CLINICAL STUDY

Advantages of combined technetium-99m-sestamibi scintigraphy and high-resolution ultrasonography in parathyroid localization: comparative study in 91 patients with primary hyperparathyroidism

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Abstract

Objective: To evaluate the usefulness of the combination of 99mTc-sestamibi/99mTc-pertechnetate subtraction scintigraphy (SS) and high-resolution neck ultrasonography (US) in patients with primary hyperparathyroidism (pHPT) undergoing parathyroidectomy.

Design and Methods: Ninety-one patients with proved pHPT were studied, excluding patients with persistent or recurrent disease. There were 65 (71.4%) women and 26 (28.6%) men, with a median age of 59 years (range 18–78 years). All patients underwent both SS and US prior to surgery, and the results were compared with operative and histological findings. The intraoperative quick-parathyroid hormone assay was available for 52 (57.1%) patients. When multiglandular disease was found, both SS and US were considered truly positive only when at least two enlarged parathyroid (PT) glands had been localized.

Results: Eighty-three (91.2%) solitary PT adenomas and three (3.3%) carcinomas were found. Moreover, two (2.2%) patients had a double adenoma and three (3.3%) patients had diffuse PT hyperplasia. The overall sensitivity of combined SS + US was 94.5% (86.8% and 80.4% for SS and US respectively). There was a significant \(P < 0.05\); Student’s t-test) difference in size between the PT glands correctly identified and undetected by SS, whereas the site of the removed PT tumors significantly \(P < 0.05\), Fisher exact test) influenced only the US sensitivity.

Conclusions: When the preoperative localization of the PT glands is chosen, the combination of SS and US represents a reliable noninvasive localization technique and should be considered for use in each patient with pHPT undergoing surgery.

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Introduction

The incidence of primary hyperparathyroidism (pHPT) is increasing and was estimated to be 42/100 000 per year, while in women over 60 years of age the average annual incidence rate approaches 190 cases/100 000 per year (1, 2). Parathyroidectomy (PTx) should be considered in most symptomatic patients with confirmed pHPT, and bilateral neck exploration represents the standard initial surgical procedure since, in recent series, the overall reported cure rates may reach 95–98% (3, 4). Localization studies were often performed to simplify and shorten surgical exploration, but nevertheless a significant reduction in morbidity and duration of surgery was not reported in all studies and, for some surgeons, preoperative imaging of the parathyroid (PT) glands was unnecessary (5–8).

The aim of this study was to evaluate sensitivity and usefulness of high-resolution neck ultrasonography (US) and 99mTc-sestamibi/99mTc-pertechnetate subtraction scintigraphy (SS) as preoperative noninvasive localization procedures in patients with pHPT undergoing PTx.

Subjects and methods

Ninety-one consecutive patients (26 (28.6%) men and 65 (71.4%) women, median age 59 years, range 18–78 years) with proved pHPT underwent both US and SS prior to successful PTx. Patients undergoing reexploration for recurrent or persistent pHPT were excluded. All patients were cured of hypercalcemia.

US was performed using 7.5- or 10-MHz real-time transducers and images were obtained from the angle
of the mandible to the sternal notch. The sonographic appearance of an enlarged PT gland on grey-scale imaging was a hypoechoic nodule posterior or lateral to the thyroid lobe, but separate from it and nonadherent to surrounding tissues.

SS was carried out using a single detector gamma camera with a parallel-hole high-resolution collimator interfaced to a computer. Patients were injected with 370 MBq $^{99m}$Tc-methoxyisobutylisonitrile (sestamibi) and 3 planar images (neck and mediastinum, anterior view, matrix $256 \times 256$, 300 s per view) were obtained 2–15 min later. Three more images were acquired after 150 MBq $^{99m}$Tc-pertechnetate administration. Image subtraction was obtained according to standard techniques and positive scan imaging was defined as a relative increased sestamibi uptake area persisting after images subtraction, as previously described (9).

In any case, a successful bilateral neck exploration was performed and the excised PT glands were measured by the pathologist. Operative and histological findings were compared with the results of each localizing procedure. Intraoperative quick-parathyroid hormone (PTH) assay was available for 52 (57.1%) patients and the serum PTH levels were assayed prior to PT gland excision and 10–15 min after PTx.

