Mini Review

Parathyroid glands: variation in number, size and location

Abstract

Parathyroid glands (PTGs) develop from the pharyngeal pouches. Their anatomy exhibits variations regarding their number and locations. Parathyroid surgery is mostly gratifying in experienced hands but sometimes failing due to the possibility of ectopic positions of the glands. Abnormal descent of the PTGs, during development, is responsible for these ectopic positions. Supernumerary PTGs are usually diseased and ectopic inside the thyroid gland, inside the thymus gland, or elsewhere in the mediastinum. In parathyroidectomies for primary and secondary hyperparathyroidism, preoperative techniques for accurate localization of the PTGs are recommended, like ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), four-dimensional computerized tomography (4DCT), aminolevulinic acid-induced fluorescence, Technetium Tc 99m sestamibi scanning (MIBI), Tc-99m RBC imaging, arteriography and selective venous sampling for parathormone. For a successful parathyroidectomy, a surgeon must be excellently aware of the anatomical variations, development and pathophysiology of the PTGs.

Keywords: parathyroid glands, development, localization, number, size, hyperparathyroidism, surgeries

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Abbreviations: CT: computerized tomography; 4DCT: four-dimensional computerized tomography; MGD: multi-gland disease; MIBI: sestamibi; MRI: magnetic resonance imaging; PHPT: primary hyperparathyroidism; PTGs: parathyroid glands; SGD: single gland disease, SHPT: secondary hyperparathyroidism

Introduction

Parathyroid glands (PTGs) play an important role in controlling calcium level which influences muscular contraction and neuronal transmission. The parenchyma of the PTGs develops from the endodermal lining of the third and fourth pharyngeal pouches. The thymus gland and inferior PTG (parathyroid III) are derived from the third pharyngeal pouch while the superior PTG (parathyroid IV) develops from the fourth pouch.[1]

The anatomy of the PTGs is greatly variable among individuals. A parathyroid surgery is considered successful when followed by normal levels of serum parathormone and calcium. Preoperative localization of the PTGs is mandatory in patients who have undergone previous parathyroidectomy but still have persistent hyperparathyroidism. During recurrent parathyroidectomy, the remaining parathyroid tissue is hardly detected due to increased scarring, loss of normal tissue planes, and most likely to an ectopic position of this tissue. In experienced hands, the inferior PTGs, localized within the thymus gland or more inferiorly in the mediastinum, represent the main reason for failure of the surgery.

Location, number and size of PTGs

A cadaveric study, in Athens, on 3,796 PTGs revealed a fifth gland in 5%, three glands in 2% and ectopic PTGS in 8.5% of specimens: in the thyroid parenchyma (0.2%), in different regions of the neck (2%), or in the mediastinum (6.3%) particularly the superior mediastinum. The same study observed the superior PTGs to be larger than the inferior ones with non-significant sex-differences related to the size of the glands.[2] In another study, 95% of patients had four PTGs of which 15.9% were ectopic in position: 11.6% in the neck (in retroesophageal/paraesophageal space or inside the thyroid gland) and 4.3% in mediastinum.[3] In 416 parathyroidectomies, 19% of the PTGs were aberrant in position; half of them were situated alongside the oesophagus, or in the anterior mediastinum within the thymic remnant. Supernumerary PTGS, mostly pathological and ectopic, were detected in 5% of cases.[4] All ectopic positions of PTGs are due to lack of descent or excessive descent of the glands in relation to structures concomitantly developing from the pharyngeal pouches like the thyroid and thymus glands.[5] In another autoptic study on 503 PTGs there were four PTGs in 84%, three glands in 3%, and a fifth supernumerary gland, often within the thymus, in 13% of specimens. Symmetrical positions of the glands, on both sides, were observed in 80% of specimens. The superior PTGs frequently lay just above the site of passage of the recurrent laryngeal nerve through the terminal branches of the inferior thyroid artery whereas the inferior PTGs lay close to the inferior thyroid pole or within the thymus gland.[6] In 60 Bangladeshi cadavers, two pairs of PTGs (in relation to thyroid gland) were grossly visible in 50% of specimens; the middle one-third of the posterior border of the thyroid gland accommodated most of the PTGs in 60-65% of specimens.[7]

In a different cadaveric study, four or more PTGs were detected in 89.3% with a mean glandular weight of 33.1 mg and a mean glandular size of 6.7×3.9×2.0mm. The superior PTGs were medially located whereas the inferior ones were laterally located in relation to the thyroid gland. At least one PTG was ectopic in 42.8% of specimens: in the mediastinum, thymus, thyroid subcapsular area, or thyroid parenchyma.[8] In a study on chronic hemodialysis patients, the efficacy of total parathyroidectomy and bilateral cervical thymectomy was evaluated for the treatment of medically refractory secondary hyperparathyroidism (SHPT). Four distinct sites were described for

each of the superior (zones I-IV) and inferior (zones V-VIII) PTGs. About 90% of the detected superior PTGs lay in zones I and II whereas 28% of the inferior PTGs were ectopic and located in zones VII and VIII. When superior PTGs did not lie in zones I-III, total thyroidectomy on the same side was recommended.[9] A hyperactive parathyroid adenoma, located in middle mediastinum, could not be approached via cervical subtotal parathyroidectomy with bilateral thymectomy, but through a successful thoracoscopic technique.[10] It has been also mentioned that thyroidectomy may be associated with incidental parathyroidectomy often due to intrathyroidal location of the PTGs.[11] About 80% of the excised specimens, in parathyroidectomies, were diagnosed as parathyroid tissue whereas the remaining 20% were assessed to be lymph nodes, fat tissue, thyroid tissue or thymic tissue. The inferior thyroid artery and the recurrent laryngeal nerve were taken as guide to the inferior PTG.[12]

