The variability in location of the Parathyroid gland is Justified by their embryology

Superior Parathyroid Embryology
The superior parathyroid glands (SPG) arise from the dorsal wing of the 4th pharyngeal pouch. At gestational week 7, the glands lose connections with the pharynx and attach themselves to the thyroid gland, which is migrating caudally, albeit far less a migration than the thymus. Because of the lesser length of migration, the SPG (IV) are in a more constant location than the IPG (III). The SPG are generally located more posterior and medial than the IPG, and their final resting point is usually on the dorsal surface of the thyroid gland, outside the fibrous capsule of the thyroid gland.

Inferior Parathyroid Embryology
The IPG arise from the dorsal wing of the 3rd pharyngeal pouch, that differentiates at gestational weeks 5-6, with the ventral wing becoming the thymus. The thymus then migrates caudally and medially, pulling the IPG with it; therefore, IPG III is further inferior than are SPG IV. The IPG usually stop at the dorsal surface of the thyroid gland, outside of the fibrous capsule.
Parathyroid Anatomy

Location
• 70-80% typical

• 20% Ectopy:
  intrathyroid (3%)
  posterior timus-mediastinum
  carotid space
  paraesophageal space

Size: 5x3x1 mm

Weigh: 25-40 mg

Number: 85-90% 4
        3-5%  <4
        5-10% 5-7
Low circulating serum calcium concentrations stimulate the parathyroid glands to secrete PTH, which mobilizes calcium from bones by osteoclastic stimulation. PTH also stimulates the kidneys to reabsorb calcium and to convert 25-hydroxyvitamin D3 (produced in the liver) to the active form, 1,25-dihydroxyvitamin D3, which stimulates GI calcium absorption. High serum calcium concentrations have a negative feedback effect on PTH secretion.
Hypercalcemia may be related to:

**Associated to PTH**
- Primary hyperparathyroidism
- Lithium
- FHH (Familial hypocalciuric hypercalcemia)

**Associated to neoplasms**
- Lytic Metastasis (breast, lung, kidney)
- Hematological malignancies
- Paraneoplastic Hypercalcemia

**↑ D Vitamin**
- D vit. Intoxication
- Granulomatous disease
- Idiopathic hypercalcemia of infants

**↑ Turnover osseo**
- Hypertiroidis
- Immobilization
- Thiazidic diuretics
- A vit. Intoxication

**Associated to kidney diseases**
- Tertiary hyperparathyroidism
- Milk Alcali syndrome
Hyperparathyroidism

Primary

Sporadic

Hereditary syndrom

MEN-1
MEN-2
FIHP
NSHPT/(FHH)
HPT-JT

Renal failure
D vit. Deficit
Ca Deficit
Hyperphosphatemia
Farmaci

Secondary

tertiary

Autonomuos development after secondary h., refractory to therapy
Primary sporadic hyperparathyroidism

Epidemiology: Incid. 0.5/1000, F/M → 2:1
max. V/VII decad

ADENOMA (80-85%)
HYPERPLASIA (15-20%)
CARCINOMA (1-2%)

Genic alterations
- Deletions 1p, 6q, 9p, 11q, 15q
- Inversion 11p/11q (**PRADI**)
CLINICAL FEATURES

**Symptoms**
- weakness
- Dehydration
- Ectopic calcifications

**Bone**
- Osteopenia/osteoporosis (max. osso corticale)

**CNS**
- Depression, confusion, lethargy, coma

**Gastrointestinal symptoms**
- Anorexia, nausea, vomiting, constipation, ulcer, pancreatitis, polydipsia

**Renali symptoms**
- Polyuria, Kidney Stones, nefrocalcinosis, renal failure

**Cardiovascular symptoms**
- ↓ QT, hypertension
DIAGNOSIS OF PRIM.
HYPERPARATHYROIDISM.

PTH e Calcemia ↑
Phosphoremia ↓
> of 1-hydroxililasis

Calciuria =/↑
Phosphaturia ↑

Some difficult clinical scenarios (eg. pre-existeny D vitamin deficit)
NIH conference. Diagnosis and management of primary hyperparathyroidism: consensus development conference statement.

