Turk J Med Sci
34 (2004) 81-84

PERSPECTIVES IN MEDICAL SCIENCES

The Intellectual and Scientific Basis of Parathyroid Surgery

Seza A. GÜLEÇ[1], Ömer UĞUR[2]
[1]John Wayne Cancer Institute, Department of Surgery, Santa Monica, CA, U.S.A
[2]Department of Nuclear Medicine, Faculty of Medicine, Hacettepe University, Ankara - Turkey

Received: October 24, 2003

Primary hyperparathyroidism (PHPT) is a disorder caused by excessive secretion of parathormone by one or more enlarged parathyroid glands. Primary hyperparathyroidism has become a common disease, affecting an estimated 28 per 100,000 people in the United States. There have been significant changes in the understanding of the disease process and advances in the management of PHPT in the last decade. The increased recognition of PHPT due to the more widespread use of screening tests resulted in a new clinical profile of hyperparathyroidism, characterized by mild hypercalcemia with absent or subtle symptoms. Consequently, the number of parathyroidectomies performed for PHPT has also increased worldwide. Minimally invasive parathyroidectomy (MIP) has replaced the traditional 4 gland exploration as the procedure of choice in many institutions, with comparable cure rates (1,2).

The goal of surgery for PHPT is to return the patient's calcium level to normal. This should be accomplished with minimal morbidity, no mortality and low recurrence rates, at a reasonable cost.

The standard parathyroidectomy was first performed in 1925 with bilateral neck exploration, and it has remained the standard treatment of PHPT (3). In this standard approach, when one gland is determined to be grossly enlarged, excision of this abnormal parathyroid is performed with or without biopsy of the remaining glands. When more than one gland is enlarged, the operative techniques include a 31/2-gland resection (leaving approximately 50-100mg of the most "normal-appearing" gland), excising only those glands that are grossly enlarged at the exploration, and less commonly a 4-gland parathyroidectomy with subsequent autotransplantation. Success with this approach as measured by return to normal calcium levels depends primarily on the experience and judgment of the surgeon in recognizing the difference between enlarged and normal sized glands. Although the size of the parathyroid gland does not always correlate well with the secretion of the parathyroid hormone, and may be problematic, in expert hands the cure rate of standard 4 gland exploration parathyroidectomy is over 95%, even with 4 gland hyperplasia (4,5).

The success of surgical treatment depends on success in the localization and identification of abnormal glands. Difficulties associated with parathyroidectomy for PHPT relate to the variability in the number of parathyroid glands, the different locations of normal and abnormal glands, and problems distinguishing normal glands from those that are subtly diseased.

The surgical anatomy of parathyroid glands is intricate and variable. In most cases, normal upper glands are located in the posterior to the middle and upper third of the thyroid lobe and posterior to the recurrent laryngeal nerves. The location of normal inferior parathyroid glands, however, is more variable. In approximately 50% of explorations they are found posteriorly or laterally to the lower pole of the thyroid lobe. With decreasing frequency, they are found within the thyrothymic ligament and the thymus in the mediastinum or are intrathyroidal. When parathyroid glands become adenomatous/hyperplastic and enlarge, their location may change somewhat. Although 80% to 85% of parathyroid adenomas are found adjacent to the thyroid gland in their normal location, 15% to 20% are ectopically placed. Ectopic abnormal glands may be found in the anterior-superior mediastinum, either within or outside the thymus, along the esophagus into the posterior-superior mediastinum, or very rarely in the middle mediastinum. Occasionally, they may be found within or even lateral to the carotid sheath. Rarely, an undescended lower parathyroid gland is found high in the neck, anterior to the carotid bifurcation. Finally, 3% to 5% of all parathyroid adenomas are intrathyroidal, usually within the lower pole of the thyroid gland. Approximately 85% of individuals have 4 glands, 5% have 5, and 10% have 3 glands identified. The variability in the number of glands may lead to situations in which a patient has 4 normal glands in the neck and an abnormal fifth one located in the mediastinum (6,7).

