

# Localisation studies

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venous sampling for the PTH gradient. Nuclear medicine-based studies (sestamibi scanning) The use of sestamibi (2-methoxy-2-methylpropylisonitrile [MIBI]) for parathyroid localisation was first described in 1989 and is now regarded as the most accurate and reliable method for imaging the parathyroid glands. It is safe and reproducible and, while it has a sensitivity and specificity similar to ultrasonography, it may image glands in ectopic positions better (Figure 56.3a). Sestamibi accumulates in mitochondria and therefore washes out at differential rates depending on the number of mitochondria within individual tissues. Parathyroid adenomas often have a high concentration of oxyphilic cells with high mitochondrial content. These retain tracer, and adenomas are therefore associated with a slow washout when compared with the thyroid gland. There are three different protocols for sestamibi scanning: single-isotope dual-phase scan, dual-isotope Karl Hürthle, 1866–1945, histopathologist, Breslau, Germany (now Wrocław, Poland). tomography (SPECT). The sensitivity and specificity of sestamibi, regardless of the protocol used, are 79% and 90%, respectively. False positives are rare but may arise from some solid thyroid nodules, such as Hürthle cell nodules, that are associated with high oxyphilic content. These can be reduced by the addition of a thyroid-specific radioactive tracer, such as <sup>99</sup>Tc-pertechnetate and subsequent subtraction images. Ultrasonography - Ultrasonography is a non-invasive, inexpensive method of imaging the parathyroid glands (Figure 56.3b). Parathyroid adenomas are typically oval or elongated, bi- or multilobed hypoechoic structures. Rarely, adenomas may be cystic or heterogeneous in nature. Giant adenomas are described as those over 3 cm in size. Ultrasonography is not associated with any radiation exposure and has the advantage of being able to identify and facilitate biopsy of any concomitant thyroid pathology. However, ultrasonography is operator, lesion size and location dependent. Critically, ultrasonography may

(a) Figure 56.3 Sestamibi scan (a) demonstrating right inferior adenoma, with concordant ultrasonography (b).

or retrotracheal areas. It can also be difficult to differentiate between a small parathyroid gland and a normal-appearing lymph node. A meta-analysis of preoperative localisation techniques in PHPT demonstrated that ultrasonography and sestamibi-SPECT have comparable accuracy, with pooled sensitivities of 76.1% and 78.9%, respectively, and positive predictive values (PPVs) of 93.2% and 90.7%, respectively (Krakauer et al., 2016). Four-dimensional computed tomography scanning/positron emission tomography-computed tomography Multiphase CT imaging (4D-CT) has become widely utilised to localise disease (Figure 56.4). It gives both anatomical and functional information about the parathyroid glands. Using precontrast, postcontrast and delayed images, it demonstrates not only detailed anatomical localisation but, combined with rapid uptake and washout, allows hyperfunctioning glands to be differentiated from lymph nodes that demonstrate a progressive enhancement pattern. The potential disadvantage of 4D-CT scanning is the higher radiation dose when compared with traditional imaging modalities. Modification of the protocol now allows fewer phases to be obtained without compromising outcomes. The initial study in 2006 reported a sensitivity of 88% for lateralisation and 70% for localisation of parathyroid adenomas (Rodgers et al., 2006). A more recent meta-analysis, although limited by the small number of studies, demonstrated a sensitivity and PPV of 89.4% and 93.5%, respectively, when 4D-CT was used as the primary imaging modality. This was reduced to 71.8% and 74.9%, respectively, in cases of negative or inconclusive prior imaging (Cheung et al., 2012). Positron emission tomography (PET) scanning remains expensive and is not widely available. However, recent data suggest that there may be an incremental value to F-fluoro choline PET with the addition of CT scanning for localisation of ectopic adenomas. Magnetic resonance imaging (MRI) is not commonly used to image the parathyroid glands. However, on T2-weighted images, enlarged parathyroid glands demonstrate significantly increased intensity. In reoperative cases or where the adenoma is located in the mediastinum, MRI may be beneficial, with higher reported sensitivities (50–88%). While the sensitivity of MRI is slightly better than that for CT (64–88%) in primary disease, it has significant limitations. It is expensive, patients can be poorly compliant owing to claustrophobia and the resolution for normal glands or adenomas <5 mm is poor. Similarly, it can be difficult to localise superior glands because of their posterior location, which allows them to be obscured by the thyroid gland. Parathyroid angiography and venous sampling for parathyroid hormone Parathyroid angiography is reserved for reoperative cases and is now rarely required owing to improvements in non-invasive imaging modalities. It involves examination of - both thyrocervical trunks, both internal mammary arteries and both carotids, with occasional selective superior thyroid artery catheterisation. Vascular parathyroid adenomas appear as a persistent oval or round 'stain' on angiography. Serious complications such as contrast-induced renal failure, embolisation and neurological damage have limited its utility. Selective venous sampling for PTH can allow accurate localisation of adenomas but an experienced interventional radiologist is vital for success. The venous drainage of the lesion is established when there is a twofold drop in the PTH between the sampled blood and the serum PTH. The sensitivity is reported to be 80% and is equally effective in localising cervical and mediastinal adenomas. However, the false-positive to reoperative rate of between 6% and 18% limits its utility cases.

(b) Figure 56.4 (a, b) Four-dimensional computed tomography scanning demonstrating a right inferior parathyroid adenoma (arrows).



above the upper limit serum calcium of normal Skeletal BMD by DEXA; T score  $-2.5$  at lumbar spine, total hip, femoral neck or distal one-third of radius Vertebral fracture Renal Creatinine clearance  $<60$  mL/min 24-hour urinary calcium  $>10$  mmol/dL ( $>400$  mL/day) or increased risk of stone formation by risk analysis Age  $<50$  years BMD, bone mineral density; DEXA, bone densitometry. Adapted from Bilezikian et al . (2014).

