

# Unilateral Surgery for Primary Hyperparathyroidism on the Basis of Technetium Tc 99m Sestamibi and Iodine 123 Subtraction Scanning

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**Hypothesis:** Parathyroid scanning, based on simultaneous recording of technetium Tc 99m sestamibi and iodine 123 images, is able to identify patients with multiple parathyroid gland disease and is a safe imaging technique for unilateral parathyroid surgery.

**Design:** Scintigraphic criteria of eligibility for unilateral surgery were prospectively tested against findings of conventional bilateral surgery.

**Setting:** Patients referred to an endocrine surgeon in a university hospital.

**Patients:** Seventy consecutive patients with primary hyperparathyroidism had dual-isotope scanning before conventional surgery. Forty-one patients had scan findings compatible with unilateral surgery, with a single focus of high intensity seen on the anterior and lateral views. The remaining 29 patients had 1 or more criteria of ineligibility: (1) scan findings pointing to multiple gland disease, (2) no well-identified focus, (3) contralateral thyroid nodule requiring surgical management, or (4) fam-

ily history of hyperparathyroidism or multiple endocrine disease.

**Main Outcome Measures:** Number of enlarged parathyroid glands at surgical inspection and calcemia follow-up.

**Results:** None of the 41 patients, with a single well-defined focus on the scan image, showed evidence of multiple parathyroid involvement. Each parathyroid adenoma was resected from the precise site predicted by the subtraction scan. Nine patients (13%) had surgical findings of multiple parathyroid gland disease. All 9 were ineligible based on preoperative image findings.

**Conclusions:** Unilateral surgery can be safely offered to 60% of patients with primary hyperparathyroidism, on the basis of simultaneous <sup>99m</sup>Tc-sestamibi and <sup>123</sup>I scanning. This may reduce the length of the operation, anesthesia requirements, and hospital stay, and the risks of hypoparathyroidism and injury to the recurrent laryngeal nerve.

*Arch Surg.* 2000;135:1461-1468

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**P** RIMARY hyperparathyroidism (PHP) is a long-standing, surgically correctable disease with the third highest incidence of all endocrine disorders after diabetes mellitus and hyperthyroidism.<sup>1</sup> The average annual incidence of PHP is 28 per 100 000 population and rises to 188 cases per 100 000 population among women older than 60 years.<sup>2</sup> Conventional surgical teaching states that during first-time exploration for PHP, both sides of the neck must be opened to identify the 4 parathyroid glands. Grossly enlarged glands (estimated weight >50 mg) should be removed, and normal-appearing glands be left untouched. With this approach, multiple parathyroid gland disease (MGD), due either to hyperplasia or to multiple adenomas, is found in 10% to 15% of pa-

tients.<sup>3,4</sup> Most cases of MGD are sporadic, while a small number are associated with multiple endocrine neoplasia or non-multiple endocrine neoplasia familial hyperparathyroidism.<sup>4</sup>

Therefore, in 85% to 90% of patients with PHP, removal of the single enlarged parathyroid gland resolves the problem. This led some pioneering authors<sup>5-8</sup> to propose a unilateral approach in which "if the expected enlarged parathyroid is found and resected and a normal one is identified on the first-operated side, the operation is ended." Arguments for preserving one side of the neck are several, including reduction of the operation time and anesthesia requirements, lower risks of pretracheal hematoma, lower risks of injury to the recurrent laryngeal nerve, lower risk of hypocalcemia, and less obliterative scarring that might hinder any fu-

## PATIENTS AND METHODS

Seventy consecutive patients referred to a single-surgeon practice (D.M.) for first surgery of PHP form the basis of this study. The mean age was 57.8 years (range, 21-88 years), and 54 (77%) of the patients were women. Primary hyperparathyroidism was apparently sporadic, except in a 40-year-old woman who had a family history of hyperparathyroidism and kidney stones. All patients had laboratory signs of PHP. Plasma total calcium levels ranged from 2.30 to 3.56 mmol/L (mean, 2.80 mmol/L; reference range, 2.20-2.62 mmol/L). Plasma intact parathyroid hormone (PTH) levels ranged from 5.3 to 219.7 pmol/L (mean, 23.5 pmol/L; reference range, 1.1-6.1 pmol/L). Plasma ionized calcium and additional assessment of phosphorus and calcium metabolism were needed in some patients to reach the final diagnosis.

