Evaluation and Management of Hyperparathyroidism

Susan Edionwe, MD, PGY 3
Faculty Mentor: Susan McCammon, MD
The University of Texas Medical Branch (UTMB Health)
Department of Otolaryngology
Grand Rounds Presentation
February 24, 2012
In humans, the superior parathyroid glands are derived from the fourth branchial pouch, which also gives rise to the thyroid gland. The third branchial pouches give rise to the inferior parathyroid glands and the thymus.
Superior Parathyroid glands: Most commonly found:

- 80% at the upper and middle third of the thyroid lobe
- at the level of the cricothyroid junction (cricoid cartilage)
- near the point where the recurrent laryngeal nerve passes beneath the inferior pharyngeal constrictor to enter the larynx

Parathyroid Anatomy: Superior glands
Inferior Parathyroid glands are usually found:

- near the lower pole of the thyroid lobe
- below the lobe in the thyrothymic ligament.

They commonly lie:
- below the inferior thyroid artery
- anterior to the recurrent laryngeal nerve.

Have a more varied location than the superior parathyroids and may be more difficult to locate because of the longer migratory descent during development.

Parathyroid Anatomy: Inferior glands
Hyperparathyroidism

- Calcium:
  - 47% - bound to serum proteins → not physiologically active
  - 10% - bound to albumin proteins → not physiologically active
  - 43% - free ionized form in serum → PHYSIOLOGICALLY ACTIVE
    - Regulates PTH release
    - Reflects the balance between calcium influx into and calcium efflux out of the ECF.

- Hypercalcemia reportedly occurs in 1-4% of the gen pop and 0.2-3% of the hosp pop.

- Excess PTH production or hyperparathyroidism is the most common cause of hypercalcemia
  - NR 8.5-10.5 mg/dL

- Hyperparathyroidism is the most common cause of hypercalcemia in non-hospitalized patients; malignancy is the most common etiology for hospitalized patients

- The most common form of hyperparathyroidism is primary hyperparathyroidism.
Normal Calcium Regulation
Evaluation & Work Up

- **H&P:**
  - "moans, stones, groans, psychogenic overtones"
  - Nonspecific symptoms: Fatigue, Lethargy, and Depression
  - 30-40% are asymptomatic
  - Medical history: Lithium, thiazide diuretics, estrogen or androgens, excess vitamin D
  - Physical exam: Vitals, neck/lymphadenopathy, CV, Respiratory, Abdominal

- **Labs:**
  - PTH level/Calcium level
  - Chemistry panel
  - 24hr urine calcium excretion
  - GFR
  - Vitamin D levels

- **Imaging:**
  - Localization studies:
    - Sestamibi
    - H&N US
  - CT or MRI
  - Consider KUB, IVP, or CT for evaluation of renal disease

- **Nuclear medicine**
  - Wrist, spine, and hip DEXA
Types of Hyperparathyroidism

- Primary Hyperparathyroidism
  - Parathyroid adenoma, parathyroid lipoadenoma, parathyroid hyperplasia, parathyroid carcinoma, and neck or mediastinal parathyroid cyst.
- Secondary Hyperparathyroidism
- Tertiary Hyperparathyroidism
- Hypercalcemia of malignancy
- MEN 1 and 2a
- Familial Hypercalcemic Hypocalcuria (FHH)
- Normal calcemic primary hyperparathyroidism
J.E. is a 55 year old female who presents for evaluation hypercalcemia. She has a recent history of discharge from UTMB for nephrolithiasis treated with lithotripsy.