- A diagnosis of hyperparathyroidism is established by showing persistent hypercalcemia and an elevated serum parathyroid hormone concentration.
- The current and acceptable treatment for hyperparathyroidism is surgery.
- The diagnosis of hyperparathyroidism in an asymptomatic patient does not in all cases mandate referral for surgery.
- Conscientious surveillance may be justified in patients whose calcium levels are only mildly elevated and whose renal and bone status are close to normal.
- Preoperative localization in patients without previous neck operation is rarely indicated and has not proved to be cost effective.

Ann Intern Med 1991 Apr 1;114(7):593-7
Well trained surgeons, adopting bilateral wide neck exploration, have a 95% success rate in pts with primary hyperparathyroidism.

The best preoperative localization study is to go out and localize an experienced parathyroid surgeon.

J. Doppman
Prog. Surg. 1986
**Intraoperative PTH**

PTH levels were measured 5 min after excision of a suspected abnormal gland and compared with preoperative or pre-excision samples. A fall of at least 50% in PTH levels was considered confirmation of complete excision of all abnormal parathyroid tissue.

The sensitivity of this test in predicting postoperative calcium levels has been reported as 94%.

Carty SE et al. Surgery 1997;122:1107
Role of non-invasive Imaging

The importance of sonography and sestamibi scintigraphy in the preoperative evaluation of patients with primary hyperthyroidism has increased with the adoption of minimally invasive parathyroidectomy techniques at most medical centers. When the results of these studies are concordant, the cure rates of minimally invasive surgery equal those of traditional bilateral neck exploration.

1995-2001

- unilateral neck Exploration
- mini-invasive surgery: radioguided endoscopic videoassisted
• Decrease in surgery time, of in-hospital stay, in costs
• Scar size reduction
• Decrease of peri-operative side effects and complications
• Surgery during local anesthesia: possible
“Experienced scintigraphers may be the most important factor to achieve maximum success”

Pre-Operative Imaging

- **Ultrasounds**
  - Sensitivity 65-85% in adenoma; 30-90% in hyperplasia
  - Sub-optimal results in pts. With nodular goiter, short neck, gland ectopy (15-20%)
  - Needs combination with scintigraphy

- **Sestamibi**
  - 85-95% accuracy in primary hyperPTH

- **Sestamibi-SPECT**
  - 60% Sensitivity for hyperplasia e 98% for solitary adenoma

- **TC con MDC/thin section**
  - Sensitivity del 46-87%
  - Usefull in Ectopic glands

- **MRI**
  - Sensitivity 65-80%
  - Usefull in Ectopic glands
The overall sensitivity of combined SS+US was 94.5% (86.8% and 80.4% for SS and US respectively).

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.

Tracers for Parathyroid imaging

No specific tracers for parathyroid targeting.

All gamma emitting tracer detect cell density and/or metabolic behavior of anomalous tissues:

- 201TI (K analogue)
- **lipophilic cations**
  - $^{99m}$Tc-metoxy-isobutyl-isonitrile-$^{99m}$Tc-MIBI
  - $^{99m}$Tc-1,2-bis(bis(2-ethoxyethyl)phosphino) ethane-$^{99m}$Tc-Tetrofosmin

All tracers are taken-up by both thyroid and parathyroid adenoma
• Cell density plays an important role as it amplifies the cell metabolic gradient. Detectability of lesions depends on contrast resolution related to local blood flow, metabolic state, cell density and mass.

• Partial volume can limit the ability to detect very small lesions.
Scintigraphic techniques:

- **Tracer: 99m-Sestamibi** (oxyphil cell content, volume of parathyroid lesions and the functional status of the parathyroid adenomas)
  

- **Dual tracers subtraction**
  

- **“Dual phase” 99m-Tc Sestamibi imaging**
  
Parathyroid Imaging Protocol.

