Standard surgical treatment of primary hyperparathyroidism until the 1990s:

Conventional Neck Exploration

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Introduction

Sandström [1] first described a small gland located in the vicinity of the thyroid gland in 1880 and gave it the name of 'glandula parathyroidea'. The first anatomic description in humans was published by Welsh [2] in 1898, and by Halsted and Evans [3] in 1907. After the first successful parathyroid operation was performed by Doctor Felix Mendl in Vienna in 1925 for a patient with primary hyperparathyroidism (pHPT) and osteitis fibrosa cystica, parathyroidectomy has been the treatment of choice for patients with pHPT [4]. It was not until the late 1960s that most cases of pHPT were detected by routine biochemical screening rather than because of specific associated symptoms or complications such as renal colic, parathyroid bone disease, peptic ulcer disease, gout, or pancreatitis. Routine multichannel biochemical screening of serum calcium came to widespread use at the beginning of the 1970s, resulting in a rapidly increasing total number of patients diagnosed with mild to moderate hypercalcemia. Primary hyperparathyroidism is nowadays the most common cause of hypercalcemia in nonhospitalized patients and, along with (dissiminated) cancer, accounts for 90% of all patients with hypercalcemia [5].

Clinical Presentation and Diagnosis

Most patients are detected by routine screening before presenting with (severe) clinical symptoms. The diagnosis pHPT is based upon documentation of persistent hypercalcemia and elevated parathyroid hormone (PTH) level without hypocalciuria. Immunoassays for intact PTH using double-antibody methods are highly sensitive and represent a major advance in the diagnostic process [6]. The majority of patients with pHPT have unequivocal elevated PTH levels, whereas patients with hypercalcemia from other causes, such as malignancy and sarcoidosis have low, normal, or suppressed values [6]. Other tests that sometimes are useful (but not diagnostic) are the blood alkaline phosphatase level, which is elevated in high turnover parathyroid bone disease and the blood phosphate level which is decreased in about 50% of patients with pHPT. This, simultaneously with an increased blood chloride level (in about 40% of patients) elevates the chloride/phosphate ratio in most patients [7].

The clinical manifestation of pHPT varies from asymptomatic disease to a picture which has been described as 'painful bones, kidney stones, abdominal groans, psychic moans, and fatigue overtones'. Most patients (about 80%) are diagnosed

Table 1

Symptoms in patients with primary hyperparathyroidism.

Bone Pain
Constipation
Depression
Exhaustion
Fatigue
Joint pain
Loss of appetite
Memory loss
Nausea
Nocturia
Poliuria
Polydipsia
Renal colic
Weakness

with pHPT without having any symptoms or with subtle symptoms as fatigue and muscular weakness. **Table 1** shows the spectrum of symptoms which may be present in pHPT.

Anatomy and Embryology

The superior parathyroid glands originate along with the lateral lobes of the thyroid (ultimobranchial body) from the dorsal tips of the pharyngeal fourth pouch. Because the superior glands migrate only slightly their position is relatively constant, cephalad to the inferior thyroid artery and dorsal in respect to the recurrent laryngeal nerve. The inferior glands arise along with the thymus from the dorsal part of the third branchial pouch and migrate downward during fetal life. The position of the normal inferior parathyroid gland is less constant because it travels so far in embryonic life. It can be found anywhere from the angle of the jaw to the pericardium, but is found caudal to the inferior thyroid artery and ventral to the recurrent laryngeal nerve in approximately 55% of cases [8]. In addition, enlarged parathyroid glands may migrate secondarily in adult life and become ectopic. The superior gland tends to fall back and displace in a posterior and caudal direction. It descends along the tracheo-esophageal groove even

