Operative Techniques in Otolaryngology (2016) 27, 117–121

ELSEVIER

Operative Techniques in Otolaryngology

Anatomy and embryology of the parathyroid gland

Joseph Scharpf, MD, FACS,[a] Natalia Kyriazidis, BS, MS,[b] Dipti Kamani, MD,[b] Gregory Randolph, MD, FACS, FACE[b,c]

From the [a]Cleveland Clinic Foundation, Head and Neck Institute, Clevland, Ohio; [b]Division of Thyroid and Parathyroid Surgery, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts; and the [c]Department of Surgical Oncology, Massachusetts General Hospital, Harvard Medical School, 243, Charles st, Boston, MA 02114

KEYWORDS
Parathyroid glands anatomy;
Recurrent laryngeal nerve;
failed surgical explorations;
Parathyroid gland embryology;
ectopic locations;
supernumerary glands

Experienced parathyroid surgeons recognize that the embryology of the parathyroid glands would guide them in their anatomic dissections to localize the abnormal glands. This becomes particularly important in circumstances when the glands are not in their "normal" locations. Surgeons must be familiar with the embryology that is so inherently linked with the final anatomic location of the glands. It is not uncommon for patients to have undergone failed surgical explorations secondary to parathyroid glands being in ectopic locations that were not appreciated. Parathyroid embryology knowledge can bridge that gap and direct the surgeon to those sites. In this article, variations in anatomic location, relation to critical structures including the recurrent laryngeal nerve, the number of glands, and even gland size and morphology would be explored and thereby provide the platform for parathyroid surgery.

Introduction

A comprehensive understanding of the embryology of the parathyroid glands is requisite to the successful surgical management of parathyroid disease conditions. Although a sound knowledge of embryology is important in all aspects of head and neck surgery, an argument may be made that there is no area in the head and neck where this is as critical as in the surgical management of hyperparathyroidism. Experienced parathyroid surgeons recognize that the embryology of the parathyroid glands would guide them during surgical dissections to localize the abnormal glands. This is readily evident when the glands are not in their "normal" locations. Surgeons must be well acquainted with the embryology since it is integrally linked with the final anatomic location of the glands. Not appreciating the parathyroid glands that are located in the ectopic locations is often the reason behind failed surgical explorations. A thorough knowledge of parathyroid embryology can aid the surgeons by directing them to the possible ectopic sites. We endeavor to explore the variations in anatomic location, relation to critical structures including the recurrent laryngeal nerve (RLN), the number of glands, and even gland size and morphology to provide the platform for parathyroid surgery. This information is invaluable not just during surgery but even in the presurgical evaluation phase when localization studies are performed to guide a directed exploration or a more extensive 4-gland exploration.

Address reprint requests and correspondence: Gregory Randolph, MD, FACS, FACE, Division of Thyroid and Parathyroid Surgery, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, 243, Charles st, Boston, MA 02114.
E-mail address: Gregory_Randolph@meei.harvard.edu

http://dx.doi.org/10.1016/j.otot.2016.06.003
1043-1810/

General considerations

Parathyroid glands, first discovered by Sandstrom,[1] arise from the endoderm epithelial cells of the pharyngeal pouches in weeks 5-6 of gestation. In the seventh week of

gestation, they begin to migrate with the thyroid and thymus, both caudally and medially to their final position in the lower neck. Provided that a normal migration takes place, the inferior glands would pass beyond the superior glands and occupy a position on the dorsal surface of the lower pole of the thyroid gland or slightly more caudal in the thyrothymic ligament or the thymus (Figure 1).[2] The parathyroid glands have been described as flat-bean or leaf-like shaped, yellow-tan, caramel, or mahogany in color and thus may be distinguished from the brighter, less distinct yellow fat with which the parathyroids are typically closely associated. They are ovoid glands weighing roughly 35-40 mg and measuring 3-8 mm in all dimensions. They can be observed as discrete bodies gliding within the more amorphous fat surrounding them as this fat is gently manipulated.[3] They are composed of chief and oxyphilic cells but also consist of adipose tissue and fibrovascular stroma.[4]

