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Correlations between biochemical testing, pathology findings and preoperative sestamibi scans: a retrospective study of the minimally invasive radioguided parathyroidectomy (MIRP) approach

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Abstract

BACKGROUND: Sestamibi imaging is the most widely used preoperative localization study for patients with hyperparathyroidism. Previous reports examine the relationship between the weight and volume of excised parathyroid glands and preoperative serum calcium and parathyroid hormone (PTH) levels. The aim of this study was to examine whether these variables correlate with the results of preoperative Sestamibi scans.
MATERIAL AND METHODS: A retrospective review of 150 consecutive patients who underwent preoperative sestamibi imaging for primary hyperparathyroidism between 1998 and 2007 was performed. Variables studied included patient demographics, diagnostic test (sestamibi) results, operative/pathology findings and surgical outcome (normocalcaemia vs. persistent hypercalcaemia). Sestamibi scans were designated as either “negative” (NSS) or “positive” (PSS), where PSS correctly localized abnormal gland(s) enabling a focused neck exploration. The results of sestamibi imaging were correlated with calcium/PTH levels, weight/volume of excised glands and patient outcomes and demographics.
RESULTS: Total excised gland weight/volume and preoperative serum calcium levels were significantly higher with PSS (all, $p < 0.04$). Higher preoperative serum calcium levels and greater total gland weight/volume were significantly associated with successful operative outcome (presence of postoperative normocalcaemia; all, $p < 0.01$). Factors associated with operative failure included multi-gland disease ($p < 0.01$) and NSS ($p < < 0.01$). Higher diagnostic PTH levels (> 150 pg/mL) were associated with greater excised gland mass ($p < 0.05$) and volume ($p < 0.05$). Male gender was associated with higher preoperative serum calcium levels ($p < 0.02$). Of interest, patients with single-gland disease had significantly higher preoperative PTH levels than patients with multi-gland disease (155 vs. 109 pg/mL, $p < 0.05$).
CONCLUSION: Positive sestamibi scans are associated with heavier/larger parathyroid glands and higher preoperative serum calcium levels. Male gender was associated with higher preoperative serum calcium levels, while single-gland disease was associated with higher preoperative PTH levels. In addition, successful surgical outcome was associated with higher preoperative serum calcium levels and with greater excised parathyroid gland mass/volume. Surgical failure was associated with multi-gland disease and negative sestamibi.
Key words: parathyroid hormone, PTH, sestamibi imaging, minimally invasive radioguided parathyroidectomy, MIRP

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Introduction

Sestamibi imaging is the most frequently utilized preoperative localization study for patients with primary hyperparathyroidism [1, 2]. Studies comparing the relationship between volume and weight of excised parathyroid glands and the diagnostic levels of calcium and parathyroid hormone (PTH) have been previously reported [1, 3–8]. However, there are no large series that investigate the correlation between these variables and preoperative sestamibi scan results [9].

The purpose of this study was to evaluate the relationship between preoperative sestamibi scans and preoperative serum calcium/PTH levels, excised parathyroid gland volume/weight, and surgical outcome.

Material and methods

All patients who underwent preoperative sestamibi imaging at our institution for biochemically proven primary hyperparathyroidism between 1998 and 2007 were included in the study. We identified 150 patients from our hospital records. Data pertaining to patient age, gender, diagnostic serum calcium and PTH levels, weight and volume of the excised glands, and surgical outcome were recorded. Weight and volume of excised parathyroid glands were obtained from surgical pathology reports. The volume of each gland was obtained by multiplying the three specimen dimensions as listed on the pathology report. Total gland weight/volumes were obtained by adding weights and volumes of all excised abnormal parathyroid tissue for each patient.

The findings of the preoperative sestamibi scan were correlated with diagnostic criteria (serum calcium and PTH levels), operative findings (weight and volume of excised glands) and surgical outcome (corrected hypercalcaemia versus persistent hypercalcaemia). A successful outcome was defined as correction of hypercalcaemia postoperatively, while an unsuccessful outcome was defined as persistent postoperative hypercalcaemia. Additional comparisons included examinations of the pathology and biochemical parameters when grouped by patient gender, age (< 65 years vs. ≥ 65 years), single- versus multi-gland disease and parathyroid hormone level (< 150 pg/mL vs. ≥ 150 pg/mL).