Another challenging aspect of parathyroid surgery is to distinguish an adenoma from hyperplasia. This distinction is not only difficult intraoperatively, but histopathologically as well. The histopathologic criteria used to distinguish adenoma from hyperplasia are not well defined. Current facts regarding the histopathogenesis of parathyroid adenoma and hyperplasia are also not conclusive. Most adenomas are monoclonal proliferations suggesting a neoplastic origin. However, there is histopathologic and cytogenetic evidence suggesting evolution to a monoclonal adenoma from polyclonal hyperplasia and vice versa (8). Parathyroid adenoma and hyperplasia could well be the same disease entity, representing opposite ends of the spectrum of phenotypic expression. To avoid confusion and speculations, we prefer to use the term “adenoma” interchangeably with “single gland disease”, and “hyperplasia” interchangeably with “multigland disease”. Multiple endocrine neoplasia and the familial hyperparathyroidism syndromes are associated with multigland disease as a rule. In sporadic cases, classically, single gland involvement (adenoma) is observed in approximately 80% to 85% of cases, and hyperplasia is seen in 15% to 20% of cases. In general most experienced surgeons think that by evaluating the size, shape and color of the parathyroid glands at operation, they can distinguish normal glands from abnormal ones. If one gland is enlarged and the others are perfectly normal, visually the diagnosis is an adenoma. Some surgeons attempt to confirm this with a frozen section of a biopsy from a normal gland. Hyperplasia (multigland disease) should result in enlargement of all 4 glands. However, asymptomatic hyperplasia may appear with 1 or 2 normal sized glands confusing the diagnosis even when a biopsy is used. The prevalence of hyperplasia varies considerably in different series. There appears to be a strong influence of clinical (surgical) diagnosis on the pathologist’s diagnosis. When subtotal parathyroidectomy is performed, more hyperplasia is diagnosed. When a focused operation is performed with removal of a single gland, it is likely to be called an adenoma. The importance of mild hyperplasia and the best way of diagnosing this condition are yet to be determined.

The radiologic localization of abnormal parathyroid glands has also been extremely challenging. Ultrasound imaging has a localization accuracy of 70-80% in unoperated patients. However, this falls to 40% in patients who have had prior failed surgical exploration. The sensitivity of CT scans ranges from 45% to 75%, being lower in reoperated patients. MRI sensitivity is similar to that of CT scans, with slightly better (50-80%) accuracy in reoperative cases (9). The less than optimal sensitivity of these diagnostic imaging modalities supported the rationale for traditional neck exploration. The NIH consensus statement on the treatment of PHPT in 1990 stated that preoperative localization in patients without prior neck surgery was rarely indicated and not proven to be cost-effective. The surgeon should localize the glands by direct visualization intraoperatively (10).

In 1989, Coakley et al. incidentally noted that Tc^{99m} sestamibi exhibited uptake and retention in abnormal parathyroid glands. Prior to this, the Tl^{201} - Tc^{99m} pertechnetate substraction scan was being used with no better yield than other conventional imaging techniques (11,12). Shortly after this original report, many investigators reported the successful localization of abnormal parathyroid glands in patients with PHPT. Sestamibi imaging drastically affected the management of patients with PHPT in a remarkably short period of time. A number of studies reported the successful utilization of sestamibi imaging in abnormal gland localization (13,14). Sestamibi localization in adenomatous parathyroid cells has been shown to be in the mitochondria, and uptake is a function of blood flow, gland size and mitochondrial activity (15,16). The differential retention of sestamibi relative to thyroid tissue, however, has been shown to be a function of p-glycoprotein down-regulation, which acts as an out-flux carrier molecule in the parathyroid tissue (17,18).

High quality scans accurately locate parathyroid adenomas in 75-85% of patients with PHPT. The utility of sestamibi imaging is markedly improved with SPECT. The precision of localization of difficult ectopic sites, such as retroesophageal space or mediastinum, is only possible with high quality SPECT acquisition and interpretation (19,20).

With the introduction of sestamibi localization, and the identification of parathyroid adenoma location, the era of focused exploration or minimally invasive parathyroidectomy began. The different techniques associated with focused/minimally invasive parathyroidectomy include gamma probe-guided exploration, and novel endoscopic techniques. The sophisticated techniques of parathyroid imaging allow the surgeon to plan a localized exploration designed to remove the common single focus of disease. The incision is small, dissection is minimal, postoperative pain is less, and hospital stay is shorter.