Mirror-image symmetry usually occurs for the upper parathyroids as well as for the lower parathyroids. Finding a left gland can then assist in finding the corresponding right gland.[3] This symmetry has been detailed in an anatomic series that has reported 80% symmetry when comparing right and left superior parathyroid glands and 70% for the inferior glands.[5] The glands are primarily subserved by the inferior thyroid artery, which is the primary vascular supply to both upper and lower parathyroid glands in 76%-86% of cases.[6] Most parathyroid anatomic descriptions are based on surgical data. This can lead to limitations in the literature including anatomic descriptions based on the disease process, limited site exposure and search efforts as well as the natural prioritization of surgical objectives over data collection.[7]

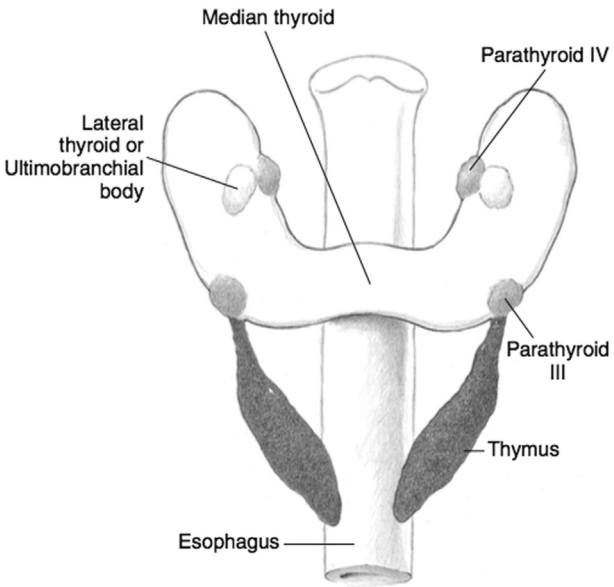

Figure 1 A schematic representation depicting the locations of the thyroid, lateral thyroid, thymus, and parathyroid glands. During embryological development, the parathyroid III and the parathyroid IV migrate together with the thymus and ultimobranchial bodies, respectively. (Reprinted with permission from Randolph G. Surgery of the thyroid and parathyroid glands. Philadelphia: WB Saunders, 2012.)

Most commonly there are 4 parathyroid glands. However, there can be 5 or more glands present, or in rare circumstances less than 4 glands. Large autopsy series have provided insight into the numeric variation of the glands. A 13% incidence of supernumerary glands has been described. The supernumerary parathyroid glands by majority were quite small, less than 5 mg, and were located in close proximity to normal glands. In that same series, 4 glands were seen in 84% of patients and 3% of the patients had only 3 glands.[5] In another large series consisting of over 400 patients, 0.5% had 6 glands, 25% had 5 glands, 87% had 4 glands and 6.1% of the patients had 3 glands.[6] This numeric variation must be considered by surgeons performing parathyroid explorations. The supernumerary glands are also often located in the thymus and in the mediastinum.[7]

Superior parathyroid glands

The superior parathyroid glands originate from the fourth branchial pouch and are associated with the lateral thyroid anlage or C-cell complex (Figure 2). Because of this origin, they are also referred to as parathyroid IV (PIV). They have further been indicated as thyroid parathyroids because of their common origin with the lateral thyroid.[8] As they lose their attachment with the pharyngeal wall, they attach to the posterior surface of the caudally migrating thyroid gland. As such, the superior parathyroid glands track closely with the posterolateral aspect of the respective thyroid lobes.[3,9] The final adult position of the superior parathyroid is less variable than that of the inferior parathyroid because of its shorter embryologic migratory path. The area of dispersal of the superior parathyroid gland is demonstrated in Figure 3.