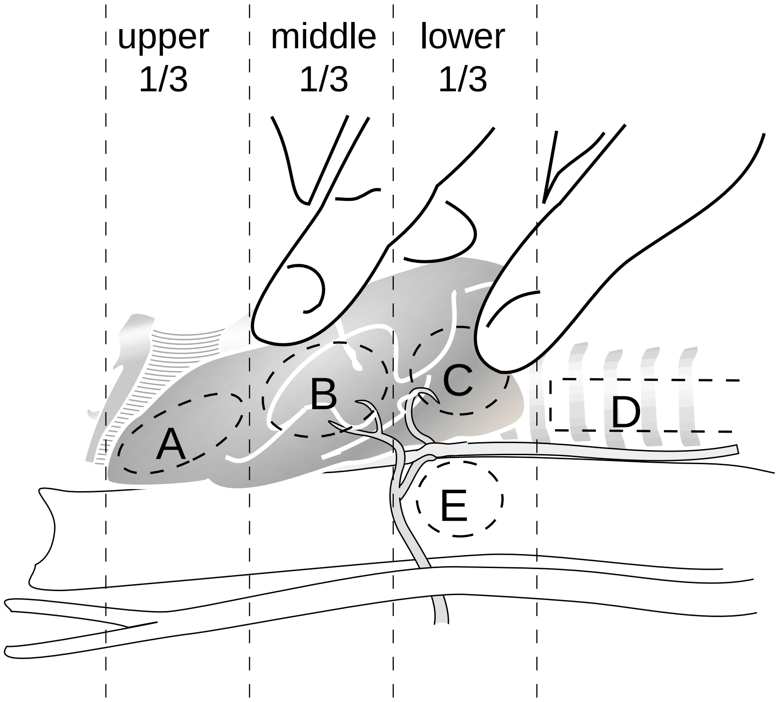

Figure 1 *The relative frequency with which the parathyroid glands are found in the various locations. The superior gland is usually (75%) found on the posterior portion of the middle third (B) of the thyroid. In about 9% the gland is found more cephalad at the upper pole (A) of the thyroid. The location of the inferior gland is more variable; approximately 55% is found on the posterior surface of the lower pole (C), 25% below the lower pole (thymus or lower) (D), 10% deep medio-posterior of the thyroid (E).*

as deep as the posterior mediastinum. The inferior parathyroid gland tends to move in an anterior-caudal direction and may descend in the anterior mediastinum [9].

The average weight of a normal parathyroid gland is 35-50 mg. Parathyroid glands are small (2-5 mm), usually yellowish-brown and sometimes look like fat, which make them difficult to find for the inexperienced operator. In approximately 75% of cases the superior gland is to be found on the posterior portion of the middle third of the thyroid. As already indicated the position of the normal inferior gland is more variable and can be found in approximately 75% of cases on the lateral or posterior surface of the lower pole of the thyroid gland, or not more than 0.5 cm below the lower pole [10] (**Figure 1**).

Parathyroidectomy

Surgery offers the only definitive treatment for patients with pHPT [11]. The primary goal of parathyroidectomy is to establish normocalcemia with minimal complications (these include persistent or recurrent hyperparathyroidism, postoperative transient or persistent hypoparathyroidism, and recurrent laryngeal nerve injury).
The gold standard in parathyroid surgery is the conventional neck exploration (CNE), a very safe procedure with success rates exceeding 95% and minimal morbidity (**Table 2**) [12 13 14 15 16]. The most important variable that influences the success of parathyroidectomy is the experience of the surgeon. The rate of persistent hyperparathyroidism can be as high as 30% in less experienced hands [17].

Conventional neck exploration is preferentially performed under general anesthesia with endotracheal intubation. The patient is positioned in supine position, the neck extended dorsally to provide maximal access to the neck. A low, symmetric Kocher transverse incision is made 3 to 4 cm cranial to the suprasternal notch. After incision of the platysma muscle, the strap muscles (m. sternohyoid, m. sternothyroid) are divided in the median raphae, separated from each other and may be cleaved. The sternocleidomastoid muscle and internal jugular vein are lateralized. The fascia between common carotid sheath and thyroid is opened alongside the carotid artery in order to mobilize the thyroid gland in medioventral direction, whereafter the loose areolar tissue of the tracheoesophageal groove is entered. Care is taken in identifying the delicate recurrent laryngeal nerve.
After identification of the four parathyroids, the adenoma(s) is resected and sent for histological examination. The assessment whether a parathyroid is normal or diseased is determined by the surgeon and is based upon macroscopical features such as size and color. Some authors rely on microscopical features in frozen section to distinguish adenomas from hyperplastic glands [18 19]. However, no single criterium has irrefutably proven to be useful in discriminating between adenoma and hyperplasia [20]. Therefore, we agree with the statement that the role of the pathologist intraoperatively is limited simply to the identification of parathyroid tissue [21].