The results were considered true-positive (TP) when the abnormal PT gland(s) found at operation had been correctly detected by the imaging techniques, false-positive (FP) when US or SS did not show any diseased gland, and false-negative (FN) if no enlarged PT glands were localized. In patients with multiglandular disease both SS and US were considered TP only when at least two hyperfunctioning PT glands had been correctly identified. Sensitivity was defined as TP/(TP + FN) and the positive predictive value (PPV) was defined as TP/(TP + FP). All reported data are expressed as means ± standard deviation (s.d.) and comparisons between different groups were performed using two-tailed Student’s t-test and the Fisher exact test, when appropriate. The analysis of variance was also used, and in all cases, differences were considered significant at $P < 0.05$.

### Results

In the overall population, the analysis of variance showed a significant ($F = 125.82, \; r = 0.5359, \; P = 0.00$) correlation between mean serum calcium (2.89 ± 0.36 mmol/l) and intact-PTH (185.5 ± 155.3 ng/l) levels. No difference ($P = 0.00$) in age between male (M) and female (F) patients (M = 52.0 ± 16.4; F = 58.2 ± 12.6 years) was found, whereas the mean serum calcium (M = 3.03 ± 0.47; F = 2.83 ± 0.28 mmol/l) and PTH (M = 235.8 ± 210.3; F = 169.4 ± 119.5 ng/l) values were significantly ($P < 0.05$) lower in women.

Histopathological findings included 83 (91.2%) solitary adenomas, two (2.2%) double adenomas and three (3.3%) PT carcinomas; moreover, three (3.3%) patients had diffuse PT hyperplasia. The mean size (maximal diameter) of the removed PT glands was $19.32 \pm 9.41$ mm (median = 17, range = 8–40 mm) and they were in a typical site in 74 (81.3%) patients. Only in patients with solitary adenomas ($n = 83$) were the PT glands in an ectopic position ($n = 17$), mainly in the upper mediastinum ($n = 6$) and behind the esophagus ($n = 4$) or the trachea ($n = 4$). In all patients ($n = 52$), the intraoperative quick-PTH assay significantly (mean PTH values = 150.80 ± 27.83 compared with 19.70 ± 6.65 ng/l; $P = 0.00$) fell after removal of the abnormal PT gland(s).

Table 1 shows the sensitivity and PPV of SS and US. False positive results using US occurred in two patients with an ectopic PT adenoma and in two patients with multinodular goiter. SS was negative in 7/70 (10.0%) patients with TP US, and US was negative in 11/79 (13.9%) patients with TP SS.

In the group of patients with solitary tumors ($n = 86$), the sensitivity of SS and US was 88.4% and 82.1% respectively. US correctly localized the PT adenomas in 7 out of the 10 patients with negative SS, thus the overall sensitivity of combined SS and US was 96.5%. In the patients with multiglandular disease ($n = 5$), 16 enlarged typically located PT glands (4 adenomas and 12 hyperplastic PT glands) were found and subtotal PTx was performed in patients ($n = 3$) with diffuse hyperplasia. Both SS and US correctly localized the PT carcinomas ($n = 3$), the double adenomas ($n = 2$), two abnormal PT glands in one patient with PT hyperplasia and one enlarged gland in the others.

There was a significant ($P < 0.05$) difference in the mean size of solitary PT adenomas ($n = 83$) correctly identified and undetected by SS (Table 2). The site (typical or ectopic) of the removed abnormal PT glands did not affect ($P = 0.08$) the results obtained by SS, but influenced ($P < 0.05$) US sensitivity (Table 3).

### Discussion

In the 1980s, sensitivity for PT localization in patients with pHTP without previous surgery ranged between 35 and 74% (PT scintigraphy) and between 34 and 82% (US) (10). The 1990 National Institutes of Health (NIH) Consensus Development Conference concluded that preoperative imaging was rarely indicated, had not proven to be cost-effective and did not shorten surgical
time (11). However, since 1996 sensitivity of non-invasive techniques has improved, especially in patients with solitary PT adenoma, reaching 77–100% (SS) and 77–91% (US) with an average of 87% and 77% respectively (Tables 4 and 5). A few studies have reported results of US and MIBI techniques (15, 21, 33) but none reported sensitivity of combined US + SS in patients with pHPT. In our series, patients undergoing re-exploration were excluded, and the overall sensitivity of combined SS and US was 94.5%, whereas in those with single or double parathyroid tumors (n = 88) it was 96.6%. Moreover, SS sensitivity did significantly (P < 0.05) correlate with the size of the PT adenoma, as previously observed (12, 13) but not with the site of the abnormal PT glands, and thus SS and US should be considered complementary.