During the entire study, the surgeon's (D.M.) policy was to perform bilateral surgery except in a minority of surgical-risk patients. Each scan report provided all details concerning the number and position of suspected enlarged parathyroid glands. If the surgeon was willing to perform unilateral surgery in a given patient, the scan report would mention if this surgery can be offered. When the surgeon intent was to perform conventional surgery, the first author (E.H.) indicated in his files whether scan findings could allow unilateral surgery. Early data from 30 patients have been published, when reporting on our new scanning protocol.<sup>17</sup>

### PARATHYROID SUBTRACTION SCINTIGRAPHY

Sodium iodine 123 (10 MBq) was administered intravenously, followed 2 hours later by 550 MBq of <sup>99m</sup>Tc-sestamibi (Cardiolite; Dupont Pharma, Paris, France). The patient was then positioned for imaging. The distribution images of <sup>99m</sup>Tc-sestamibi and <sup>123</sup>I were simultaneously recorded using 2 nonoverlapping windows.<sup>17</sup> The energy windows were set at 140 keV ± 7% for <sup>99m</sup>Tc-sestamibi and 159 keV with 4% lower and 10% upper limits for <sup>123</sup>I. Three to 5 minutes after <sup>99m</sup>Tc-sestamibi injection, an anterior view of the neck and mediastinum was acquired for 5 minutes to detect any ectopic uptake, from the angle of the mandible to the heart.<sup>19</sup> The parallel-holes collimator was then replaced by a pinhole collimator and an anterior view of

the thyroid region was obtained for 10 minutes. The <sup>123</sup>I image was subtracted from the <sup>99m</sup>Tc-sestamibi image. The degree of subtraction was chosen interactively, monitored by a real-time display. Subtraction was considered to have reached an optimal level when <sup>99m</sup>Tc-sestamibi activity in the thyroid gland became similar to that of neighboring tissues (**Figure 1A**). If a single residual hot spot was seen on the subtraction image, a lateral view lasting 5 minutes was obtained to further document the position of the lesion in the neck (**Figure 1B**). Camera occupation time was 30 minutes on average.

### INTERPRETATION CRITERIA

Patients were "eligible" for unilateral surgery if a single lesion of high intensity was clearly seen on the anterior view and was also well defined (relative to the thyroid body) on the corresponding lateral view.

Patients were considered "ineligible" if they had any of the following: (1) more than 1 focus on the subtraction image (to maximize safety, no distinction was made between scan results suggesting MGD and those suggesting associated thyroid abnormalities); (2) no well-identified focus (ie, no focus of residual activity on the subtraction image or only a low-intensity, ill-defined focus); (3) a contralateral large thyroid nodule, cold on the <sup>123</sup>I image, warranting surgical resection; or (4) family history of hyperparathyroidism or multiple endocrine disease.

The predictive value of the selection criteria was tested prospectively, considering both surgical findings and postoperative plasma calcium measurements (average follow-up, 20 months).

### SURGERY

All patients in good general condition had conventional standard bilateral neck exploration under general anesthesia. Parathyroid glands larger than 50 mg were removed and those of borderline size underwent biopsy. Six elderly patients (mean age, 77 years) in poor general condition were offered unilateral surgery aimed at resecting the adenoma and inspection of the companion ipsilateral parathyroid gland. This unilateral surgery was carried out under general anesthesia in 1 patient and under local anesthesia in the other 5.

ture neck surgery. Shorter hospital stays, less pain and discomfort, and quicker return to "normal" life can also be expected. Targeted unilateral cervical explorations used results from preoperative thallium-technetium scan<sup>7</sup> or ultrasound.<sup>8</sup> Trends toward unilateral surgery were, however, severely contested.<sup>4,9</sup> Objectors stressed that neither thallium-technetium scans nor ultrasonography were sensitive enough to recognize patients with MGD, so that the unilateral surgery would fail in many patients with bilateral adenomata or asymmetric hyperplasia.<sup>4,9</sup> They also stressed the difference between the intention to use unilateral surgery and what was actually done in practice. Indeed, misorientation from imaging techniques often necessitated conversion to bilateral surgery.

The recently introduced <sup>99m</sup>Tc-sestamibi scanning<sup>10</sup> is now considered the most sensitive imaging technique

in patients with PHP.<sup>11-13</sup> However, while the sensitivity for parathyroid adenomas has been consistently high, reported sensitivity in primary parathyroid hyperplasia is variable. When <sup>99m</sup>Tc-sestamibi is used as a single tracer with imaging at 2 time points—"the double-phase method"<sup>14</sup>—sensitivity for primary hyperplasia is quite low.<sup>15</sup> Subtraction scanning, using either iodine 123<sup>11-13</sup> or <sup>99m</sup>Tc-pertechnetate,<sup>16</sup> in addition to <sup>99m</sup>Tc-sestamibi, improves sensitivity for hyperplastic glands. A well-known difficulty with subtraction imaging, however, is maintaining the patient absolutely still during the time necessary to scan the thyroid, to inject <sup>99m</sup>Tc-sestamibi, and to record the image of this tracer. Simultaneous recording of <sup>123</sup>I and <sup>99m</sup>Tc-sestamibi has been forwarded as a simple answer to these difficulties.<sup>17</sup> Simultaneous double-window acquisition prevents arti-

facts on subtraction images due to patient motion, improves the detection of tiny parathyroid tumors, and shortens the imaging time.<sup>17</sup> Encouraging results with this technique have been obtained in PHP<sup>17</sup> and in secondary hyperparathyroidism due to parathyroid hyperplasia in patients with renal failure.<sup>18</sup>