In 273 patients operated for primary hyperparathyroidism (PHPT), single PTG adenoma was found in 80%, hyperplasia in 15%, two adenomas in 2.6% of patients. The larger the adenoma, the more likely it was to be ectopic. Right superior PTG adenomas had mean size of 2.6 cm and were ectopic in 39%. Left superior PTGs had mean size 2.62 cm and were ectopic in 36% of cases. No superior parathyroid adenomas were intrathyroidal. Almost all inferior PTG adenomas within the thymus gland could be excised through the cervical incision.[13]

Methods of preoperative localization of PTGs

Surgery for PHPT is commonly satisfying; however, sometimes it could be extremely frustrating due the variability in the number and locations of the PTGs.[14] The saying that "the best way to localize the PTGs is to localize an experienced parathyroid surgeon" probably remains valid.[15] An effective preoperative localization technique must be determined in patients with PHPT or SHPT to facilitate the surgery, diminish patient morbidity, and decrease the number of recurrent surgeries.

Contact endoscopy is suggested as an additional method for detection of PTGs during thyroid surgeries.[16] Ultrasonography helped to identify 50% of patients with PHPT and SHPT. Computerized tomography (CT) was also successful in identifying retrosternal and other ectopic PTGs.[17] In patients with PHPT, preoperative sestamibi (MIBI) scanning and ultrasonography were combined to identify the ectopic PTGs; when the two methods failed to agree on the same abnormal location of the glands, a magnetic resonance imaging (MRI) was utilized to confirm the exact location.[18] Technetium Tc 99m sestamibi scanning (MIBI) is generally considered as the gold procedure for preoperative localization of PTGs with a reported sensitivity of 75%-100%. Positive scans are attributed to the oxyphil cell content of the PTGs. However, some preoperative MIBI scans appeared either equivocal or negative; false-negative scans can occur with PTGs containing abundance of clear cells.[19] In another study, MIBI was found to be significantly less sensitive and specific for diagnosis of parathyroid lesions in patients with multi-gland disease (MGD) than in those with single-gland disease (SGD); decreased sensitivity of MIBI was not related to PTG weight or location.[20] Tc-99m MIBI imaging alone was mentioned to be insufficient for detection of ectopic PTG tissue in the mediastinum. Concomitant Tc-99m RBC and Tc-99m MIBI imaging facilitated accurate localization of mediastinal PTG tissue in four reported patients.[21] Also, it has been stated that discordant preoperative diagnostic imaging modalities did not discriminate between single gland and multi-gland diseases in PHPT.[22]

Complex methods of localization of PTGs, like arteriography and selective venous sampling for parathormone, are rarely adopted.[4] Four-dimensional computerized tomography (4DCT) of the neck is a radiation exposure that is relatively high in evaluation of PHPT. Percentage arterial enhancement can be used as an objective radiological index for accurate detection of parathyroid adenoma/hyperplasia, and for discriminating parathyroid lesions from thyroid tissue and lymph nodes.[23] In aminolevulinic acid-induced fluorescence technique, adenomatous and atrophied PTGs could be easily detected and excised due to their intense red fluorescence whereas surrounding thyroid and muscle tissue remained nonfluorescent and easily discriminated from the PTGs.[24]

Comparative studies

In a study on two suborders of birds, Accipitres and Falcones, the location of the PTGs in common kestrel was relatively constant. Seven topographical patterns of location of PTGs were described in Accipitridae. The parathyroid glands were supplied by 1-3 parathyroid arteries: cranial, middle and caudal; these thyroid arteries arose from the common carotid, ascending cervical or oesophago-tracheo-bronchial artery. The artery for the cranial PTG mostly arose from the caudal thyroid artery while that for the caudal PTG from the oesophago-tracheo-bronchial artery.[25] In a morphological study on the house shrew (Suncus murinus) there were two pairs of PTGs located in the upper part of the thyroid gland; their volumes ranged from 0.014 to 0.079 mm^3.[26]

Conclusion

Parathyroidectomy is a difficult surgery because of the small size of the glands and the variability in their number, size and locations. Detailed knowledge of the embryology, gross anatomy, pathology of the PTGs is crucial to avoid postoperative hypoparathyroidism, secondary hyperparathyroidism and recurrence of surgeries.

Acknowledgments

None.

Conflicts of interest

The author declares no conflict of interest.