H&P: also significant for fatigue, no other significant PMH, FH, or SH; no obvious physical findings

Lab review:
- Ca^{2+} level 11.7 mg/dL
- PTH 148
- GFR (NR)
- 24 hr calcium clearance is ___ (normal)

What does she have? What is your next step?
a. Secondary hyperparathyroidism, sestamibi
b. Primary hyperparathyroidism, sestamibi
c. Tertiary hyperparathyroidism, CT
d. Familial hypercalcemic hypocalcuria, sestamibi
Primary Hyperparathyroidism

- Estimated incidence is 1 case per 1000 men and 2-3 cases per 1000 women
  - Incidence increases above age 40
  - Most patients with sporadic primary hyperparathyroidism are postmenopausal women with an average age of 55 years

- Most common cause of hypercalcemia; in fact, it is a rule that patients with hypercalcemia and elevated PTH have primary hyperparathyroidism until proven otherwise.

- By far, the most common lesion found in patients with primary hyperparathyroidism is the solitary, benign parathyroid adenoma
  - >80% of cases are caused by a solitary parathyroid adenoma
  - Approximately 10% are caused by “double adenoma”

- The diagnosis of primary hyperparathyroidism is confirmed by the biochemical findings of ↑calcium, ↑PTH, and elevated or normal levels of calcium in the urine.
  - The serum calcium is not usually greater than 1mg/dl above the limits of normal.
  - Low normal phosphate levels
  - Elevated alkaline phosphate
  - High normal 1,25 OH₂ Vit D
  - Normal GFR
Case 2

D.B is a 65 year old AA male who presents for a routine evaluation his renal failure. He complains of nocturia and muscle cramps and bone pain.

H&P: PMH: PMH: stage IV CKD, palpitations, MI; no pertinent FH, or SH; no obvious physical findings

Lab review:
- Ca$^{2+}$ level 8.5 mg/dL
- PTH 200
- Cr 3.50
- 24 hr calcium clearance is elevated__ (normal)
- Phosphate level ____

What does he have?
Case 2

- a. Secondary hyperparathyroidism
- b. Primary hyperparathyroidism
- c. MEN 1 parathyroid disease
- d. Familial hypercalcemic hypocalcuria
Secondary & Tertiary Hyperparathyroidism

- **Physiologic** Secondary Hyperparathyroidism:
  - insufficient calcium intake, decreased intestinal calcium absorption, insufficient vitamin D intake or malabsorption,
  - represents the homeostatic attempt to maintain a normal serum calcium level by any means necessary.

- **Pathologic** Secondary hyperparathyroidism and tertiary hyperparathyroidism:
  - occur as a result of renal insufficiency or renal failure.
  - results from subtle ionized hypocalcemia persisting over months to years → chronic stimulation of the parathyroid glands.
  - Tertiary hyperparathyroidism is when the parathyroid glands may become *autonomous* after long-standing renal disease, and consequently no longer respond to regulation by serum ionized calcium; CLUE: intractable hypercalcemia, inability to control osteomalacia despite Vitamin D.

- Labs:
  - Low normal $\text{Ca}^{2+}$ and $\uparrow$ PTH
  - GFR/CR indicative of renal disease
## Causes of Hypercalcemia of Malignancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone–related protein secretion</td>
<td>Lung, esophagus, head and neck, renal cell, ovary, bladder, and pancreatic cancers; thymic carcinoma; islet cell carcinoma; carcinoid; sclerosing hepatic carcinoma</td>
</tr>
<tr>
<td>Ectopic parathyroid hormone secretion</td>
<td>Small cell lung cancer, small cell ovarian carcinoma, squamous cell lung carcinoma, ovarian adenocarcinoma, thymoma, papillary thyroid carcinoma, hepatocellular carcinoma, undifferentiated neuroendocrine tumor</td>
</tr>
<tr>
<td>Ectopic 1,25-dihydroxyvitamin D production</td>
<td>B-cell lymphoma, Hodgkin’s disease, lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>Lytic bone metastases</td>
<td>Multiple myeloma, lymphomas, breast cancer, invasive sarcoma</td>
</tr>
<tr>
<td>Tumor production of other cytokines</td>
<td>T-cell lymphomas/leukemias, non-Hodgkin’s lymphoma, other hematologic malignancies</td>
</tr>
</tbody>
</table>
Case 3