Concordant Discordant MIBI and US imaging imaging Pre-op

marking 4D CT with US Pre-op 4 gland MIP marking with exploration US and MIP Figure 56.5

Localisation paradigm and management strategies. 4D /uni00A0 CT, four-dimensional computed tomography; MIBI, 2-methoxy-2 methylpropylisonitrile; MIP , minimally invasive parathyroidectomy; US, ultrasonography. (a) (b)

Figure 56.6 (a) Minimally invasive parathyroidectomy through a lateral approach; (b) the excised parathyroid adenoma.

hypocalcaemia, shorter operating times, potentially less pain and better cosmesis. The need to convert from a focused to a cervical exploration may be guided by the use of intraoperative PTH measurements. Routine use is, however, controversial owing to high false-positive and false-negative rates. The basic concept is that the half-life of circulating PTH is 3-5 minutes and there should therefore be a significant drop detected in the plasma PTH following resection of a single adenoma. If no such drop is detected, then multigland disease may be suspected and conversion to a bilateral neck exploration should be considered. The Miami criteria were developed to determine the extent of resection. A drop in the PTH into the normal range and to less than half the maximum preoperative PTH at 10 /uni00A0 minutes appears to accurately predict single-gland disease ( Figure 56.7 ). Bilateral neck exploration A traditional cervical neck exploration is required where imaging is negative or discordant, in MEN (type 1 or type 2A) or in lithium-induced PHPT . A

transverse collar (Kocher's) incision is made and the subplatysmal plane developed. The deep cervical fascia is divided between the strap muscles and these are retracted. The thyroid lobes are mobilised and the middle thyroid vein may be divided when present. Identification of the recurrent laryngeal nerve and the middle thyroid artery allows a starting point for a systematic exploration (see Chapter 55). All four glands are identified. Three and a half glands are resected, with half of a vascularised parathyroid left in situ. The other half of the gland should be sent for frozen section to confirm the presence of parathyroid tissue (Figure 56.8). Ideally the most normal-appearing parathyroid is left in situ. With this caveat in mind, where possible an inferior gland should be left. It is marked with a non-absorbable suture to aid identification in the presence of recurrent disease, where resection can be achieved without increasing the risk of damage to the recurrent laryngeal nerve. Alternatively, all four glands can be resected and a forearm autotransplant created. Small pieces of parathyroid are sutured into pockets created in the brachioradialis muscle. Cure rates and rates of persistent and recurrent disease appear to be similar, regardless of the Emil Theodor Kocher, 1841–1917, surgeon, Berne, Switzerland, awarded the Nobel Prize in Physiology or Medicine in 1909 for his research on the thyroid. - - - type of procedure used. However, in recurrent disease it can be difficult to identify the location of the recurrent tissue when an autotransplant is performed. Thymectomy and resection of mediastinal adenomas The incidence of clinically significant supernumerary glands is increased in patients with multigland disease or those with hereditary syndromes. A thymectomy should be routinely undertaken for patients with MEN1 - associated PHPT or in secondary hyperparathyroidism. A cervical thymectomy is performed by dissecting close to the thymic capsule, exploring the cervical part of the gland. The mediastinal part of the gland can be removed by gentle upwards traction, with ligation of the veins draining into the innominate vein. The end of the

120 100 80 60 40 20 % PTH remaining 0 0 5 10 15 Time (min) Figure 56.7 Miami criteria for intraoperative parathyroid hormone (PTH) measurement. Drop of PTH into the normal range and less than half the maximum value at 10 minutes postresection. (b) Figure 56.8 Parathyroidectomy with exposure of the left superior and inferior parathyroid glands (white arrows) in situ (a) and left superior gland mobilised on its vascular pedicle (b).

sternotomy is not required where a prophylactic thymectomy is being performed. Mediastinal adenomas are rare, accounting for less than 1% of all parathyroid adenomas. They will be typically identified on preoperative imaging. Resection can be achieved either by an open sternotomy or increasingly by a thoracoscopic approach. A minimally invasive approach can be particularly effective where the abnormal gland lies immediately deep to the mediastinal pleura. It can confer significant advantages in length of hospital stay and complication rates. Localisation studies

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disease is defined as an elevated serum calcium within 6 weeks of surgical intervention and recurrent disease is defined as an increase in - calcium levels after 6 months but with an intervening period of normocalcaemia. Minimally invasive (focused) parathyroidectomy - Minimally invasive approaches are based on the principle that over 80% of individuals with PHPT have a single adenoma. Although there is no strict definition of the procedure, it commonly refers to the removal of a localised abnormal - parathyroid gland through an incision less than 3 /uni00A0 cm in length ( Figure 56.6 ). The term encompasses open approaches (central and lateral incisions) and video-assisted and radio- guided parathyroidectomies. A number of randomised studies have shown that the focused approach has similar cure rates to

**TABLE 56.2 Consensus guidelines for surgical intervention in asymptomatic primary hyperparathyroidism.**

**Measurement of 0.25 /uni00A0 mmol/L (1.0 /uni00A0 mg/dL) above the upper limit serum calcium of normal Skeletal BMD by DEXA; T score  $-2.5$  at lumbar spine, total hip, femoral neck or distal one- third of radius Vertebral fracture Renal Creatinine**

clearance  $<60$  mL/min  
24-hour urinary calcium  $>10$   
mmol/dL ( $>400$  mL/day) or increased risk of stone  
formation by risk analysis Age  $<50$   
years BMD, bone mineral density;  
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Concordant Discordant MIBI and  
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