Can simultaneous <sup>99m</sup>Tc-sestamibi–<sup>123</sup>I subtraction scanning be used to guide unilateral surgery in PHP? A parathyroid scan preceding unilateral surgery would obviously need to be interpreted with criteria different from those preceding bilateral surgery. Specific requirements are (1) maximal sensitivity for MGD and (2) low percentage side errors so that the planned surgery and anesthesia need not be modified during the operation. We previously noted that PHP is often associated with nodular thyroid disease.<sup>12</sup> Scan images in such patients may show multiple foci of activity, and it may be difficult to ascertain the absence of a second enlarged parathyroid gland. Concerning the risk of side errors, previous experience has shown that a low-intensity <sup>99m</sup>Tc-sestamibi focus can be misleading.

In the light of these simple restrictive criteria, we tested the ability of simultaneous <sup>99m</sup>Tc-sestamibi–<sup>123</sup>I subtraction scanning to select patients in whom unilateral surgery would be appropriate.

## RESULTS

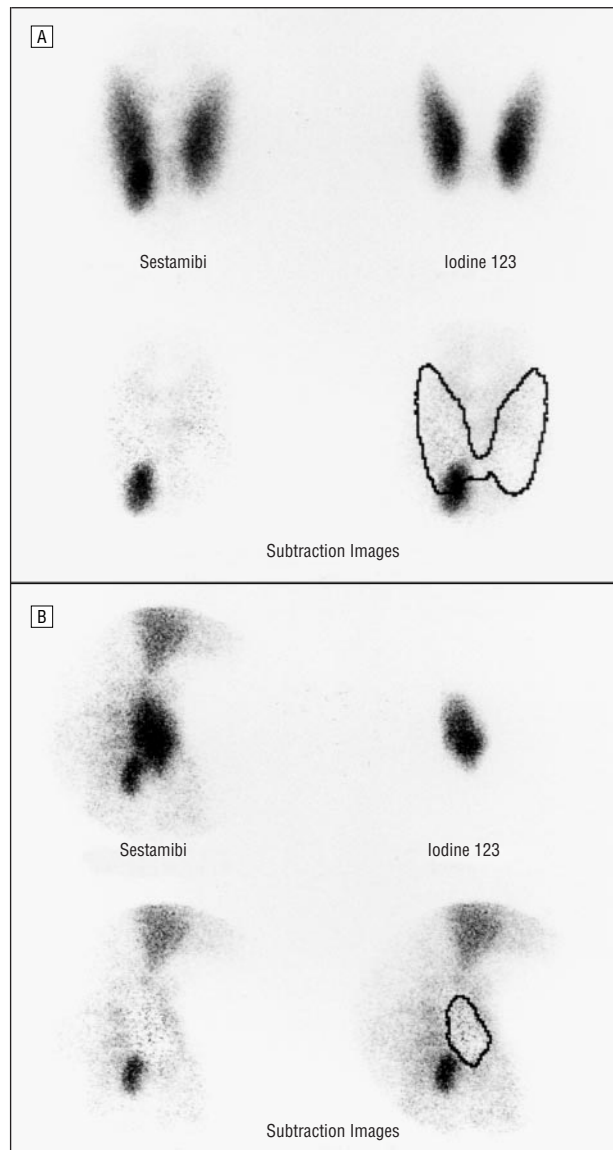
On the basis of parathyroid <sup>99m</sup>Tc-sestamibi–<sup>123</sup>I subtraction scintigraphy, 41 (59%) of the 70 patients met the eligibility criteria for unilateral surgery. The other patients were considered as ineligible for the following reasons: more than 1 residual focus of activity (n=18), no high-intensity focus (n=8), and contralateral surgical thyroid nodule (n=3).

### SURGICAL FINDINGS IN THE 41 ELIGIBLE PATIENTS

Data on the 41 eligible patients are given in **Table 1**. In these patients, a total of 131 parathyroid glands were inspected. All 41 eligible patients had an enlarged parathyroid gland at the precise site predicted by the scan (Figure 1, A-B). The weight of the resected adenomas ranged from 60 to 10260 mg (Table 1). None of the 41 eligible patients was found to have a second enlarged gland at further surgical dissection. Also, none of the 41 eligible patients had evidence of persistent or recurrent hypercalcemia.