Double-phase sestamibi imaging was performed using a General Electric Millennium Gamma Camera (GE Medical Systems, Waukesha, WI, USA). Patients were injected intravenously with 25–30 mCi technetium (Tc) 99m sestamibi. Planar imaging with a 256 × 256 matrix was performed with a low-energy, high-resolution (LEHR) collimator 15 minutes after injection and 1.5–2 hours later. Images were repeated at a preset time of 10 minutes, from the level of the oropharynx to the top of the myocardium. A double-phase study was considered "positive" for single or multiple gland disease when foci of increased radiotracer uptake on initial images persisted on delayed images. Whenever possible, the exact location, side, upper or lower pole and suspected ectopic parathyroid gland presence was identified and recorded.

All sestamibi scans were interpreted by a radiologist and subsequently ranked according to a scale from 0 to 3 as follows:

0 — scans technically inadequate;

1 — scans technically adequate with no identifiable lesion [i.e. negative scan];

2 — scans with moderate suspicion of a lesion [i.e. identified laterality but not exact location of gland(s)];

3 — scans with high suspicion of a lesion [i.e. clearly identified and localized abnormal gland(s)].

The sestamibi scan was considered "positive" (PSS) when the scan correctly identified abnormal gland or glands (scan rank 2 or 3). This, in turn, enabled directed minimally invasive unilateral exploration in cases of single-gland disease or limited bilateral approach in cases of clearly defined bilateral disease. Conversely, "negative" (NSS) scans did not clearly visualize abnormal gland(s), and bilateral neck exploration was performed.

Statistical analysis was conducted using SPSS™ for Windows™ software and included χ^2 test, two-sample t-test, Mann-Whitney U-test and coefficient of correlation, as appropriate. Statistical significance was set at alpha = 0.05.

Results

One hundred and fifty patients with adequate preoperative imaging studies were identified. The mean age was 59.4 ± 14.6 years (age range 20 to 93 years; median age 61.5 years). There were 41 men and 109 women. Of note, men were significantly younger (55.2 ± 13.2 years) than women (61.0 ± 14.9 years) at the time of initial presentation ($p < 0.03$).

The preoperative sestamibi scan clearly indicated the location of the gland(s) in 109 patients (PSS, scan rank 2 or 3). Of those, nine patients (8%) had clearly defined multiple gland disease, with 6/9 (67%) confined to the same side and 3/9 (33%) located on opposite sides of the neck. Unilateral exploration was performed in 106/109 patients (97%) and resulted in correction of hypercalcaemia in 103/106 cases (97%). Of the three failures, 1/3 had an initial sestamibi scan showing unilateral two-gland disease and 2/3 patients had an initial sestamibi scan showing single-gland disease, with 2/3 patients subsequently found to have small contralateral abnormal glands and 1/3 found to have an ectopic upper mediastinal parathyroid gland. Three patients (3/109, or 3%) with PSS underwent limited bilateral exploration due to the presence of well-defined bilateral disease (≥ 2 glands clearly visualized on sestamibi), with 100% normocalcaemia, postoperatively.

In 41 patients, the sestamibi scan could not accurately localize the abnormal lesion(s) (NSS, scan rank = 0 or 1), and formal bilateral exploration was performed. Single-gland disease was found in 27/41 patients (66%) and multiple gland disease in 14/41 (34%) patients upon bilateral exploration. In the NSS group, 26/27 (96%) of patients with single-gland disease and 8/14 (57%) of patients with multi-gland disease were normocalcaemic postoperatively. Operative failures in the NSS group were attributed to ectopic parathyroid gland location (3/7, 43%) or to glands that were missed during the initial exploration (4/7, 57%).

Overall, hypercalcaemia was corrected postoperatively in 34/41 (83%) patients in the NSS group and in 16/23 (70%) patients with multi-gland (≥ 2 gland) disease. This is in contrast to the success rates seen with PSS (106/109, 97%) and with single-gland disease (124/127, 98%). Consequently, factors associated with operative failure included the presence of multi-gland disease ($p < 0.01$) and initial negative sestamibi scan ($p < 0.01$).