Difficulties associated with parathyroid surgery relate to the variety in location, and to a lesser extent, the number of the (diseased) glands, and to the problem of differentiating normal glands from slightly diseased ones. In an extensive postmortem study Gilmour [22] found that 80% of individuals had four parathyroids, 6% had five and 13% had three. Others report different frequencies of supernumerary glands: Boyd [23] found five or six glands in 14%, Alveryd [24] reported fewer than four glands in less than 1%. Without neglecting these figures, it is of utmost importance to identify four parathyroids. Even if an adenoma and two normal parathyroids are identified the surgeon should endeavor to find the unidentified parathyroid,

Table 2 Success rate after Conventional Neck Exploration, review of literature.

Author	n	period	median follow up	success (%)	morbidity (%)	mortality (%)
Bruining HA, et al. [13]	615	1950-1979	5.6 years	96.4	laryngeal nerve 0 hypocalcemia 1.1	0
Saaka MB, et al. [15]	316	1960-1986	6 years	92.1	laryngeal nerve 1 hypocalcemia 0.8	0
Low RA, Katz AD [16]	866	1960-1997	1-96 months	98.2	laryngeal nerve 0.3 hypocalcemia 1	0.3
Russel CF, Edis AJ [12]	500	1974 -1980	NA	92.2	laryngeal nerve 0.2 hypocalcemia 0	0.2
Heerden JA, Grant CS [14]	384	1983-1984	4 years	99.6	laryngeal nerve 0.8 hypocalcemia 0.3	0.3

laryngeal nerve: damage to the recurrent laryngeal nerve.

NA: not available.

because missing at its normal localization can indicate a migrated second enlarged parathyroid. If during exploration one or more parathyroids are missing or the adenoma cannot be found the following rules should be remembered. Firstly, as has been succinctly stated by Rothmund [25], the majority of all parathyroids are located within a 1-2 cm circle around the intersection of the inferior thyroid artery and the recurrent laryngeal nerve. The superior gland situated cephalad to the artery and dorsal in respect to the nerve, the inferior caudal to the artery and ventral to the nerve [26]. Secondly: it may be assumed that the gland on the contralateral side is located symmetrically to the one found at the 'identified side'. Thirdly: If the missing adenoma is of superior origin, the space dorsal to the thyroid gland and the oesophagotracheal groove should be explored. The common origin of the superior parathyroid and thyroid accounts for the occasional intrathyroidal location found in less than 1% of all cases [25 26]. The tongue of the thymus (thyrothymic ligament) should be explored for a missing inferior gland since this is the second most common location after the lower pole of the thyroid. If the adenoma is still missing after thymectomy an intrathyroidal parathyroid should be considered necessitating thyroidotomy or lobal thyroidectomy. However rare, a missing inferior adenoma can be found anywhere along the path of descensus, from the angle of the jaw to the pericardium [10 25]. Finally, a primary sternotomy should only be considered after a thourough, systematic, but negative exploration in patients with life threatening hypercalcemia [27].

A major and recurrent problem during exploration is the differentiation between an adenoma and a hyperplastic gland, or single gland disease from multiple gland disease. Since microscopic examination durante operationem is of no added value, making decision relies upon the macroscopic features and thus on the surgeon's judgement and experience. Classically, an adenoma has been defined as an enlarged gland with a rim of normal tissue. However, this histological appearance can be found in cases of hyperplasia as well. Significant differences in histological appearance could not be demonstrated in 236 patients with pHPT by Bonjer et al [20].