### SURGICAL FINDINGS IN INELIGIBLE PATIENTS

Eighteen of the 70 patients had more than 1 focus of activity on the subtraction image. In 9 of them, MGD was documented by surgical inspection and histologic examination. The distribution of enlarged parathyroid glands was as follows: 4 patients had double adenomas, 3 had hyperplasia of 3 parathyroid glands, and 2 had hyperplasia of the 4 parathyroid glands (**Table 2**). All these MGD cases were recognized by the preoperative scan. The image scan from double adenomas were very clear even



**Figure 1.** A, Parathyroid technetium Tc 99m sestamibi–iodine 123 subtraction scintigraphy in a 43-year-old woman with primary hyperparathyroidism (calcium level, 2.92 mmol/L; parathyroid hormone level, 8.4 pmol/L). The computed subtraction image shows a single site of preferential <sup>99m</sup>Tc-sestamibi uptake. On this anterior view, the center of the presumed parathyroid adenoma is at the level of the lower right pole of the thyroid. B, Right lateral view. The computed subtraction image shows that the presumed parathyroid lesion is located behind the lower right pole of the thyroid gland. At conventional bilateral surgery, a solitary adenoma weighing 1870 mg was excised at the exact site predicted. All 3 remaining parathyroid glands were inspected and were normal looking. Her plasma calcium level 12 months after surgery was 2.20 mmol/L.

when there was a large difference in size between the 2 lesions (**Figure 2**). In patients with 3- or 4-gland hyperplasia, <sup>99m</sup>Tc-sestamibi uptake intensity varied among the enlarged parathyroid glands. Identification of MGD on the scan image was nevertheless easy (**Figure 3**). In the other 9 patients, with more than 1 focus of activity, the surgeon found a parathyroid adenoma associated with a nodular thyroid. Some of the patients with additional thyroid disease underwent a thyroid procedure, the extent of which was based on surgical findings and a case-by-case evaluation.

**Table 1. Surgical Results in Patients With a Single Focus on Scanning\***

Patient No./ Age, y	Calcium, mmol/L	Parathyroid Hormone, pmol/L	Type of Surgery	Resected Parathyroid Gland	Gland Weight, mg	Site Prediction	Other Enlarged Glands
1/30	2.75	28.9	Bilateral	LL	1250	+	-
2/34	2.72	23.2	Bilateral	UR	2020	+	-
3/35	3.25	45.3	Bilateral	LR	10 260	+	-
4/38	3.00	11.1	Bilateral	LR	1000	+	-
5/41	2.90	12.0	Bilateral	LL	938	+	-
6/43	2.98	11.5	Bilateral	LL	995	+	-
7/43	2.92	8.4	Bilateral	LR	1870	+	-
8/49	2.62	9.5	Bilateral	UR	214	+	-
9/49	2.95	8.0	Bilateral	UR	670	+	-
10/50	2.60	7.5	Bilateral	LR	4442	+	-
11/54	2.80	7.9	Bilateral	UR	1600	+	-
12/54	2.62	7.8	Bilateral	UR	2000	+	-
13/55	2.80	10.1	Bilateral	LR	60	+	-
14/55	2.65	9.5	Bilateral	UL	995	+	-
15/56	2.90	14.4	Bilateral	LL	600	+	-
16/57	2.72	9.5	Bilateral	LL	817	+	-
17/59	2.75	10.9	Bilateral	UR	1535	+	-
18/61	3.00	19.6	Bilateral	LR	1860	+	-
19/62	3.25	8.4	Bilateral	UL	600	+	-
20/64	2.80	5.3	Bilateral	LR	163	+	-
21/65	2.62	12.6	Bilateral	LL	646	+	-
22/65	2.70	9.2	Bilateral	LR	500	+	-
23/65	3.08	37.9	Bilateral	LR	4090	+	-
24/66	2.65	12.6	Bilateral	LL	700	+	-
25/67	3.00	16.7	Bilateral	UR	2690	+	-
26/67	3.05	33.2	Bilateral	LL	2331	+	-
27/68	2.62	9.5	Bilateral	LR	459	+	-
28/69	2.68	20.0	Bilateral	LR	562	+	-
29/69	3.30	19.8	Bilateral	LL	237	+	-
30/70	3.00	147.4	UL/GA	UR	8000	+	-
31/72	2.62	8.1	Bilateral	LR	196	+	-
32/73	2.90	16.8	Bilateral	UR	1150	+	-
33/73	2.80	8.6	UL/LA	LR	337	+	-
34/73	2.90	171.0	UL/LA	LR	3590	+	-
35/77	3.00	9.5	Bilateral	LL	323	+	-
36/78	2.95	16.8	UL/LA	LR	810	+	-
37/79	2.48	157.9	Bilateral	LR	600	+	-
38/79	2.60	5.5	Bilateral	UR	228	+	-
39/81	3.58	41.1	UL/LA	UR	1610	+	-
40/83	2.75	7.1	Bilateral	LL	130	+	-
41/88	2.80	43.1	UL/LA	LR	720	+	-

\*UL indicates unilateral surgery; GA, general anesthesia; LA, local anesthesia; LL, lower left; UL, upper left; LR, lower right; UR, upper right; plus sign, correct site prediction; and minus sign, absence of other enlarged parathyroid glands at surgical inspection.