The superior parathyroid gland is typically located at the level of the cricothyroid articulation of the larynx,

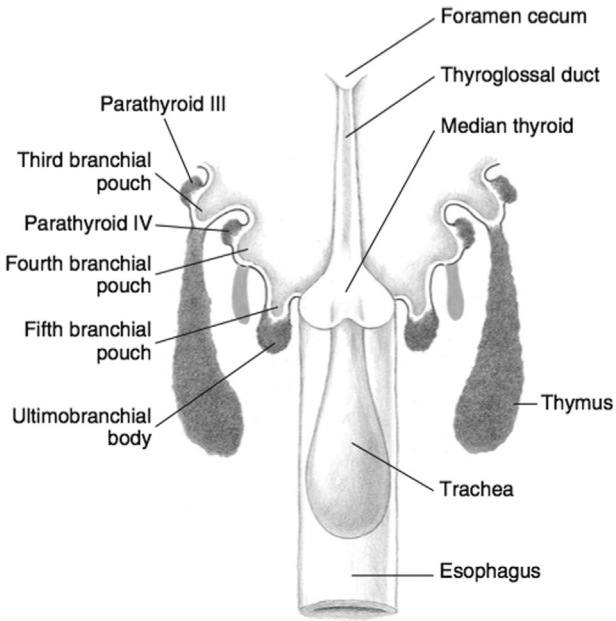

Figure 2 Schematic representation of the primitive pharynx of an 8- to 10-mm embryo. (Reprinted with permission from Randolph G. Surgery of the thyroid and parathyroid glands. Philadelphia: WB Saunders, 2012.)

Figure 3 The short embryonic course of the superior parathyroid glands results in a limited area of dispersal of the PIVs. (Reprinted with permission from Randolph G. Surgery of the thyroid and parathyroid glands. Philadelphia: WB Saunders, 2012.)

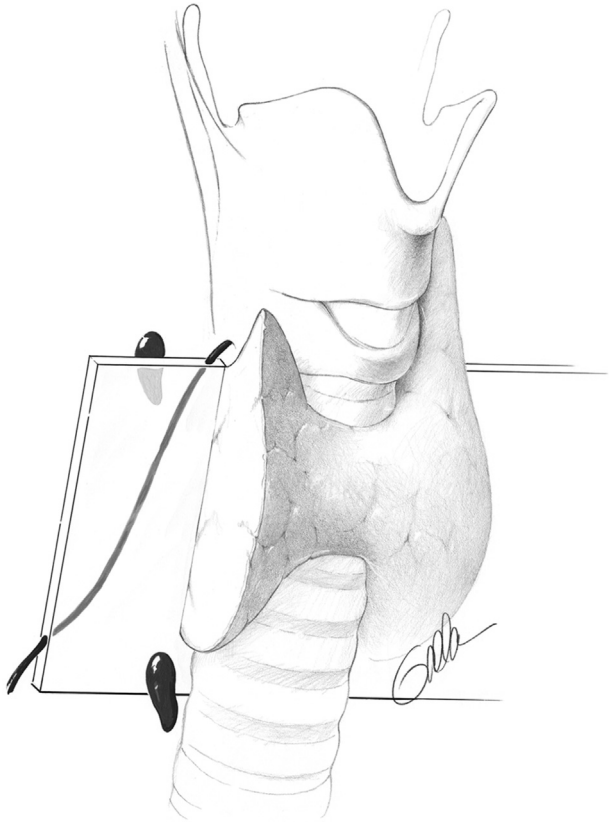

Figure 4 The parathyroid glands and their anatomic relation to the RLN coronal plane in the neck. The superior parathyroid glands lie dorsal (deep) and the inferior parathyroid glands lie ventral (superficial) to the RLN plane. (Reprinted with permission from Randolph G. Surgery of the thyroid and parathyroid glands. Philadelphia: WB Saunders, 2012.)