Data from recent studies showed that more than 95% of PT adenomas may be correctly detected by 99mTc-sestamibi scintigraphy (16, 20, 22). Different techniques were used in performing PT scintigraphy, both with 99mTc-sestamibi alone (12, 29, 30) and 99mTc-sestamibi in conjunction with 123I or 99mTc-pertechnetate for thyroid image subtraction (9, 26, 27), with similar results. Dual phase imaging with single-photon emission computer tomography (SPECT) seems to be a promising procedure for the detection of hyperfunctioning PT tissue, both increasing the sensitivity of 99mTc-sestamibi scintigraphy and appearing particularly useful in localizing mediastinal glands (38, 39). In recent reports US sensitivity ranges between 76% and 91% and may improve using color and power Doppler sonography (36, 40). Increased sensitivity using PTH assay in the needle aspirates of suspicious PT adenomas was also reported (41).

Since the usefulness of localization procedures correlates with the number of preoperatively detected hyperfunctioning PT glands, sensitivity in patients with pHPT due to multiglandular disease may be lower, although it has also been suggested that SS can help distinguish hyperplasia from adenomatous disease (17). However, in 85–90% of the patients pHPT is attributed to a single PT adenoma, even if a great variation exists in the reported incidence of multiglandular disease (42). PT carcinoma is a rare tumor that in our experience was easy to detect preoperatively because of its relatively large size, usually ranging between 1.5 and 4.5 cm (43).

Unilateral neck exploration and minimally invasive, radioguided or endoscopic surgery would be feasible if the site of the abnormal PT glands were known preoperatively. In this setting, the importance of noninvasive localizing procedures becomes evident (44–47). In any case, a careful bilateral neck exploration should be performed in the following situations: (i) no enlarged PT glands visualized, (ii) equivocal results of localizing procedures, (iii) SS and US not in agreement, or (iv) detection of two or more enlarged PT glands (33, 47).

After excision of each abnormal PT gland, an intraoperative PTH assay represents the principal determinant of correction of the hyperparathyroid state and should be available for all patients with pHPT undergoing surgery (42, 48, 49). In most studies, routine use of 99mTc-sestamibi scintigraphy, neck ultrasonography and quick-PTH measurement was considered safe and cost-effective, significantly reducing operative time, facilitating successful limited neck exploration and improving the success rate of PTx.

<table>
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<th>Parameters</th>
<th>Scintigraphy</th>
<th>Ultrasonography</th>
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<tbody>
<tr>
<td></td>
<td>TP</td>
<td>P</td>
</tr>
<tr>
<td>No. of patients</td>
<td>73 (88.0%)</td>
<td>10 (12.0%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.5 ± 14.4</td>
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<tr>
<td>Ca (mmol/l)</td>
<td>2.89 ± 0.36</td>
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<tr>
<td>PTH (ng/l)</td>
<td>181.9 ± 133.9</td>
<td>0.144</td>
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<tr>
<td>Size (mm)</td>
<td>20.0 ± 9.6</td>
<td>0.034</td>
</tr>
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Table 3 Results obtained in patients with PT tumors localized in typical (n = 66) and ectopic (n = 17) sites using SS and US. Four patients (2 with ectopic parathyroid adenomas and 2 with tumors in typical site) had false positive results using US (Site = site of the PT adenomas; P values using Fisher’s exact test).

<table>
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<th>Site</th>
<th>Scintigraphy</th>
<th>Ultrasonography</th>
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<tbody>
<tr>
<td></td>
<td>TP</td>
<td>P</td>
</tr>
<tr>
<td>Typical</td>
<td>59 (89.4%)</td>
<td>7 (10.6%)</td>
</tr>
<tr>
<td>Ectopic</td>
<td>14 (82.4%)</td>
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especially in patients with ectopic PT glands (9, 16, 34, 50–52). Some authors estimated that US and PT scintigraphy charges accounted for only 2% and 5% respectively of the total charges for PTx, and that the added cost of protracted or failed exploration neutralized the costs of SS and US which are equivalent to 60 min operative time or less (13, 48, 53). In spite of that some surgeons, on account of low sensitivity obtained with preoperative localization procedures in their experience, consider imaging of the PT glands unnecessary and recommend a careful bilateral neck exploration in all patients with pHPT (6, 8, 54).

In conclusion, when a preoperative localization of the PT glands is chosen, the combination of SS and US represents a reliable noninvasive technique and should be considered for use in each patient undergoing surgery for pHPT.

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References


26. Arkes BL, Jones T, Hicks RJ, Luise MA & Chou ST. Impact of complementary parathyroid scintigraphy and ultrasonography