Eight patients were excluded because of low-intensity images. In 5 cases the adenoma was at the site predicted, while in 3 cases the adenoma was on the opposite side.

Three patients were ineligible because they had a contralateral cold thyroid nodule. (Papillary thyroid carcinoma was diagnosed in 1 of them.)

Overall, the surgical success rate was 100%. No case of persistent or recurrent hypercalcemia was documented (average follow-up, 20 months). Preoperative imaging was contributive for cure in 2 patients who had an ectopic parathyroid gland. One ectopic tumor was located in the right lobe of the thyroid gland and the second was located in the sheath of the right carotid artery. Summarized data on this series of 70 PHP patients are given in **Table 3**.

#### COMMENT

The introduction of calcium autoanalyzers in the early 1970s led to changes in the incidence of PHP and deeply modified the clinical spectrum of the disease at diagnosis.<sup>1,2,20</sup> Most new cases are biologically mild without overt symptoms.<sup>1</sup> Surgery remains the only solution to this chronic disorder, although new classes of drugs are under intensive investigation.<sup>21</sup> The National Institutes of Health Consensus Development Conference recommended surgery for all young individuals and established criteria for surgical decisions in patients who were 50 years old or older.<sup>22</sup> It appears, however, that the latter thresholds are diminishing.<sup>23</sup> This may be due to recent studies suggesting that some patients with even minor laboratory signs can have sig-

**Table 2. Patients With Multiple Gland Disease**

Patient/ Age, y	Calcium, mmol/L	Parathyroid Hormone, pmol/L	Resected Glands*	Weight, mg†	Scan Result‡
A/32	3.25	24.8	UR	8100	+
			LR	205	+
			LL	436	+
B/40	2.68	21.8	LR	480	+
			UL	1162	+
			LL	120	+
C/50	3.15	13.3	UR	2165	+
			UL	1863	+
D/51	2.68	6.6	UR	60	+
			LL	90	+
E/52	2.82	8.8	UR	430	+
			LR	318	+
F/58	2.65	131.4	UR	237	+
			LR	1690	+
			UL	240	-
			LL	530	+
G/59	2.75	219.6	LR	70	+
			LL	2300	+
H/64	2.30	6.4	UR	75	+
			LR	75	+
			LL	446	+
I/71	3.00	14.8	UR	125	+
			LR	70	-
			UL	2280	+
			LL	70	-

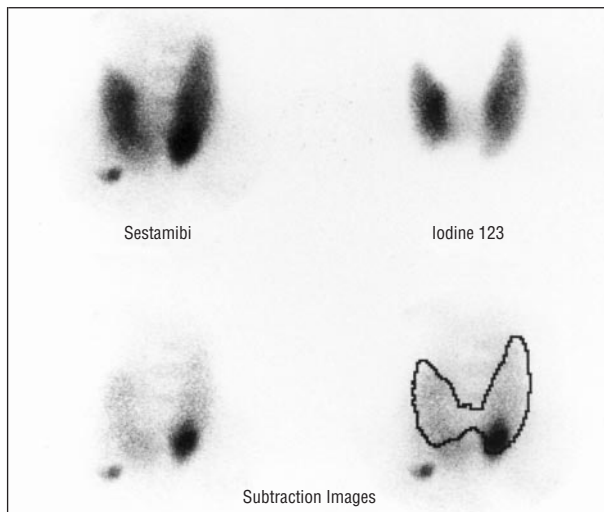
\*In each patient, the surgeon inspected the 4 parathyroid glands. UR indicates upper right; LR, lower right; LL, lower left; and UL, upper left.

†Nonresected glands were normal looking, with an estimated weight far below 50 mg.

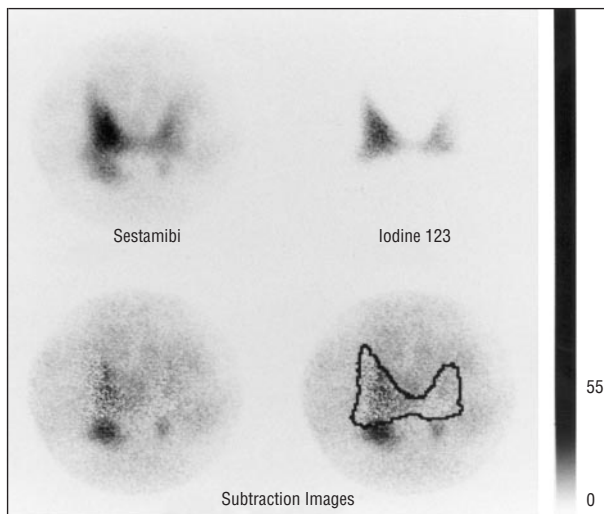
‡Sensitivity of technetium Tc 99m sestamibi-iodine 123 subtraction scintigraphy in diagnosing multiple gland disease was 100%. The sensitivity in locating individual parathyroid glands in patients with multiple gland disease was 88% (22/25).