- A 24 year old man is brought to the ED by his friends for confusion. They report he has been stressed with exams but deny any drug or ETOH abuse. More history could not be obtained.
- Physical:
  - General: confused
  - HEENT: refer to image
- PMH: unremarkable; PSH: none; Allergies: NKDA
- Meds: No medications
- FH: unknown; SH: no TOB or ETOH use
- Labs:
  - BSG 49 (NR 70-110 mg/dL), Insulin 340 pmol/L (NR 43-208)
  - Ca^{2+} 11.2 mg/dL
  - PTH 159
- Radiology:
  - CT scan reveals a 2 cm mass in the head of the pancreas concerning for an insulinoma.

What does this man have?
Case 3

a. Normocalcemic hyperparathyroidism
b. Primary hyperparathyroidism
c. MEN 1
d. Familial hypercalcemic hypocalcuria
MEN 1

- Autosomal dominant
- PHPT is often the first and most common endocrinopathy of MEN 1 and reaches nearly 100% penetrance by age 50.
- 3P’s: pituitary, pancreas, and parathyroid
- Pancreatic islet cell tumors occur in 60 to 70% of patients.
- Prolactinoma is the most common pituitary tumor.
- Recognition of PHPT in a young adult (usually by the 2nd decade) can lead to the discovery of MEN 1.
- The presence of a tumor involving any one of the three organ systems in a first degree family member also confirms the presence of familial MEN 1.
- Gene testing of family members; Menin gene encodes for menin.
- Angiofibroma are commonly associated with MEN 1 and are reported in 5%, 8%, 22%, 43%, 64%, and 88% of patients with MEN1. Lipomas and collagenomas are also associated.
MEN 2a (Sipple’s Syndrome)

- Autosomal dominant
- MTC (100%), pheochromocytoma, and parathyroid disease (70%)
- Germline mutation of the RET-proto-oncogene located on chromosome 10.
- Screening for medullary thyroid carcinoma is done with the pentagastrin stimulation test, measuring serum calcitonin at baseline and at 2, 5, and 10 minutes.
  - Diagnostic outcome:
    - Urinary catecholamines and metanephrines screen for pheochromocytomas
    - Gene testing for family members
A 50 year old female presents for a routine examination. She reports she is in her usual state of health and does not complain of any symptoms.

PMH: HTN; PSH: none; allergies: KNDA

SH: No TOB or ETOH

FH: noncontributory

Labs:
- BMP reveals Ca^{2+} level 11 mg/dL
- PTH 65
- 24 hr urine calcium:Cr ration 0.008

What does this woman have?
Case 4

a. Normocalcemic hyperparathyroidism
b. Primary hyperparathyroidism
c. MEN 1
d. Familial hypercalcemic hypocalcuria
Familial Hypocalcuric Hypercalcemia

- Autosomal dominant and typically presents during childhood
- Serum calcium is mildly to moderately elevated BUT urine calcium is normal to low normal (which is abnormal in the setting of elevated blood calcium)
  - 24 hour urine calcium and creatinine clearance yielding a ratio of <0.01
- + Family history
- Generally asymptomatic and no treatment is required
- Pathophysiology: mutation of the calcium-sensing receptors of parathyroid cells (CASR gene)
Familial Hypocalcuric Hypercalcemia

- Autosomal dominant and typically presents during childhood
- Serum calcium is mildly to moderately elevated BUT urine calcium is normal to low normal (which is abnormal in the setting of elevated blood calcium)
  - 24 hour urine calcium and creatinine clearance yielding a ratio of <0.01
- + Family history
- Generally asymptomatic and no treatment is required
- Pathophysiology: mutation of the calcium-sensing receptors of parathyroid cells (CASR gene)
Pre-operative localizing studies

- Ultrasound: 35-75% sensitive (88.5%)
- CT: 42-68% sensitive
- MRI: 57-88% sensitive
- Tc 99M sestamibi: 70-91% sensitive (88%)
- Selective venous cath: up to 80% sensitive

“The only localization study needed for initial surgery for hyperparathyroidism is to localize an experienced parathyroid surgeon.”