approximately 1 cm above the intersection of the RLN and inferior thyroid artery. It is closely related to the posterolateral aspect of the superior thyroid pole, often resting on the thyroid capsule in this location. It can be in a more caudal position and can sometimes be partially obscured by the RLN, inferior thyroid artery, or tubercle of Zuckerkandl.[8] They can even reside further inferior at a considerable distance posterior to the lower thyroid pole. Rarely, in less than 1% of cases, the superior glands may be located above the upper thyroid pole.[8] They may lie quite deep in the neck toward a retrolaryngeal or retroesophageal location.[3] In the aforementioned autopsy study, 80% of the superior glands were located on the posterior aspect of the thyroid gland within a circumscribed area of 2 cm in diameter, about 1 cm above the crossing point of the RLN and inferior thyroid artery.[5]

The superior parathyroid is located at a plane deep (dorsal) to the plane of the RLN in the neck (Figure 4). An interesting recent publication has examined the anatomic proximity of parathyroid tumors to the RLN in patients with primary hyperparathyroidism undergoing parathyroidectomy.[10] In this prospective study consisting of 136 patients with primary hyperparathyroidism, intraoperative nerve monitoring was used to confirm RLN identification and to record the distance from the anatomically confirmed RLN to the parathyroid tumor. The findings confirmed that the RLN often lies in close proximity to the parathyroid adenoma at an average of just 0.52 cm. The tumors in the right upper position were on average only 0.25 cm from the nerve with 47% of the tumors in the right upper position abutting the nerve.[10] The tumors in the right upper position were most commonly abutting the RLN as compared to the tumors in other positions.

Ectopic anatomic locations of the superior parathyroid glands

The location of the superior parathyroid glands is more constant and they are seldom found in ectopic positions because they undergo less embryologic migration during development. Most ectopic locations are rare and may result from descent failure or laterally directed descent.[8] Ectopic locations include the tracheoesophageal groove, posterior mediastinum, retroesophageal, and retropharyngeal positions in the carotid sheath or intrathyroidal locations.[11] In Akerstrom's anatomic autopsy study, the ectopic superior parathyroid glands were found at the level of the upper pole of the thyroid gland in 2% of subjects and above the pole in less than 1% of patients. The other ectopic positions included the posterior neck, retropharyngeal, and retroesophageal locations. Rarely, intrathyroidal positioning can be present.[5,12,13] The intrathyroidal location results from the abnormal migration pattern whereby the superior glands can join the ultimobranchial body as it fuses with the median thyroid.[2] In addition to

ectopic location from embryologic development variability, acquired ectopic localization can occur from pathologic gland enlargement. Enlarged glands can migrate under the influence of gravity and from the dynamic movements of the larynx and pharynx during swallowing.[8] This is more commonly seen in the superior parathyroid glands than the inferior glands, which are less prone to this acquired migration because of anatomic constraints that theoretically prevent this gravity-induced displacement.[8]

Inferior parathyroid glands

The inferior parathyroid glands derive from the third branchial pouch and migrate with the thymus anlage. The inferior parathyroid glands have thus been also named parathyroid III (PIII) and the thymic parathyroid, analogous to the nomenclature of the superior parathyroid glands and their embryologic derivation.[8] The dorsal wing of the third pharyngeal pouch gives rise to the inferior parathyroid glands, and the ventral wing gives rise to the thymus. The inferior parathyroid glands lose their connection to the pharyngeal wall and join the thymus as it travels to the mediastinum via a medial and caudal route.[9,14] This results in the inferior parathyroid glands having a more varying adult position than the superior glands and accounts for their position in a plane ventral to that of the superior parathyroid glands.[10] The area of dispersal of PIII glands is demonstrated in Figure 5 and stands in contrast to the dispersal area of PIV (Figure 3) with a much greater area of dispersal. The inferior parathyroid is found in close association with the inferior pole of the thyroid, often on the posterolateral aspect of the capsule of the inferior pole or within 1-2 cm. It is often closely associated with the thickened fat of the thyrothymic horn (ie, thyrothymic ligament). The inferior parathyroid is generally located superficial (ventral) to the RLN (Figure 4).[3]