nificant psychological symptoms, increased bone loss (in a population already prone to osteoporosis), and increased risk factors for cardiovascular disease.<sup>24-26</sup> It has also been suggested that the cost of early operation for PHP would be exceeded by the cost of 5.5 years of medical follow-up.<sup>2</sup> Sosa et al<sup>27</sup> estimated at 37000 the number of patients who undergo first operations for PHP yearly in the United States. In view of recent recommendations of parathyroidectomy in all patients with a secure diagnosis of PHP,<sup>28,29</sup> this number is expected to increase.

Unguided bilateral exploration that dissects all potential sites in the neck can achieve cure in 90% to 95% of patients. The success rate was 92.2% in one large series of patients operated on by Edis between 1974 and 1980,<sup>30</sup> at a time when imaging techniques could not have influenced the surgical results. Repeated surgery is associated with a dramatic reduction in the success rate and an increase in surgical complications.<sup>23</sup> We therefore advocated <sup>99m</sup>Tc-sestamibi-<sup>123</sup>I scanning for first-time parathyroidectomy.<sup>12</sup> Scanning with sestamibi is now increasingly ordered on a routine basis.<sup>23</sup> Most surgeons appreciate having information concerning the site of the neck with which to start dissection and concerning the possibility of ectopic parathyroid glands. The results of bilateral surgery with preoperative imaging are excel-



**Figure 2.** Parathyroid technetium Tc 99m sestamibi-iodine 123 subtraction scintigraphy in a 59-year-old woman with primary hyperparathyroidism (calcium level, 2.75 mmol/L; parathyroid hormone level, 219.6 pmol/L). The computed subtraction image shows 2 sites of preferential <sup>99m</sup>Tc-sestamibi uptake: one at the lower third of the left thyroid lobe and the second lateral to the lower pole of the right thyroid lobe. Two adenomas were excised: a left parathyroid adenoma weighing 2300 mg and a right adenoma weighing 70 mg. Both tumors were at the exact sites predicted by subtraction scanning. The 2 remaining parathyroid glands had a normal appearance, and each had an estimated weight of less than 30 mg. Her plasma calcium level 24 months after surgery was 2.22 mmol/L.



**Figure 3.** Parathyroid technetium Tc 99m sestamibi-iodine 123 subtraction scintigraphy in a 58-year-old man with primary hyperparathyroidism (calcium level, 2.65 mmol/L; parathyroid level, 131.4 pmol/L). At surgery, 4 hyperplastic parathyroid glands were identified (right lower gland, 1690 mg; right upper, 237 mg; left lower, 530 mg; left upper, 240 mg). Three enlarged parathyroid glands were seen at preoperative imaging. The upper left parathyroid gland was not reported. His plasma calcium level 12 months after surgery was 2.18 mmol/L.

lent in terms of low rate of persistent hyperparathyroidism.<sup>31</sup>

Why develop strategies for unilateral surgery? In the selection of the most appropriate approach, efficacy should not be the only criterion. The fact that surgical inspection of the contralateral side can be accomplished with minimal risk does not mean it is justified. A recent survey of US endocrine surgeons showed that primary parathyroid surgery was associated with minor complica-

**Table 3. Summary of Data on the 70 Patients With Primary Hyperparathyroidism**

Datum	% (No.)
Prevalence of single adenomas	87 (61/70)
Positive predictive value of technetium Tc 99m sestamibi and iodine 123 subtraction scintigraphy (both diagnosis and site prediction) in eligible patients	100 (41/41)
Patients with single adenoma who were eligible	67 (41/61)
Prevalence of multiple gland disease	13 (9/70)
Sensitivity of preoperative scanning for detecting multiple gland disease	100 (9/9)
Prevalence of major parathyroid ectopy	3 (2/70)
Sensitivity of preoperative scanning for detecting ectopic parathyroid tumors	100 (2/2)

tions (wound infection, urinary retention) in 2.9% of patients, permanent hypocalcemia in 2.7%, and major complications other than hypocalcemia (laryngeal nerve injury, hematoma requiring surgical evacuation, and perioperative myocardial infarction) in 1%.<sup>23</sup> In addition, the mortality rate in the hands of surgeons performing fewer than 50 parathyroid operations per year was close to 1%.<sup>23</sup> In another study, Willeke and colleagues<sup>32</sup> assessed the impact on the vocal cords in 230 surgical patients. They found that 2.2% of the patients had permanent laryngeal nerve palsy and 5.7% had transient injury. As the trend is to operate earlier, usually on patients with few symptoms,<sup>28,29</sup> the classical bilateral approach may appear excessive, and an increasing number of authors are seeking to develop minimal surgery.<sup>33-39</sup>