- John Doppman
Tc 99m Sestamibi Scan

- Proposed in 1992 by Taillefor et al.
- Patient is injected with 20-25mCi of Tc 99m sestamibi. Subsequent images are taken at 10-15 minutes and again at 2-3 hours.
- Why does this work?
  - Thyroid and thyroid nodules clear uptake faster than parathyroid neoplasms do.
  - Tc 99m is incorporated into the cytoplasm and mitochondria. Parathyroid tissue has a large number of mitochondria in its oxyphil cells compared to thyroid tissue, thus allowing Tc99m to enter parathyroid tissue more intensely
- Limitations: The literature records a 1% to 3% false-positive rate; cannot identify multiglandular disease.
Surgeon-performed ultrasound
Indications:
- Simply put... a clearly symptomatic patient is an indication for surgery.
- What of the asymptomatic patient?

Bilateral Parathyroid exploration:
- Bilateral exploration – gold standard but being phased out. Still the procedure of choice for four gland hyperplasia.

Unilateral Parathyroid exploration
- In performing parathyroidectomy for primary hyperparathyroidism, if on the first side there is 1 definite adenoma and 1 normal gland, the second side need not be explored.
- Rationale for this approach is that greater than 85% of cases of sporadic hyperparathyroidism are caused by a solitary adenoma. These groups hypothesized that the morbidity associated with a standard four-gland parathyroid exploration could be minimized with a less invasive procedure while maintaining the same level of success at curing the disease.
- Subsequent reports based on similar principles have concluded that UNE can be performed with results comparable to a BNE.
- Limitations: Unilateral parathyroid exploration is limited by the intrinsic 15% rate of multiglandular primary hyperparathyroidism, combined with the imperfections of preoperative localizing techniques.

Minimally Invasive surgery?
The Asymptomatic Patient

- Three International Workshops by the NIH to date that have proposed and refined the indications for parathyroidectomy in asymptomatic patients.

- Why is this important? Most patients with primary hyperparathyroidism are asymptomatic. A recommendation for invasive surgery is not always readily accepted by the patient.

- What is the latest criteria?

- What about asymptomatic patients who opt for conservative measures? What are their outcomes?
Objective: Asymptomatic primary hyperparathyroidism (PHPT) is a common clinical problem. The purpose of this report is to guide the use of diagnostics and management for this condition in clinical practice.
Participants: Interested professional societies selected representatives for the consensus committee and provided funding for a one-day meeting. A subgroup of this committee set the program and developed key questions for review. Consensus was established at a closed meeting that followed and at subsequent discussions.
Evidence: Literature review, expert opinion (Level IV)?
Goal: To answer 22 questions designed to clarify:
1. Diagnosis of PHPT (questions 1–7)
2. Presentation of PHPT (questions 8–13);
3. Surgery for PHPT (questions 14–18);
Example:
- Question #3: Have genetic tests for the calcium-sensing receptor gene and multiple endocrine neoplasia-related genes become suitable for routine evaluation of all genetic forms of PHPT?
- Question #10: What is the natural history of asymptomatic PHPT?
- Question #15: Who should perform parathyroid surgery?
- Question #21: How effective is raloxifene in preventing the skeletal complications of PHPT and in lowering PTH and serum calcium?
Criticism:
1. Definition of asymptomatic unclear?
2. Are these indications too limited?

NIH Criteria for Parathyroidectomy in Asymptomatic PHPT: Are they too limited?

Eigelberger et al.
“The extent of surgery in the treatment of primary hyperparathyroidism should be based on the pathologic entity of the disease. In neoplasia (either the common adenoma or the rare carcinoma), excision of the diseased parathyroid will generally suffice to cure the disease, but in primary hyperplasia, the removal of all the diseased glands except for a small amount of glandular tissue is required.”

(unilateral parathyroidectomy)

What is Minimally Invasive Surgery?