- SNM procedure guidelines approved June 2004. (SPECT/CT not mentioned)
- 3 mci. Tc-99m pertechnetate i.v.
- Anterior 10 minute Neck/chest image
- 25 mci. Tc-99m Sestamibi i.v.
- Serial anterior neck/chest images
  - 20, 30, 40, 60 min and 2-3 hr delay
- Computer assisted pertechnetate subtraction from sestamibi
- Additional delays, SPECT/CT and pinhole optional
A – 99mTcO₄⁻ 74 MBq

B – KCl 200 -400 mg

C – 99mTc MIBI 740 MBq

D – C – A

delayed imaging
Scintigrafia con doppio tracciante e tecnica di sottrazione

$^{99m}$Tc-MIBI

$^{99m}$Tc-Pertecnetato

Immagine di sottrazione adenoma paratiroido
99mTc-MIBI dual-phase imaging

- 15' early imaging
- 90' delayed imaging
Differential Wash out: dual-phase technique

Right Adenoma in pt with previous right lobectomy
dual-phase technique

Ectopic upper mediastinal adenoma

Early MIBI 10 min

Late MIBI 2h
Planar images  128 × 128 or larger matrix using a low-energy, high-resolution, parallel hole collimator. The patient must be in the supine position with arms down. Early (10–15 min post-injection) and delayed (1.5–2.5 h post-injection) high count images (at least 600 s/per image) are obtained. Further delayed images (4 h post-injection) can be obtained if thyroid washout is poor.

SPECT imaging should be acquired immediately following early planar acquisitions (to avoid false-negative results due to parathyroid adenomas with rapid washout) with the patient in the same position, using a matrix of 128 × 128 for 120 projections every 3° (360° rotation) and with an imaging time of 15–25 s/per projection and suitable zoom factor.

SPECT/CT provides fused images of functional and anatomical modalities which considerably improve the interpretation of findings of individual procedures. This innovation might improve the relatively poor results obtained in the detection of multiglandular hyperplastic disease, but further data are needed to establish its role in the field.
## Dual phase vs Subtraction

<table>
<thead>
<tr>
<th>Primary hyperparathyroidism</th>
<th>Secondary hyperparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>99mTc-Sestamibi</strong></td>
<td><strong>99mTc-Tetrofosmin</strong></td>
</tr>
<tr>
<td><strong>Subtraction</strong></td>
<td><strong>93%</strong></td>
</tr>
<tr>
<td><strong>dual phase</strong></td>
<td><strong>88%</strong></td>
</tr>
</tbody>
</table>

Dual-Phase vs Sottrazione

- **False positive:** (specificità)
  - **thyroid nodules**

- **Falsi negativi:** (sensibilità)
  - dimensioni
  - cellularità (contenuto di cellule ossifile)
  - espressione di P-glicoproteina/MDR related protein gene
Dual-phase vs Subtraction

- More simple, fast, cost saving
- Lower radiation exposure
- No pt prolonged immobilization
- No requirements of technical skill for processing
- Effective in pt with inhibited function
SPECT prolonged acquisition time but

Sensitivity (90-95%)

- better contrast
- 3-D
- Resolution??!!

Moko et al. surgery 2000;128:29-35
<table>
<thead>
<tr>
<th>Sensibilidad %</th>
<th>Metodo</th>
<th>Referencia</th>
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<tbody>
<tr>
<td>96</td>
<td>Sub+SPECT</td>
<td>Eur J Endocrinol 2000 Dec;143(6):755-60</td>
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<tr>
<td>87</td>
<td>Dual Phase</td>
<td>Radiology 2001 Mar;218(3):783-90</td>
</tr>
<tr>
<td>85</td>
<td>Dual Phase</td>
<td>Acta Otorhinolaryngol Belg 2001;55(2):103-17</td>
</tr>
<tr>
<td>68</td>
<td>Subtraction</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of SPECT/CT, SPECT, and Planar Imaging with single and dual-phase

