaged parathyroid glands, 15.6 ± 8.1 mm SD (range, 5 to 36 mm), was significantly different from the mean largest diameter of the nonimaged parathyroid glands, 8.3 ± 2.9 mm SD (range, 6 to 16 mm) ($p = 0.005$). The sensitivity for detecting individual abnormal parathyroid glands in the presence of diffuse hyperplasia was 79%, with a positive predictive value of 100%. Overall Tc-99m-sestamibi plus Tc-99m-pertechnetate subtraction scanning showed a sensitivity rate of 79% and a positive predictive value of 100% for diagnosing diffuse hyperplasia in previously unoperated patients.

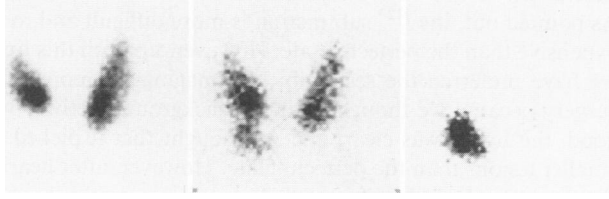

Figure 1. Tc-99m-pertechnetate thyroid scan (*left*), Tc-99m-sestamibi scan (*middle*), and subtraction scan (*right*) show a solitary parathyroid adenoma.

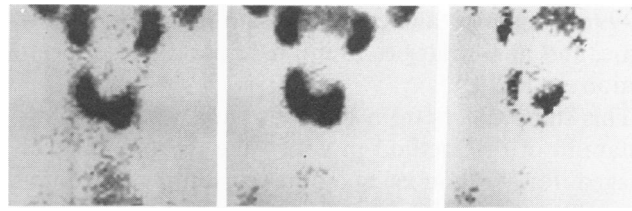

Figure 2. Tc-99m-pertechnetate thyroid scan (*left*), Tc-99m-sestamibi scan (*middle*), and subtraction scan (*right*) show diffuse bilateral parathyroid hyperplasia.

DISCUSSION

Surgical exploration and resection of abnormal parathyroid glands is successful at the initial operation in as many as 95% of patients with hyperparathyroid disease. Failure of the initial operation is most often due to the ectopic location of the solitary adenoma in patients with primary hyperparathyroid disease.[5] In patients with diffuse parathyroid glandular hyperplasia, with either primary or secondary hyperparathyroid disease, ectopic glands or supernumerary glands located outside the field of surgery may explain continuing hyperparathyroid disease after operation.

Most experienced surgeons who routinely perform parathyroidectomy for parathyroid disease do not use preoperative localization tests. Bilateral neck exploration under these circumstances is associated with a high success rate and a low rate of complication. The most commonly used methods, technetium-99m-pertechnetate and thallium-201 radionuclide scanning, high-resolution ultrasonography, computed tomography, and magnetic resonance imaging lack sufficient sensitivity for routine preoperative use and are used predominantly after failed initial operations.[6] Tc-99m-sestamibi, a new radiopharmaceutical developed for myocardial perfusion studies, is approved by the Federal Drug Administration for cardiac imaging. Recent studies showed that Tc-99m-sestamibi is very sensitive for imaging abnormal parathyroid glands, particularly solitary adenomas. In our previous work analyzing iodine-123 and Tc-99m-sestamibi radionuclide scanning, we found a sensitivity rate of 100% and positive predictive value of 79% for solitary parathyroid adenomas, and a sensitivity rate of 67% and a positive predictive value of 94% for hyperplastic glands.[7] The best method for using this new radionuclide has not been determined.[8] Current strategies use subtraction imaging with iodine-123 or prolonged imaging with

Tc-99m-sestamibi alone. Both methods are cumbersome, and new strategies to improve parathyroid localization are needed.

This study differs from previous work with Tc-99m-sestamibi in the method in which the thyroid gland is imaged. Rather than using a time-consuming and cumbersome iodine-123 subtraction technique, we imaged the thyroid gland using a rapid Tc-99m-pertechnetate technique. Because one of the most important aspects of parathyroid localization is the ability to subtract the thyroid image completely, adequate thyroid imaging without motion artifacts is crucial. In this prospective study of Tc-99m-pertechnetate and Tc-99m-sestamibi subtraction scanning, we achieved a high sensitivity rate for localizing solitary parathyroid adenomas or residual hyperplastic parathyroid glands. Because the parathyroid glands are located near the thyroid gland and hyperplastic glands are smaller compared with a dominant solitary adenoma, Tc-99m-sestamibi imaging of diffuse parathyroid glandular hyperplasia does not always occur. When both isotopes are used, there may not be enough contrast to separate the thyroid and the parathyroid glands, especially in multiple gland hyperplasia. The radionuclide localization of solitary parathyroid adenomas or solitary residual hyperplastic parathyroid glands may be more successful because of increased concentration and uptake of Tc-99m-sestamibi in a single focus of abnormal parathyroid tissue. Glandular size ultimately may be the important determinant for the limits of resolution of Tc-99m-sestamibi radionuclide imaging. The results of this study compare favorably with results of previous work using iodine-123 subtraction or Tc-99m-sestamibi alone. Direct comparison to determine which technique is better cannot be done now. Tc-99m-sestamibi subtraction imaging of abnormal parathyroid glands is less cumbersome and quicker using a Tc-99m-pertechnetate technique.

Most experienced surgeons who perform parathyroid operations advocate bilateral neck exploration to ensure the success of the initial operation. If a radiologic method that could localize every abnormal parathyroid gland were developed, it might be possible to limit the extent of surgical exploration for parathyroid disease and to reduce the morbidity from complete neck exploration. In this study, although no effect was evident in those patients having initial neck exploration for hyperparathyroid disease, the radionuclide scans did help direct the surgeon to the area of abnormal parathyroid glands in those patients having reoperation. Above all, a thorough understanding of the principles and physiology of hyperparathyroid disease should guide the surgeon in the operation for that disease. Until more studies have elucidated the mechanisms and limitations of Tc-99m-sestamibi parathyroid imaging, clinical and operative decisions should not be based only on radiologic images.

Acknowledgment

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Discussion

DR. WILLIAM C. MCGARITY (Atlanta, Georgia): We do not use routine localizing studies before the initially neck exploration in parathyroids in patients with primary hyperparathyroidism, except as already mentioned in patients who have had previous neck surgery and in an occasional poor risk patient. Our experience with technetium 99m sestamibi iodine 123 imaging reoperative parathyroid surgery has been very good. And, Dr. Mansberger, we have also found that the technique is better in identifying adenomas than hyperplasia. In our series, 14 patients had 14 adenomas correctly localized. Seven of these were reoperative case, four were in the mediastinum, and we had three false positives due to thyroid lesions. There were no false negatives. However, only 11 of the 15 enlarged glands were correctly localized in patients with hyperplasia. There were two false positives due to thyroid lesions and four false negatives. As pointed out, the I^{123} subtraction is more difficult and more expensive than the pertechnetate. However, up until this time, we have preferred the sestamibi I^{123} imaging for reoperative surgery because we thought that the background activity was good, the image was clear, and we thought that it picked up smaller lesions than the pertechnetate. However, after hearing the paper by Dr. Mansberger this morning, we may have to rethink our position in that regard. For reoperative surgery, we need the best study available. Dr. Mansberger, I'd like to ask you the following questions. What tissues in the neck take up