- Though the concept of unilateral exploration was introduced as early as 1981, parathyroidectomy with less than four-gland exploration did not gain wide acceptance until the 1990s, when a number of different minimally invasive techniques were introduced.

- Initially, movement was market/patient driven and not evidence based.
Variables examined for correlation with incision size for parathyroidectomy:
1) BMI, Patient’s age, operative time
2) Resident clinical training level
3) type of operation (bilateral, unilateral, or focal parathyroid exploration)
4) extent of cervical exploration (number of parathyroid glands located and number of parathyroid glands resected),
5) indications for surgery (primary or secondary hyperparathyroidism),
6) size of resected parathyroid gland(s), and
7) whether or not thymectomy was performed

“We propose that this term be used only to describe thyroid and parathyroid procedures that are routinely associated with an incision shorter than 3.0 cm for thyroidectomy and 2.5 cm for parathyroidectomy.”
Figure 1. Box plots of length of incision according to resident clinical training level (R1 through R5) and type of surgery. The incision was shorter when a senior resident (R4 or R5) assisted the surgeon for total thyroidectomy ($P<.03$) and parathyroidectomy ($P = .009$) (Mann-Whitney test). Boxes indicate the 25th and 75th percentiles; horizontal lines in boxes, mean; and limit lines, SD.
Minimally Invasive Surgery

- Videoendoscopic – gasless
- “Video-assisted” (MIVAP)
- Radioguided (MIRP)
- Focused central mini-incision (2.5 cm, direct view)
- Focused lateral mini-incision (1.5-2.0 cm, direct view)
Background: Minimally invasive parathyroidectomy (MIP) involves scan-directed removal of a single adenoma through a 2·0-cm mini-incision without intraoperative monitoring. The aim of this study was to analyze the outcomes of MIP using such a simplified technique.

Methods: The study group comprised 500 consecutive patients undergoing MIP via a lateral mini-incision from August 2000 to September 2005. Levels of parathyroid hormone (PTH) were measured after operation solely to aid informed discharge.

Technique:

- Inclusion criteria: unequivocal single site of uptake on sestamibi parathyroid nuclear scanning.
- Focused ultrasonography was subsequently performed, either before operation by a radiologist or during operation by the surgeon, solely to guide placement of 2cm lateral neck incision and aid anatomical dissection.
  - Patients with negative findings on sestamibi localization study and those with multiple sites of uptake underwent standard four gland BNE via a cervical collar incision.
- Removal of enlarged glands was based solely on visual appreciation of enlargement at the site concordant with preoperative imaging.
- Frozen-section examination was not used.
- The procedure was performed under either general or local anesthesia with a superficial cervical block supplemented by local infiltration.
- Preoperative and postoperative PTH levels were measured routinely on the afternoon of surgery. The results were available on the same day and used assist appropriately.
Conclusion:

Using this MIP technique a cure rate of 97.4 per cent was achieved in 500 consecutive patients.

These results are equivalent to those in most other published series of both open parathyroidectomy and MIP using a variety of open, endoscopic or video-assisted techniques, and employing either intraoperative PTH measurement, a nuclear probe, or both.

Lateral incision has better access to parathyroid-bearing tissue than central mini incision

Less complex than the video-assisted techniques
Focused mini-incision

Fig. 1 Diagram demonstrating the rationale behind the use of a lateral mini-incision with placement based on preoperative localization rather than the standard central mini-incision.
Focused lateral mini-incision
Endoscopic surgery for primary hyperparathyroidism (PHPT) started in 1996 with a parathyroidectomy performed by Michel Gagner.

February 1997 to October 2003, n= 370/520 (71%) underwent MIVAP.

Criteria:
1. sporadic form of PHPT
2. preoperative localization of at least one affected parathyroid gland smaller 3 cm in its largest diameter,
3. no suspicion of parathyroid carcinoma
4. absence of a concomitant bulky thyroid disease or thyroiditis.

These criteria became less strictly followed with the growing experience of the surgical team.