The use of an intraoperative gamma probe facilitates the surgical exploration. The operation could be performed through a smaller incision. The surgeon can locate the abnormal gland readily in the direction of the probe tip where a hot spot is identified. The identification of the parathyroid adenoma is more challenging than it is for sentinel node localization. Background activity in the thyroid gland is significant and the target to background activity ratio is variable depending on both the thyroid and parathyroid washout rates of sestamibi. The gamma probe is only helpful when there is a statistically significant differential between the thyroid and parathyroid count rates. This differential usually occurs within a window 1.5 to 3 after the sestamibi injection. Within this window, the ex-vivo count rate of an adenoma is at least 20%, and is usually higher than 50%, of the thyroid background. Selection of a gamma probe with good directionality and scatter suppression electronics is important for improving detection success. Ex-vivo activity has also proven to be 100% accurate in distinguishing parathyroid tissue from fat and lymph nodes when the excised tissue emits 20% of the background activity. This has been extremely useful in reducing the need for a frozen section to identify parathyroid tissue (21). The use of sophisticated protocols calculating the maximum parathyroid to thyroid uptake ratio, thus the optimal time to surgery, increases the success of gamma probe-guided parathyroidectomy (22).

The cost-effectiveness of the image-guided minimally invasive approach, i.e. the expense of imaging with the equipment required, has been questioned. However, the potential savings from decreased operating time and hospital stay were found to be comparable to in favor of minimally invasive approach in many analyses (23,24). A major concern when using a sestamibi-guided focused unilateral surgical approach is a possible failure to diagnose multigland disease. A recent review demonstrated that the reported incidence of multigland disease in series in which bilateral explorations were performed is 20%, whereas the incidence with focused unilateral explorations is only 5% (25). The difference could be explained by the lower sensitivity of sestamibi localization in multigland disease resulting in underdiagnosis of this occurrence. However, the possibility of overdiagnosis of multiglandular disease with a bilateral approach (biased pathology) cannot be discarded. The evidence-based support for minimally invasive parathyroidectomy comes from the fact that the recurrence rates following focused unilateral approaches have not been higher than those of the bilateral approach.

Another change in the management of PHPT has been the introduction of the rapid intraoperative parathyroid hormone assay. The assay, originally reported by Nussbaum, was refined and clinically popularized by Irwin (26,27). This assay measures intact PTH levels in the patient's plasma utilizing an immunochemiluminometric technique and can be performed during the operation. The intact PTH has a half-life of 2 to 3 min. Therefore 5 to 10 min after the removal of the abnormal gland a significant drop in PTH level is observed. A fall in the PTH level greater than 50% of the preoperative level is considered indicative of successful removal. The QPTH has a sensitivity and specificity of 98% and 94%, respectively, and an overall accuracy of 97% (28).

A recent survey of the members of the International Association of Endocrine Surgeons indicated that sestamibi-based minimally invasive parathyroidectomy has been adapted by 59% of surgeons. The most popular surgical technique (92%) is the focused approach with a small incision, followed by a video-assisted technique

(22%), and a true endoscopic technique with gas insufflation (12%). Techniques used to ensure completeness of resection include the QPTH (68%), and gamma probe (14%) (29).

Corresponding author:
Ömer UĞUR
Hacettepe University, Faculty of Medicine,
Department of Nuclear Medicine,
TR-06100, Sıhhiye, Ankara - Turkey
E-mail: ougur@hacettepe.edu.tr