Patients at specific risk of failure of minimal surgery are those with MGD. In the present series, MGD was diagnosed in 13% of cases. In the worst-case scenario, an imaging technique that orients all patients toward minimal surgery would thus be associated with an additional 13% risk of failure. Inspection of the ipsilateral "companion" parathyroid gland should reduce this risk. However, many patients with MGD have either double adenomas or asymmetric 3-gland hyperplasia.<sup>40</sup> Our data corroborate these findings (Table 2): 4 patients had double adenomas (5.7%) and 3 had asymmetric 3-gland hyperplasia (4.3%). Duh et al<sup>41</sup> had elegantly explained that, even in case the ipsilateral parathyroid gland is routinely inspected during unilateral surgery, the risk of failure should equal two thirds the prevalence of double adenomas plus half the prevalence of 3-gland hyperplasia. In sum, the specific risk of failure is approximately 13% in the case of simple adenectomy and approximately 6% if the ipsilateral parathyroid is inspected. This risk of reoperation would negate all possible advantages of unilateral surgery.

Therefore, the only criterion to judge the safety of a preoperative imaging technique is its capacity to detect MGD. Yet, most authors who use image-oriented minimal parathyroid surgery rely on results of single-tracer sestamibi scanning, either in single photon emission computed tomography (SPECT) mode<sup>33,34</sup> or in planar mode.<sup>35,36,39</sup> Recent publications from one group of authors suggest that the low sensitivity of single-tracer <sup>99m</sup>Tc-sestamibi scan for hyperplastic glands<sup>35</sup> and for double adenomas<sup>36</sup> means a low probability for decid-

ing unilateral surgery. We strongly disagree with this point of view. The sensitivity of preoperative single-tracer scanning has been extensively investigated by Martin et al.<sup>15</sup> Eleven of their patients had MGD, and scanning diagnosed a solitary adenoma in 9 of them.<sup>15</sup> An imaging technique that orients 82% of patients with MGD toward inappropriate unilateral surgery would be associated with a large increase in the surgical failure rate, with persistent or recurrent disease. Based on the risk model described in the previous paragraph, the expected increase in the rate of surgical failure is of the order of 5% to 11%, depending on whether the ipsilateral companion parathyroid gland is inspected. Surgical failure may not be apparent until a few years after surgery. Other authors have also pointed to the limitations of single-tracer <sup>99m</sup>Tc-sestamibi scanning.<sup>39,42</sup>

Some authors would combine single-tracer <sup>99m</sup>Tc-sestamibi scanning and ultrasound imaging to improve sensitivity.<sup>38,43</sup> The efficacy of ultrasound examination is highly influenced by the experience of the radiologist. In a recent evaluation by Purcell and colleagues,<sup>43</sup> sensitivity of ultrasound was 79% when the examination was performed by the one radiologist with expertise in parathyroid imaging and 33% on average when performed by the remaining radiology staff. Yet, the majority of parathyroid glands missed by the experienced radiologist occurred in patients with MGD, often resulting in a false diagnosis of single adenoma.

Rapid intraoperative measurements of plasma PTH levels have been first described by Nussbaum et al.<sup>44</sup> The technique has shown to be useful in difficult cases of reoperative parathyroid surgery.<sup>45</sup> Alternatively, intraoperative PTH monitoring is used by many authors as a "safety net" to perform unilateral surgery.<sup>33,34,39</sup> Intraoperative blood sampling is obtained before opening the skin, then before excising the "adenoma" and again 5, 10, and 20 minutes after excision.<sup>33</sup> Based on an average plasma half-life of PTH of 3 minutes, it has been suggested that if a 50% decrease in PTH levels is observed 10 minutes after excision of the "adenoma," the patient does not have MGD and the operation can be terminated.<sup>33</sup> The total turnaround time for intraoperative assessment is 30 minutes on average. Although this waiting time would allow the possibility to identify a "normal" ipsilateral parathyroid, most authors do not carry this inspection in the fear that manipulation of the ipsilateral parathyroid gland may disturb the pattern of decrease in PTH blood levels.<sup>33,38</sup> What raises concern is that authors who rely on intraoperative measurements report a very low percentage of MGD.<sup>33</sup> Combining single-tracer sestamibi SPECT and intraoperative PTH monitoring in 85 patients, Irvin et al<sup>33</sup> identified 2 cases of MGD (2.4%) and suggested that only 1 additional case was missed, due to technical problems, giving a total incidence of MGD of 3.5%, which is much lower than that generally observed.<sup>1,4</sup> Tumor size in patients with MGD can be highly asymmetric.<sup>46</sup> The high asymmetry noted in 3 of our patients (A, G, I; Table 2) suggests that a rapid decrease in PTH level of more than 50% may occur following excision of the one "dominant" tumor. Figure 2 shows the preoperative image scan from one patient (G). Given the high-intensity sestamibi uptake from the 70-mg second adenoma (as from