Technique:
1. The MIVAP procedure is characterized by a single central (or lateral) access of 1.5 to 2 cm at the notch level. The technique relies on external retraction, thus no insufflation is performed in the neck.
2. The midline is carefully individuated and incised, and the strap muscles are separated from the thyroid lobe by gentle blunt dissection, performed under direct vision, on the side of the suspected adenoma.
3. The endoscopic instruments are then introduced: we use a 30 degree 5 mm endoscope for magnification, other 2 mm instruments such as spatulas and forceps, and 2 mm titanium clips.
Results:

• The video-assisted procedure was successfully performed in 350 (94%) of the 370 patients.
• Mean operative time was $36.2 \pm 21.08$ minutes (range: 10–180 minutes). In the last 100 operations the elapsed time was 25.7 minutes, reflecting the learning curve in performing the technique.
• In 21 cases (5.6%) a concomitant procedure was associated with parathyroidectomy: thyroid lobectomy was performed in 14 cases and total thyroidectomy in 7 cases.
• 23 cases (6.2%) the procedure was converted to conventional open bilateral exploration
• 11/370 patients lost to F/U but median F/U was median follow-up of 35.1 months (range: 2–83 months).

Discussion:

• Largest series reported
• Neither persistent nor recurrent disease has increased significantly; in fact, no recurrent PHPT reported.
• This technique does not expose patients to a high complication rate. The two most common complications in patients undergoing surgery for PHPT are recurrent nerve palsy and hypoparathyroidism. Complication rates were less than 1% (0.8%) in this study.
• The technique of videoscopic accesses demonstrated both the very low rate of transient hypocalcemia (2.7%) and the absence of any definitive hypoparathyroidism in this cohort of patients.
• Postoperative bleeding or wound infection are so rare that it must be concluded that MIVAP is a safe operation that can be reproduced in many surgical settings.
“Video-assisted” Parathyroidectomy (MIVAP)
Videoendoscopic –insufflation or gasless

- “Gasless” technique - A 3-minute CO₂ insufflation (12 mm Hg) through a conventional trocar inserted under the strap muscles is used just to anatomically dissect the virtual thyrotracheal groove. Actually, the working space is maintained by means of skin retractors so as to allow needlescopic instruments to perform a parathyroid adenomectomy with the gasless procedure.
- Insufflation procedure – CO₂ insufflation the duration of the case.
- Videoendoscopic Parathyroidectomy: Gaseous or Gasless Technique? Salihoglu Z et al.
  - Compared 3 techniques: Foley catheter to make a potential space, gasless technique, and insufflation technique
  - “[surgery] performed with the third technique, the hemodynamic variables were affected, and subcutaneous emphysema has occurred”.
  - Ex: One patient’s MAP decreased from 80 mm Hg to 60 mm Hg, and heart rate increased from 72 to 125 bpm
Videoendoscopic – insufflation or gasless
Background.
- The inability to predict the location and number of diseased parathyroid glands has precluded the wide acceptance of unilateral neck exploration for primary hyperparathyroidism.
- We used intraoperative nuclear mapping in patients identified by sestamibi scanning to have a single adenoma in hopes of minimizing operative intervention while maintaining the efficacy of a full exploration.

Methods.
- Fifteen consecutive patients with primary hyperparathyroidism underwent technetium 99m-labeled sestamibi scanning 3.0 ± 0.1 hours before operation.
- Placement of the initial 2.0 cm incision and all dissection were guided by quantitative gamma counting in four neck quadrants with an 11 mm Neoprobe.
- Ex vivo radioactivity was determined for parathyroid glands, fat, and lymph nodes.
- Potential radiation hazards were assessed.
Radioguided (MIRP)