The total excised gland weight correlated highly with total excised gland volume ($R = 0.94$; $p < 0.01$, Figure 1). Weight and

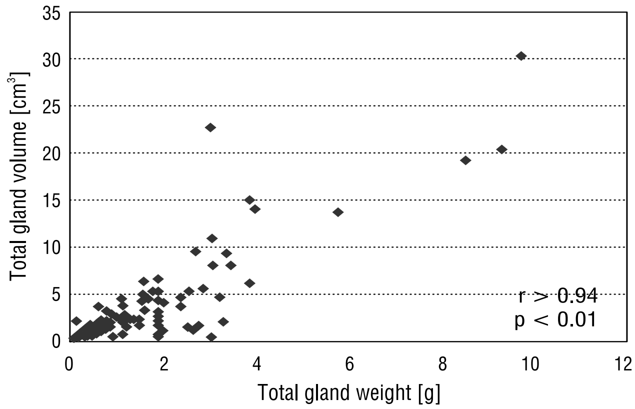

Figure 1. Scatterplot showing the relationship between total excised parathyroid gland weight (x-axis) and total excised gland volume (y-axis). The two variables demonstrated a very high degree of correlation.

volume of excised parathyroid glands significantly correlated with PSS (both measurements, $p < 0.04$, Table 1). Both volume and weight of glands removed from patients with PSS were approximately two times greater than volume and weight of glands removed from patients with NSS. Serum calcium levels were noted to be modestly higher for the PSS group ($p < 0.04$, Table 1). However, no significant relationship was found between diagnostic PTH levels and the preoperative sestamibi scan.

The mean values of all studied variables except parathyroid hormone were significantly higher in the group of patients in whom hypercalcaemia was corrected (successful outcome) after neck exploration compared with the small group of patients with continued hypercalcaemia (unsuccessful outcome, Table 2). Comparing successful with unsuccessful neck exploration, the difference between diagnostic calcium levels was modest (11.2 mg/dL vs. 10.2 mg/dL, $p < 0.01$). The total excised parathyroid gland volume and weight were between 3.0 to 3.7 times greater in the successful outcome group than in the unsuccessful outcome group (Table 2, both $p < 0.01$).

When comparing male and female patients, the only statistically significant difference noted was the preoperative calcium level (Table 3). However, the small difference of 0.4 mg/dL is unlikely to be of clinical significance. Of interest, when patients with single-gland disease were compared to patients with multi-gland disease, preoperative parathyroid hormone levels were significantly higher in the single-gland group (154.5 pg/dL) than in the multi-gland group (108.8 pg/dL, $p < 0.05$) (Table 4). None of the parameters under study was significantly different when comparing patients < 65 years old to those > 65 years old (Table 5).

A significant correlation was identified between both the volume and weight of excised glands and preoperative PTH levels (Table 6). For patients with preoperative PTH > 150 pg/dL, the excised glands were heavier and larger than for patients with preoperative PTH < 150 pg/dL (both, $p < 0.05$). For diagnostic calcium levels, these correlations were not identified.

Discussion

This study examines the relationship between preoperative sestamibi scan and diagnostic calcium/PTH levels, the weight/ /volume of excised parathyroid glands, and postoperative outcome. This study shares some similarities with other studies in terms of patient demographics [10, 11] and the characteristics of sestamibi imaging [1, 4, 8–10, 12]. While the overall reported ses-

Table 1. Correlation of preoperative sestamibi scan result (positive vs. negative) with diagnostic calcium and parathormone (PTH) levels and weight/volume of excised glands

Scan designation	Calcium [mg/dl]*	PTH [pg/dl]*	Total volume [cm³]	Total weight [gm]
Positive (n = 109)	11.2 ± 0.746	147.6 ± 103.6	3.27 ± 4.89	1.48 ± 1.76
Negative (n = 41)	10.9 ± 0.806	147.0 ± 95.5	1.50 ± 1.42	0.861 ± 0.736
Significance	p < 0.04	p = NS	p < 0.03	p < 0.04