<table>
<thead>
<tr>
<th>Type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>Overall</td>
<td>59.8</td>
<td>98.7</td>
<td>79.3</td>
<td>79.8</td>
<td>96.7</td>
</tr>
<tr>
<td>Early planar</td>
<td>34.0</td>
<td>99.0</td>
<td>66.5</td>
<td>74.7</td>
<td>94.7</td>
</tr>
<tr>
<td>Early SPECT</td>
<td>53.5</td>
<td>98.7</td>
<td>76.1</td>
<td>77.0</td>
<td>96.2</td>
</tr>
<tr>
<td>Early SPECT/CT</td>
<td>62.0</td>
<td>98.9</td>
<td>80.5</td>
<td>82.7</td>
<td>96.9</td>
</tr>
<tr>
<td>Delayed planar</td>
<td>45.0</td>
<td>98.6</td>
<td>71.8</td>
<td>72.6</td>
<td>95.5</td>
</tr>
<tr>
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<td>53.5</td>
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<td>75.9</td>
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<tr>
<td>Delayed SPECT/CT</td>
<td>53.5</td>
<td>98.1</td>
<td>75.8</td>
<td>70.4</td>
<td>96.2</td>
</tr>
<tr>
<td>Early planar - Early SPECT</td>
<td>57.5</td>
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<td>96.5</td>
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W.C. Lavely et al, JNM 2007, vol. 48 (7); 1084-1089
SPECT/CT improves detectability and correct location especially of
• ectopic mediastinal adenomas and of retroesophageal space
• modified neck anatomy by previous surgery
and for
• mini-invasive surgery
MINI-INVASIVE RADIOGUIDED SURGERY

- Always pre surgical evaluation by SPECT (better SPECT/CT) in Pt with primary single adenoma with high tracer uptake
- Critical issue: Accurate pt selection
- difficult in pt with nodular (multi-nodular) goiter: consider wide neck exploration and Thyroidectomy + parathyroidectomy
- Esclude pts with MEN syndrome or familial hyperparathyroidism in whom there is higher likelihood of hyperplasia.
**Protocollo pre-operatorio**

\((^{99m}\text{Tc-Sestamibi scan and MIRS})\)

- **Single day** (Norman, 1997)

  740 MBq \(^{99m}\text{Tc-Sestamibi}: \) iniezione ev 2-3 ore prima della MIRS per avere una conferma scintigrafica e trovare il migliore T/B (15 min and 1 hr)

- **Different day** (Casara, 2000)

  \(^{99m}\text{Tc-Sestamibi scan ed ecografia eseguite nei giorni precedenti all’intervento}\)

  37-110 MBq \(^{99m}\text{Tc-Sestamibi iniettati ev 10-30 min prima della MIRS per ridurre al minimo la dose di esposizione al paziente ed al chirurgo}\)

  **Ed individuazione di eventuali adenomi con wash-out rapido**
• significant reduction in the operative time following SPECT/CT, the mean duration of surgery being 36 min with 62 min in the SPECT group (P<.0001).

• SPECT/CT correctly identified the location of all ectopic “lower” adenomas
Secondary Hyperparathyroidism

- Lower sensitivity of non-invasive diagnostic imaging: sensitivity $\approx 50\%$ due to lower metabolic activity
- Wide neck exploration in all pts
- Preoperative Sestamibi SPECT/CT to exclude the presence of ectopic glands
- 10-30% rate of persistent hyperparathyroidism after surgery
- Sestamibi SPECT/CT mandatory in re-intervention
New Modalities

**PET/CT** with $^{11}$CarbonMethionine (20 minut half-life)

- **Left superior parathyroid gland**
  - Incremental uptake of methionine related to increased protein synthesis of hyperfunctioning parathyroids

- **Right inferior parathyroid gland**
take home message

- Parathyroid Sestamibi SPECT/CT mandatory in Pts with primary (and secondary) Hyperparathyroidism:
  - in presence of single adenoma with normal thyroid gland (by US) indication to MIRS
  - In presence of multiple adenoma, multinodular goiter, secondary hyperparathyroidism indications persist for wide open neck exploration