1. Patients were scanned in the morning
2. Operation 2.5 2 0.1 hours later. A
3. After positioning, an 11 mm hand-held Neoprobe gamma counter (Neoprobe Corp., Dublin, Ohio) was used to measure radioactivity in four quadrants of the neck, defined by the upper and lower poles of the thyroid gland on each side.
4. By protocol, the initial 2.0 cm incision was placed according to the expected location of the adenoma as determined by both sestamibi scanning and measurement of gamma emissions with the probe. (Incision placed higher or lower than usual were oriented transversely to allow extension as needed or even conversion to bilateral exploration if necessary.)
5. Subplatysmal flaps were created 2 to 3 cm in all directions, and radioactivity was quantitated again for all four quadrants.
6. The dissection was carried deeper as directed by increasing gamma emissions to locate the radioactive gland.
7. If the gamma emissions equilibrated in all four quadrants once the targeted gland was removed, no attempt was made to identify a normal ipsilateral gland and the wound was closed.
8. If no such equilibration was noted, further dissection was performed to identify the remaining radioactive source.

Fig. 2. Mapping of neck radioactivity during resection of left lower adenomas. Gamma emissions from four neck quadrants were obtained from five patients before making skin incision (time 0) and frequently thereafter. Once adenoma was resected, emissions from left lower quadrant decreased (*p < 0.0001) to same level as other three quadrants (difference not significant), whereas radioactivity decreased to new lower levels (#p < 0.05) in all quadrants. Data are mean ± SEM for five similar patients.
Results.

1. Intraoperative nuclear mapping discriminated between 14 solitary adenomas and one patient with four-gland hyperplasia that was not predicted on preoperative sestamibi scanning.

2. Removal of the adenoma resulted in a decline in radioactivity in that quadrant ($p < 0.001$) and the entire neck ($p < 0.01$), with equalization of all neck quadrants.

3. Ex vivo counts always identified parathyroid tissue ($p < 0.0001$ versus fat and lymph node).

4. Adenomas were located in 19 ± 1.7 minutes through a 2.3 ± 0.1 cm incision.

5. No significant radiation hazard existed, and no special handling of the specimen was required (0.06 ± 0.01 mR/hr).

Conclusions. Intraoperative nuclear mapping complements sestamibi scanning to help distinguish single-gland from multigland disease. This technique allows for a minimally invasive operation under local anesthesia in a true outpatient setting.
Radioguided (MIRP)

Sestamibi Scan

Operate only where necessary

Remove the radioactive parathyroid tumor

Measure the radioactivity in the parathyroid tumor to help make sure that the patient is cured of their disease

Use a miniature handheld radiation detecting probe to find the radioactive parathyroid
The 20% rule: A simple, instantaneous radioactivity measurement defines cure and allows elimination of frozen sections and hormone assays during parathyroidectomy.

Between February 1997 and March 1999, 345 consecutive patients referred to the University of South Florida with primary sporadic HPT were entered into a prospective protocol. All underwent a parathyroidectomy while they were radioactive, after a systemic injection of 99Tc-labeled sestamibi.
Radioguided (MIRP) – 20% Rule

Benefits:

1. Compared to intraoperative measurement of PTH: Although improved technology allows for the measurement of PTH levels by immunoradiometric assay within 12 to 15 minutes, this still requires waiting for results and, if the PTH level has not decreased an appropriate amount, continuing the dissection, localizing another parathyroid gland, and again waiting for PTH assay results.

2. Peripheral PTH levels do not direct the surgical procedure or dissection, they merely confirm with reasonable accuracy that once an adenoma is excised if it was or was not the physiologically overactive parathyroid adenoma.

3. The need for confirmation with frozen section was decreased
**Dr Ashok R. Shaha** (New York, NY). Clearly this is a tremendous progress in parathyroid surgery. But if an institution does not have a gamma probe or the coordination between the Nuclear Medicine Department, operating room, and the surgeon is not likely to form, what should they do? Shouldn’t they be doing parathyroidectomy? Or should they still use the old classical approach? It looks as if you are promoting the philosophy that this is the best way to approach hyperparathyroidism. The next question is, you average 5 specimens per case. Out of 250, there are 1,200 specimens. If the technique is so good, why do you need 5 specimens in almost every case?