all second adenomas in this study) and the typical pathologic findings, persistent or recurrent disease is possible if only "dominant" tumors were discovered and resected. Variation in the plasma half-life of PTH is another concern. Moore and colleagues<sup>39</sup> showed that among 7 patients in whom PTH levels did not fall by 50% within 10 minutes of excision of an enlarged gland, 2 were finally found to have slow metabolism of PTH with no other abnormal tissue found at complete bilateral dissection. The above suggestions concerning possible limits of intraoperative PTH assay were recently confirmed by 2 studies in which intraoperative PTH sampling was obtained, while maintaining bilateral surgery with 4 glands identification.<sup>47,48</sup> In the study by Weber and Ritchie,<sup>47</sup> intraoperative PTH sampling missed 4 of 6 cases of double adenomas and 7 of 15 cases of primary hyperplasia. Gordon et al<sup>48</sup> showed that if relying on intraoperative PTH, 6% of the patients would undergo unnecessary extended exploration and another 6% may necessitate reoperation for unidentified MGD.

Contrary to the <sup>99m</sup>Tc-sestamibi single-tracer technique, subtraction scanning has often been associated with high sensitivity for MGD, exceeding 80% in recent studies<sup>16,49</sup> and reaching 100% in the study by Borley et al.<sup>49</sup> If we apply the above-mentioned risk analysis model, it appears that unilateral surgery based on an imaging technique that detects 80% to 100% of MGD cases should be associated with a low risk of failure—no higher than 2% in case of simple adenectomy and 1% if the ipsilateral parathyroid is inspected.

Traditional arguments against subtraction scanning should be considered obsolete. Difficulties previously linked to successive tracer imaging are overcome by simultaneous acquisition.<sup>17,18</sup> Motion artifacts no longer occur, and tumors smaller than 100 mg can be detected (Tables 1 and 2). Arguments suggesting increased cost and increased radiation with the use of the second isotope are not valid. The sestamibi single-tracer technique necessitates a second "late" phase of imaging. The cost of using the gamma camera for an additional 20 to 40 minutes (according to whether planar or SPECT imaging is used) would easily exceed the cost of the second isotope (in France, \$30 for 10-MBq <sup>123</sup>I). Also, late imaging necessitates administration of higher <sup>99m</sup>Tc-sestamibi activity. We inject 550 MBq of <sup>99m</sup>Tc-sestamibi, while authors who use single-tracer imaging inject 740 to 925 MBq.<sup>14,15,33,34</sup>

The parathyroid scanning technique used herein should be less operator dependent than ultrasound imaging. Yet, rigorous interpretation and close collaboration with the surgeon is necessary. Bilateral surgery should be maintained if the scan shows the least sign of MGD. Nodular thyroid disease can be source of additional sites of uptake.<sup>50</sup> When this is the case, unilateral surgery should not be offered. Our eligibility criteria appear safe, as they were prospectively tested (except for 6 surgical-risk patients) against findings of bilateral surgery. We could thus ascertain the absence of minimally enlarged parathyroid glands that could have been responsible for late recurrence. Results of our study showed that simultaneous double-window recording of <sup>99m</sup>Tc-sestamibi-<sup>123</sup>I provides excellent sensitivity for MGD (100%). They also show that when

patients are assigned to unilateral surgery on the basis of a single lesion seen intensely on both the anterior and lateral views, the positive predictive value of such preoperative information is 100%. In this series, unilateral surgery could have been offered safely to all 41 eligible patients. None of the patients would have needed conversion to bilateral surgery, or conversion to general anesthesia in cases where local anesthesia was deemed appropriate.

## CONCLUSIONS

Surgery is the only curative treatment for PHP and indications are becoming more liberal even in the absence of symptoms.<sup>28,29</sup> Image-guided, focused surgery is fastly growing. Results from past exploratory surgery should not be used for comparison, but one should compare with recent results from image-aided bilateral surgery.<sup>31</sup> If excellent long-term results are to be obtained with unilateral surgery, MGD cases should be diagnosed. Simultaneous <sup>99m</sup>Tc-sestamibi-<sup>123</sup>I subtraction scanning provided optimal preoperative diagnosis of MGD cases, surpassing the sensitivity reported when other imaging techniques were combined with intraoperative monitoring of plasma PTH level. Preoperative selection is more advantageous as it means better planned surgery and anesthesia, savings in the setup and per-use charge of the PTH assay, and substantial reduction in the length of the operation.

*We are indebted to Pierre Galle, MD, Charles Proye, MD, and Serge Askienazy, MD, for comments and support.*

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