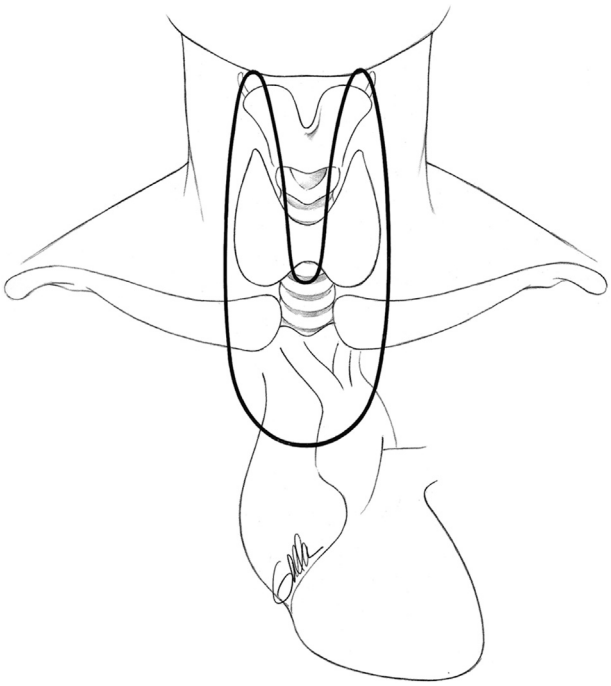

Figure 5 The long embryonic course of the inferior parathyroid gland (PIII) results in an extensive area of dispersal of the PIII, extending from the angle of the mandible to the pericardium. (Reprinted with permission from Randolph G. Surgery of the thyroid and parathyroid glands. Philadelphia: WB Saunders, 2012.)

Ectopic anatomic locations of the inferior parathyroid glands

The increased variability in position of the inferior parathyroid glands is of particular concern to the surgeon hoping for a successful exploration. The inferior glands can be found anywhere along the large area of descent up to the superior border of the pericardium.[15] The failure of an inferior gland to descend with the thymus may result in its location of embryologic origin close to the carotid bifurcation and often embedded in an ectopic thymic remnant.[5,16] Undescended parathyroid glands have been observed to occur in up to 2% of necks in anatomic study.[13,17] The clinical significance is a bit more uncertain as the incidence of undescended parathyroid glands has been shown to be less than 1% in previously unoperated primary cases[18] and as low as 0.08% in very large series of 3,000 patients.[19] Inferior parathyroid glands may be found at the level of the anterior superior mediastinum in close proximity to the upper pole of the thymic remnants, especially when there is persistence of the primitive attachment of the inferior parathyroid glands to the thymus. The implication of this embryology is the importance of superior mediastinal exploration for inferior glands that cannot be identified within the neck.[12,20] A less common but reported mediastinal location of the ectopic parathyroid gland is the aortopulmonary window.[21] In addition, the rare intrathyroidal ectopic location must also be considered. The incidence varies by series ranging from 0.7%-3.6%.[12,22,23] Intrathyroidal parathyroidal glands can be either PIII or PIV; even supernumerary glands can be intrathyroidal. An expectation that a higher percentage of intrathyroidal parathyroid glands would be represented by PIV because of inclusion within the thyroid when the ultimobranchial bodies fuse with the median thyroid remnant[8] has not been borne out in studies. In fact, some authors have found that intrathyroidal glands are primarily inferior parathyroid glands.[8] The intrathyroidal inclusion of parathyroid tissue originating from the third pharyngeal pouch can be found with the same incidence as inclusions of thymic tissue. Portions of thymic tissue may break into small fragments that sometimes persist embedded in the thyroid gland.[8]

Conclusion

Although most of the parathyroid glands can be located in a predictable anatomic location, the knowledge of embryologic

variability is critical to the successful parathyroid surgeon. Ectopic anatomic localization due to variable embryologic migration patterns of the glands, particularly the inferior parathyroid glands, can be readily managed in a logical and systematic approach by the surgeon prepared to explore anatomic sites known to harbor these glands.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