**Dr Murphy.** For this study, we prospectively collected specimens and data from normal neck structures in all of our patients to establish these radioactive ratios. Now that this study is complete, we do not biopsy any tissues. We localize the adenoma, excise it, and confirm ex-vivo that this is an adenoma based on a radioactivity ratio of greater than 20% of background. In response to your first question, no we don’t advocate this for everyone. We feel that having the appropriate probe is most important. If you don’t have a new generation probe, the procedure is much more difficult. Secondly, if you can’t operate within the 1.5- to 3.5-hour window, then this procedure is not appropriate and a standard bilateral exploration is warranted.

**Dr Francis Daniels Moore** (Boston, Mass). I Have spent some time using the gamma probe in these cases. As you move the gamma probe across the neck, there is a wide variation in the amount of radioactivity, depending on whether you are aiming at the thyroid or to the side or at the great vessels. What exactly is your technique that gives you a stable baseline that you are going to base your ratio on? I think there are 2-fold variations as you go across the neck.

**Dr Murphy.** The thyroid remains radioactive during the procedure if you operate between 1.5 and 3.5 hours after sestamibi injection. However, once an hour has passed, the hyperfunctioning parathyroid tissue will be relatively more radioactive than the thyroid. Once the adenoma has been found and removed, the neck still remains radioactive, but all 4 quadrants of the neck have equalized.
Hypothesis: Minimally invasive surgery for primary hyperparathyroidism has become an accepted part of endocrine surgical practice worldwide.

Design: Survey of members of the International Association of Endocrine Surgeons.

Setting: Clinical practice of endocrine surgeons worldwide.

Main Outcome Measures: Numbers of parathyroid procedures performed, types of minimally invasive procedures undertaken, and techniques used to ensure completeness of removal of hyperfunctioning parathyroid.

“The key to successful MIP is careful patient selection, with avoidance of those patients who are likely to have multiglandular disease, as well as confident preoperative localization with techniques such as sestamibi nuclear scanning or ultrasonography.

“The focused small-incision approach certainly shortens operative and hospital time and shortens incision length. A thorough knowledge of neck anatomy and embryology is mandatory for this approach, however, as visualization of the anatomy through the small hole is necessarily restricted.”

“The earliest reports of MIP described the use of true endoscopic and video-assisted techniques. Although it is accepted that these techniques provide excellent visualization of the anatomical structures, they can be time consuming and are associated with a steep learning curve. Many surgeons commented on having started using these techniques and having shifted to the focused small-incision techniques more recently.”
Complications of surgery

- Persistent Disease, Recurrent Disease
- Hypocalcemia
- RLN injury
- Are there increased complications with minimally invasive surgery versus traditional surgery (unilateral parathyroid exploration)?
One significant problem affecting initial descriptions of these techniques was that many groups were calling their procedures "minimally invasive" without a clear definition of what exactly the term "minimally invasive" meant. In fact, this paucity of definitions remains a problem today, raising concern among some experts over the possibility that inflated claims are being used for the purpose of self-promotion (8). The terminology problem was addressed in 2003 by Brunaud and associates from UC San Francisco, who systematically analyzed incision length for several types of endocrine operations. They recommended that the term "minimally invasive" only be applied to parathyroid procedures utilizing an incision length of less than 2.5 cm (1 in) (9).

- **Sidhu S,** Long-term outcome of unilateral parathyroid exploration for primary hyperparathyroidism due to presumed solitary adenoma, *J Am Coll Surg* 2003
- **Sackett WR,** Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy, *Arch Surg* 2002
- **Gallagher SF,** The impact of minimally invasive parathyroidectomy on the way endocrinologists treat primary hyperparathyroidism, *Surgery* 2003
- **Bilezikian J,** Primary Hyperparathyroidism, Chapter 5. Diseases of Bone and Mineral and Metabolism
- **Salihoglu et al.** Videoendoscopic Parathyroidectomy: Gaseous or Gasless Technique? *A & A* December 2002 vol. 95 no. 6 1819