References

1. Sadler TW, Thomas W, Langman J. *Langman's medical embryology*. 11th ed. Philadelphia, USA: Wolter's Kluwer, Lippincott Williams & Wilkins; 2010:385.

2. Lappas D, Noussios G, Anagnostis P, et al. Location, number and morphology of parathyroid glands: results from a large anatomical series. *Anat Sci Int*. 2012;87(3):160–164.

3. Taterra D, Wong LM, Vikse J, et al. The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. *Langenbecks Arch Surg*. 2019;404(1):63–70.

4. Hooghe L, Kinnaert P, Van Geertruyden J. Surgical anatomy of hyperparathyroidism. *Acta Chir Belg*. 1992;92(1):1–9.

5. Beahrs OH, Edis AJ, Purnell DC. Unusual problems in parathyroid surgery. *Am J Surg*. 1977;134(4):502–504.

6. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. *Surgery*. 1984;95(1):14–21.

7. Sultana SZ, Mannan S, Sultana S, et al. Morphological study of parathyroid in relation to thyroid gland of Bangladeshi people. *Mymensingh Med J*. 2007;16(2):137–142.

8. Hojaij F, Vanderlei F, Plopper C, et al. Parathyroid gland anatomical distribution and relation to anthropometric and demographic parameters: a cadaveric study. *Anat Sci Int*. 2011;86(4):204–212.

9. Uslu A, Okut G, Tercan IC, et al. Anatomical distribution and number of parathyroid glands, and parathyroid function, after total parathyroidectomy and bilateral cervical thymectomy. *Medicine (Baltimore)*. 2019;98(23):e15926.

10. Gramática L, Mercado Luna A, Verasay G, et al. Thoracoscopic resection of mediastinal hypersecretant parathyroid gland. *Rev Fac Cien Med Univ Nac Cordoba*. 2014;61(2):70–73.

11. Sakorafas GH, Stafyla V, Bramis C, et al. Incidental parathyroidectomy during thyroid surgery: an underappreciated complication of thyroidectomy. *World J Surg*. 2005;29(12):1539–1543.

12. Nanka O, Sedý J, Vítková I, et al. Surgical anatomy of parathyroid glands with emphasis on parathyroidectomy. *Prague Med Rep*. 2006;107(2):261–272.

13. Thompson NW, Eckhauser FE, Harness JK. The anatomy of primary hyperparathyroidism. *Surgery*. 1982;92(5):814–821.

14. Sakamoto W, Kishimoto T. Primary hyperparathyroidism--choice of surgical procedures and follow up after surgery. *Nihon Rinsho*. 1995;53(4):890–894.

15. Broadie TA. Location, location, location. *Am Surg*. 1997;63(7):567–572.

16. Guimarães AV, Brandão LG, Dedivitis RA. Contact endoscopy for identifying the parathyroid glands during thyroidectomy. *Acta Otorhinolaryngol Ital*. 2010;30(1):20–26.

17. Clark OH, Okerlund MD, Moss AA, et al. Localization studies in patients with persistent or recurrent hyperparathyroidism. *Surgery*. 1985;98(6):1083–1094.

18. Munk RS, Payne RJ, Luria BJ, et al. Preoperative localization in primary hyperparathyroidism. *J Otolaryngol Head Neck Surg*. 2008;37(3):347–354.

19. Westreich RW, Brandwein M, Mechanick JI, et al. Preoperative parathyroid localization: correlating false-negative technetium 99m sestamibi scans with parathyroid disease. *Laryngoscope*. 2003;113(3):567–572.

20. Nichols KJ, Tomas MB, Tronco GG, et al. Sestamibi parathyroid scintigraphy in multigland disease. *Nucl Med Commun*. 2012;33(1):43–50.

21. Mastin ST, Mancuso NM, Kiser JW, et al. Combined Tc-99m MIBI and Tc-99m RBC for anatomic localization of ectopic mediastinal parathyroid adenomas. *Clin Nucl Med*. 1996;21(12):928–931.

22. Philippon M, Guerin C, Taieb D, et al. Bilateral neck exploration in patients with primary hyperparathyroidism and discordant imaging results: a single-centre study. *Eur J Endocrinol*. 2014;170(5):719–725.

23. Goroshi M, Lila AR, Jadhav SS, et al. Percentage arterial enhancement: An objective index for accurate identification of parathyroid adenoma/hyperplasia in primary hyperparathyroidism. *Clin Endocrinol (Oxf)*. 2017;87(6):791–798.

24. Prosst RL, Willeke F, Schroeter L, et al. Fluorescence-guided minimally invasive parathyroidectomy: a novel detection technique for parathyroid glands. *Surg Endosc*. 2006;20(9):1488–1492.

25. Radek T, Piasecki T. Topography and arterial supply of the thyroid and the parathyroid glands in selected species of *Falconiformes*. *Anat Histol Embryol*. 2007;36(4):241–249.

26. Takagi I, Sakai K, Hirata M, et al. Morphological study of parafollicular cells and the parathyroid gland in the house shrew (*Suncus murinus*). *Okajimas Folia Anat Jpn*. 1992;69(2-3):99–104.