*intact PTH (normal range, 0–55 pg/ml); calcium (normal range, 8.4–10.2 mg/dl); NS — non significant

Table 2. Correlation between calcium, parathormone (PTH) and weight/volume of excised glands to outcome of neck exploration

Procedure outcome	Calcium [mg/dl]*	PTH [pg/dl]*	Total volume [cm³]	Total weight [gm]
Successful (n = 140)	11.2 ± 0.721	147.0 ± 103.0	2.94 ± 4.42	1.37 ± 1.61
Unsuccessful (n = 10)	10.2 ± 0.885	154.5 ± 73.4	0.785 ± 0.536	0.455 ± 0.308
Significance	p < 0.01	p = NS	p < 0.01	p < 0.01

*intact PTH (normal range, 0–55 pg/ml); calcium (normal range, 8.4–10.2 mg/dl); NS — non significant

Table 3. Correlation between patient gender and calcium, parathormone (PTH), weight/volume of glands

Patient gender	Calcium [mg/dl]*	PTH [pg/dl]*	Total volume [cm³]	Total weight [gm]
Male (n = 41)	11.4 ± 0.797	161.8 ± 122.2	2.62 ± 2.93	1.32 ± 1.06
Female (n = 109)	11.0 ± 0.745	142.0 ± 92.0	2.85 ± 4.73	1.31 ± 1.73
Significance	p < 0.02	p = NS	p = NS	p = NS

*intact PTH (normal range, 0–55 pg/ml); calcium (normal range, 8.4–10.2 mg/dl); NS — non significant

Table 4. Calcium, parathormone (PTH), excised gland weight/volume for single vs. multiple adenomas

Number of glands	Calcium [mg/dl]*	PTH [pg/dl]*	Total volume [cm³]	Total weight [gm]
One (n = 127)	11.1 ± 0.758	154.5 ± 107.4	2.82 ± 4.33	1.30 ± 1.51
Two or more (n = 23)	11.0 ± 0.851	108.8 ± 36.1	2.66 ± 4.22	1.37 ± 1.94
Significance	p = NS	p < 0.05	p = NS	p = NS

*intact PTH (normal range, 0–55 pg/ml); calcium (normal range, 8.4–10.2 mg/dl); NS — non significant

Table 5. Surgical outcome, calcium, parathormone (PTH), excised gland weight/volume grouped by patient age

Patient age	Successful outcome (%)	Calcium [mg/dl]*	PTH [pg/dl]*	Total volume [cm³]	Total weight [gm]
< 65 (n = 88)	93.2%	11.1 ± 0.741	145.9 ± 82.4	2.81 ± 3.82	1.32 ± 1.42
≥ 65 (n = 62)	93.5%	11.1 ± 0.820	149.6 ± 123.7	2.77 ± 4.93	1.30 ± 1.79
Significance	p = NS	p = NS	p = NS	p = NS	p = NS

*intact PTH (normal range, 0–55 pg/ml); calcium (normal range, 8.4–10.2 mg/dl); NS — non significant

Table 6. Correlation between preoperative parathormone (PTH) levels and preoperative calcium level as well as the weight/volume of excised glands

PTH level [pg/dl]*	Calcium [mg/dl]**	Total volume [cm³]	Total weight [gm]
< 150 (n = 97)	11.1 ± 0.742	2.27 ± 3.52	1.12 ± 1.26
≥ 150 (n = 53)	11.2 ± 0.828	3.75 ± 5.36	1.67 ± 1.99
Significance	p = NS	p < 0.05	p < 0.05

*intact PTH (normal range, 0–55 pg/ml); **calcium (normal range, 8.4–10.2 mg/dl); NS — non significant

tamibi sensitivity ranges between 50% and 95%, it is important to note that sestamibi imaging seems to be more sensitive for single parathyroid adenomas (90%) compared to hyperplasia or double adenomas (50–65%) [3, 13].