References

1. Bilezikian JP, Silverberg SJ. Clinical spectrum of primary hyperparathyroidism. Rev Endocr Metab Disord 1: 237-245, 2000.
2. Udelsman R. Is unilateral neck exploration for parathyroid adenoma appropriate? Advances in Surg 34:319-329, 2000.
3. Kaplan EL, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s. Choice of surgical procedures for this disease Ann Surg 215: 301-317, 1992.
4. Rose MD, Wood TF, Van Herle AJ et al. Long term management and outcome of parathyroidectomy for sporadic primary multiple gland disease. Arch Surg 136: 621-626, 2001.
5. Udelsman R. Six hundred fifty six consecutive explorations for primary hyperparathyroidism. Ann Surg 235:665-672, 2002.
6. Wang C. The anatomic basis of parathyroid surgery. Ann Surg 183: 271-275, 1976.
7. Thompson NW, Eckhauser FE, Harness JK. The anatomy of primary hyperparathyroidism. Surgery 92: 814-821, 1982.
8. DeLellis RA Tumors of the parathyroid gland. Atlas of tumor pathology, third series, Fascicle 6. Armed Forces Institute of Pathology, Washington, DC 25-51, 65-78, 1993.
9. Mitchell BK, Merrel RC, Kinder BK. Localization studies in patients with hyperparathyroidism. Surg Clin North Am 75: 483-498, 1995.
10. Anonymous. NIH conference. Diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. Consensus Development Conference, NIH. Ann Int Med 114:593-7, 1991.
11. Coakley AJ, Kettle AG, Wells CP et al. 99m-Tc-sestamibi: A new agent for parathyroid imaging. Nucl Med Commun 10: 791-794, 1989.
12. Sanata A, Wilson B, Igbal J et al. A clinical audit of thallium-technetium substraction parathyroid scans. Postgrad Med J 66: 441-445, 1990.
13. Johnston LB, Carrol MJ, Britton KE et al. The accuracy of parathyroid gland localization in primary hyperparathyroidism using sestamibi radionuclide imaging. J Clin Endocrinol Metab 81: 346-352, 1996.
14. Sofferman RA, Nathan MH, Fairbank JT et al. Preoperative technetium 99m sestamibi imaging. Paving the way to minimal-access parathyroid surgery. Arch Otolaryngol Head Neck Surg 122: 369-374, 1996.
15. Hetrakul N, Civelek C, Stagg CA et al. Invitro accumulation of technetium-99m sestamibi in human parathyroid mitochondria. Surgery 130: 1011-1018, 2001.
16. Bahatnagar A, Vezza PR, Bryan JA et al. Technetium 99m sestamibi parathyroid scintigraphy: Effect of P-Glycoprotein, histology and tumor size on detectability. J Nuc Med 39: 1617-1620, 1998.
17. Yamaguchi S, Yachiku S, Hashimoto H et al. Relation between technetium 99m metoxyisobutylisonitrile accumulation and multidrug resistance protein in the parathyroid glands. World J Surg 26: 29-34, 2002.
18. Mitchell BK, Cornelius EA, Zoghbi S et al. Mechanism of technetium 99m sestamibi parathyroid imaging and possible role of p-glycoprotein. Surgery 120: 1039-1045, 1996.
19. Sfakianakis GN, Irvin GL, Foss J et al. Efficient parathyroidectomy guided by SPECT-MIBI and hormonal measurements. J Nuc Med 37:798-804, 1996.
20. Civelek AC, Ozalp E, Donovan P et al. Prospective evaluation of delayed technetium 99m sestamibi SPECT scintigraphy for preoperative localization of primary hyperparathyroidism. Surgery 131: 149-157, 2002.
21. Norman J, Murphy C. Minimally invasive radio-guided parathyroidectomy. Operative Techniques Gen Surg 1: 28-33, 1999.
22. Bozkurt F, Ugur O, Hamaloglu E et al. Optimization of gamma probe-guided parathyroidectomy Am Surg 69: 720-725, 2003.
23. Perrier, ND, Ituarte PHG, Morita E et al. Parathyroid surgery: Separating promise from reality J Clin Endocrinol Metab 87:1024-1029, 2002.
24. Fahy BN, Bold RJ, Beckett L, et al. Modern parathyroid surgery. A cost benefit analysis of localizing strategies. Arch Surg 137: 917-923, 2002.
25. Lee NC, Norton JA. Multiple gland disease in primary hyperparathyroidism. A function of operative approach? Arch Surg 137: 896-900, 2002.
26. Nussbaum SR, Thompson AR, Hutcheson KA, et al. Intraoperative measurement of parathyroid hormone in the surgical management of hyperthyroidism. Surgery 104: 1121-1127, 1988.
27. Irvin GL. American Association of Endocrine Surgeons presidential address: Chasin' hormones. Surgery 126: 993-997, 1999.
28. Irvin GL, Carneiro DM. Rapid parathyroid hormone assay guided exploration. Operative Techniques Gen Surg 1: 18-27, 1999.
29. Sackett WR, Barraclough B, Reeve TS, et al. Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. Arch Surg 137: 1055-1059, 2002.