References

1. Sandstrom IV: Omen ny kortel hos mennisken och atskilige baggdjur lakarefore rings (ed). Upsala, 1880, pp 441-471.
2. Burke JF, Chen H, Gosain A: Parathyroid conditions in childhood. Semin Pediatr Surg 23:66-70, 2014
3. Scharpf J, Randolph G: Thyroid and parathyroid glands, chapter 33. In: KJ Lee's, Chan Y, Goddard JC, editors. Essential Otolaryngology. ed 11. McGraw Hills Company Ltd. 2015.
4. Gilmour JR: The normal histology of the parathyroid glands. J Pathol Bacteriol 48:187-222, 1937
5. Akerstrom G, Malmaeus J, Bergstrom R: Surgical anatomy of human parathyroid glands. Surgery 95(1):14-21, 1984
6. Alveryd A: Parathyroid glands in thyroid surgery. I. Anatomy of parathyroid glands. II. Postoperative hypoparathyroidism—Identification and autotransplantation of parathyroid glands. Acta Chir Scand 389:1-120, 1968
7. 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 86:204-212, 2011
8. Argarwal A, Mishra A, Lombardi C, et al: Applied embryology of the thyroid and parathyroid glands. In: Randoph GW, editor. Surgery of the Thyroid and Parathyroid Glands. Philadelphia, PA: Elsevier Saunders; 2012
9. Sadler TW, Langman J: Langman's Medical Embryology. ed 10 Lippincott Williams & Wilkins; 2006
10. Untch BR, Adam M, Danko M, et al: Tumor proximity to the recurrent laryngeal nerve in patients with primary hyperparathyroidism undergoing parathyroidectomy. Ann Surg Oncol 19:3823-3826, 2012
11. Lew JL, Solorzano CC: Surgical management of primary hyperparathyroidism: State of the art. Surg Clin N Am 89:1205-1225, 2009
12. Mohebatti A, Shaha AR: Anatomy of thyroid and parathyroid glands and neurovascular relations. Clin Anat 25:19-31, 2012
13. Wang C: The anatomic basis of parathyroid surgery. Ann Surg 183:271-275, 1976
14. Mansberger AR, Wei JP: Surgical embryology and anatomy of the thyroid and parathyroid glands. Surg Clin North Am 73:727-746, 1993
15. Gray SW, Skandalakis JE, Akin JT: Embryological considerations of thyroid surgery: Developmental anatomy of the thyroid, parathyroids and the recurrent laryngeal nerve. Am Surg 42:621-628, 1976
16. Bliss RD, Gauger PG, Delbridge LW: Surgeon's approach to the thyroid gland: Surgical anatomy and the importance of technique. World J Surg 24:891-897, 2000
17. Rioja P, Mateu G, Leyre LP, et al: Undescended parathyroid adenomas as cause of persistent hyperparathyroidism. Gland Surg 4(4):295-300, 2015
18. Akerstrom G, Rudberg C, Grimelius L, et al: Causes of failed primary exploration and technical aspects of re-operation in primary hyperparathyroidism. World J Surg 16:562-568, 1992
19. Simeone DM, Sandelin K, Thompson NW: Undescended superior parathyroid gland: A potential cause of failed cervical exploration for hyperparathyroidism. Surgery 118:949-956, 1995
20. Kurtay M, Crile G Jr: Aberrant parathyroid glands in relationship to the thymus. Am J Surg 117:705, 1969
21. Arnault V, Beaulieu A, Lifante JC: Multicenter study of 19 aortopulmonary window parathyroid window parathyroid tumors: The challenge of embryologic origin. World J Surg 34:2211-2216, 2010
22. Proye C, Bizard JP, Carnaille B, et al: Hyperparathyroidism and intrathyroid parathyroid gland. 43 cases. Ann Chir 48:501-506, 1994
23. Bahar G, Feinmesser R, Joshua BZ, et al: Hyperfunctioning intrathyroid parathyroid gland: A potential cause of failure in parathyroidectomy. Surgery 139:821-826, 2006