In our study, larger excised gland weight and volume correlated with PSS. Parathyroid glands excised from patients with PSS had a significantly greater volume and weight than parathyroid glands excised from patients with NSS. These findings are consistent with those from previous studies [3, 4, 8]. In one study, parathyroid glands identified with positive scans were ten times heavier than those of negative scans [4]. In another, both weight and volume were approximately two times greater for positive scans, a finding more consistent with our observations [3].

When PSS and NSS were correlated to PTH levels, no statistically significant relationship was found. This finding is similar to two other studies which showed no correlation between biochemical parameters and scintigraphic results [3, 4]. In our series, patients with PSS had moderately higher calcium levels than those with NSS, which is contrary to findings in other studies [3, 4]. However, it is unlikely that this small difference in diagnostic calcium levels is clinically significant.

Three variables (total gland weight, total gland volume and preoperative calcium level) were significantly higher in patients with normocalcaemia after neck exploration than in patients with continued hypercalcaemia (Table 2). Our clinical experience indicates that patients with primary hyperparathyroidism are being diagnosed earlier in the course of the disease, and it may be that parathyroid glands with lower mass and volume produce lower levels of PTH and could be more difficult to identify diagnostically and intraoperatively. In addition, two of the three failures in the PSS group in this study were due to small, contralateral glands that were not apparent on the preoperative sestamibi scan.

Preoperative parathyroid hormone levels were significantly higher for patients with single-gland disease than for those with multi-gland disease (Table 4). The fact that the total gland weight and total gland volume were not significantly different between single- and multi-gland disease groups poses an interesting question from the standpoint of differences in PTH synthetic capacity between these two groups. It is also noteworthy to mention that when grouped by PTH levels (< 150 pg/mL vs. ≥ 150 pg/mL), both total excised gland volume and total excised gland weight were significantly greater in the higher PTH group, suggesting a higher PTH output from larger and heavier parathyroid glands (Table 6). Similar relationships were not true for calcium levels, perhaps reflecting the complex metabolic interrelationships (renal, bone and gastrointestinal tract metabolism) involved in metabolic calcium processing [14].

While men had slightly higher diagnostic calcium levels, no significant differences in PTH levels, total gland weight or total gland volume were noted between men and women (Table 3). No significant differences were seen between patients < 65 years old and those > 65 years old in any of the studied variables (Table 5).

Of note, this study did not utilize the intraoperative PTH measurement as an adjunct to the MIRP technique. Nevertheless, our success rates were comparable to those of other series, many of which utilized intraoperative PTH as an intraoperative confirmatory test. A group from the University of Louisville recently reported overall operative success rates (98%) similar to ours (93%) without the utilization of intraoperative PTH measurements [15]. Others, however, advocate the use of routine intraoperative PTH determinations due to the reported operative failure rate of up to

10% (7% in this study) [16]. While it may be that intraoperative PTH levels may not be routinely needed, selective use of this technique should certainly be considered and investigated further. For example, patients with NSS, multi-gland disease and those who require re-exploration for persistent hypercalcaemia could benefit from early intraoperative identification of persistent PTH elevation due to the higher overall operative failure rates in these groups.

In addition, intraoperative use of the gamma probe proved to be extremely useful in two reoperative cases following initial operative failures in this series. In one case, the gamma probe allowed accurate identification of a 150 mg upper mediastinal parathyroid gland. In another case, an ectopic parathyroid gland in the upper neck was successfully localized using this technique.

The strengths of our study include its large sample size and the high-quality complete dataset. The weaknesses of our study include its retrospective nature, the lack of comparison to other imaging/localization modalities (i.e. ultrasound) and the lack of comparison of presence versus absence of intraoperative PTH monitoring in determining operative success rates.

Conclusions

In this study, positive sestamibi scans correlated with greater volume/weight of the excised parathyroid glands, as well as with higher diagnostic calcium levels. Preoperative PTH levels > 150 pg/dL correlated with greater volume and weight of the excised parathyroid glands. In addition, single-gland disease was associated with greater PTH levels than multi-gland disease. Successful neck exploration was associated with higher diagnostic serum calcium levels and with larger and heavier excised parathyroid glands. Failure of operative therapy was associated with negative initial sestamibi scan and with multi-gland disease.

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