Preoperative Imaging Studies

Numerous localization techniques have been used to identify the site of the abnormal parathyroid gland preoperatively, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), thallium201-technetium-Tc99m pertechnetate scanning (ThTc) and sestamibi-technetium99m scintigraphy (Sestamibi), and selective venous catherization for measurements of PTH levels.
High-resolution ultrasonography is easy to perform and is well tolerated by the patient. It does not require injection of contrast, does not emit radiation, can be done quickly and is inexpensive. Unfortunately, the retrosternal, retroesophageal, retrotracheal and deep cervical glands are difficult to locate by US. The sensitivity varies according to the ultrasonographer's experience, the frequency of the transducer, the resolution of the image, and the size of the parathyroid gland [28].
Computed tomography is relatively expensive, exposes the patient to radiation, and requires administration of (a) contrast agent(s) to obtain the highest resolution. The sensitivity of CT reportedly ranges from 41 to 86%, as compared to 57-90% [29 32] for MRI. Other advantages of MRI over CT are that the use of contrast is avoided and shoulder artefacts are not a problem.
Thallium201-technetium-Tc99m pertechnetate scanning is reported to be moderately accurate with sensitivity rates ranging 25 to 70% [29 33], whereas Sestamibi is superior with reported sensitivity rates reaching 100% in solitary disease [34 35].
Radionuclide scintigraphy is associated with low risk and minimum irradiation, and is minimally operator dependent. However, due to the high cost, its use should be restricted to a selected group of patients.
Selective PTH sampling is an invasive, expensive localization method requiring an expert radiologist. This method should, therefore, be limited to the reoperative case.

Progressive development of imaging modalities over the last ten years have made the various techniques increasingly reliable. The pace technical development should raise the accuracy and sensitivity rates of localization studies and anticipates future image-guided surgical procedures.

Discussion

Since pHPT can be diagnosed with nearly 100% accuracy and successfully treated in more than 95% of patients, surgery is the choice of treatment. Until now the gold standard in parathyroid surgery has been CNE. Routine localization studies are of no added value, since sensitivity rates in localizatory studies (reaching 85% maximum) are inferior to success rates in CNE [38]. Furthermore, accuracy of imaging techniques decreases in multiglandular disease and is therefore of little use in predicting whether a patient has uniglandular or multiglandular disease [29 31 39]. Preoperative localization may even mislead the less experienced surgeon, who might fail to identify all involved parathyroid glands [35].

With success rates exceeding 95% and virtually no complications nothing more seems to be desired. Nevertheless, since the early 1980s authors have been increasingly propagating less invasive techniques [36 37] (unilateral exploration), in order to reduce operation time and admission days, decrease operative risk during reexploration and to obtain better cosmetic results. They rely upon the high incidence of solitary adenoma (approximately 85%) and improved resolution in preoperative imaging modalities. 'Bilateralists' however, oppose such an approach because of the incidence of multiple gland disease which may be, in their opinion, as high as 30% [13]. Furthermore they are critical as far as the accuracy of localization procedures is concerned.

The ability to document PTH concentration during operation, first described by Nusbaum [40], was further developed in the early 1990s. The use of an intraoperative PTH assay could prove beneficial in the surgical management of pHPT. The biochemical confirmation of complete removal of all hyperfunctioning tissue allows less than bilateral neck explorations. Despite their helpfulness, these intraoperative assays have not gained widespread acceptance. The short half-life of isotopes and thus limiting shelf-life of these intraoperative PTH assays; the necessary safety precautions (including proper disposal of waste products); a false negative rate of 15%; and high costs initially limited its use to a few specialized centers [37].

The diagnosis pHPT is based upon biochemically proven hypercalcemia with inappropiate high levels of PTH. The treatment of choice is CNE, a highly effective procedure associated with minimal morbidity. However, because pHPT is caused by a solitary adenoma in at least 85%, and presently available localization procedures are increasingly accurate, unnecessary extensive dissection is undertaken in the vast majority of patients. The ability to ascertain success of parathyroidectomy by presently available reliable and affordable intraoperative PTH assays will lead undoubtedly towards more limited forms of parathyroidectomy.

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