

Evidence-Based Approach to a “Missing” Parathyroid Gland during Thyroid or Parathyroid Surgery

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Abstract

Failure to identify a parathyroid gland during thyroidectomy or parathyroidectomy represents a well-recognized intraoperative challenge and is most commonly explained by ectopic gland location rather than true agenesis. A comprehensive understanding of parathyroid embryology, migration patterns, and cervical anatomy is therefore essential for safe endocrine neck surgery and for minimizing failed explorations, hypoparathyroidism, and recurrent disease. This review provides a practical and surgically oriented overview of the “missing” parathyroid gland, integrating embryologic development, anatomic variability, operative identification strategies, and contemporary nomenclature systems. The embryologic descent of the superior and inferior parathyroid glands from the fourth and third pharyngeal pouches, respectively, explains the predictable distribution of ectopic glands encountered during surgery. Superior glands typically maintain relatively constant locations near the posterior aspect of the upper thyroid pole, whereas inferior glands demonstrate greater positional variability because of their longer migratory course with the thymus. Common ectopic locations include the tracheoesophageal groove, retroesophageal space, thyrothymic ligament, cervical thymus, carotid sheath, retropharyngeal region, mediastinum, and intrathyroidal or subcapsular locations. This review emphasizes operative pearls for gland identification, including recognition of key landmarks such as the inferior thyroid artery, recurrent laryngeal nerve, prevertebral fascia, cervical thymus, and characteristic parathyroid fat pads. Strategies for systematic exploration are discussed in the context of both thyroidectomy and parathyroidectomy. Additionally, the manuscript reviews the Perrier classification system for ectopic parathyroid glands and proposes

its practical application during cervical exploration to facilitate structured localization of missing glands. By combining embryologic principles with operative anatomy and contemporary surgical nomenclature, this review aims to provide endocrine surgeons, trainees, and head and neck surgeons with a clinically relevant framework for identifying orthotopic and ectopic parathyroid glands, reducing operative failure, and improving surgical outcomes in thyroid and parathyroid surgery.

Keywords

Parathyroid Gland, Ectopic Parathyroid Gland, Missing Parathyroid Gland, Parathyroid Embryology, Thyroidectomy, Parathyroidectomy, Mediastinal Parathyroid Gland, Intrathyroidal Parathyroid Gland, Perrier Classification, Surgical Anatomy, Parathyroid Localization

1. Introduction

Failure to identify a parathyroid gland during thyroidectomy or parathyroidectomy remains a well-recognized intraoperative challenge for endocrine and head and neck surgeons. In the overwhelming majority of cases, the absence of a gland during cervical exploration is attributable not to true agenesis, but rather to ectopic migration resulting from aberrant embryologic descent. Large anatomic and surgical series have consistently demonstrated that ectopic parathyroid glands occur in approximately 15% to 16% of patients, with highly predictable distributions based on their embryologic origin from the third and fourth branchial pouches [1] [2]. A comprehensive meta-analysis including 26 studies, 7005 patients, and 23,519 parathyroid glands reported an overall ectopic rate of 15.9%, with 11.6% of glands located ectopically within the neck and 4.3% within the mediastinum [1]. These findings underscore that ectopic location represents the predominant explanation when a parathyroid gland cannot be identified during routine cervical exploration.

By contrast, true parathyroid agenesis is exceedingly rare. Classic cadaveric studies have reported fewer than four parathyroid glands in approximately 3% of specimens; however, this figure is widely believed to overestimate the true incidence of agenesis due to failure to identify occult ectopic glands rather than genuine absence [1]-[3]. Isolated parathyroid agenesis outside of recognized syndromic conditions, most notably DiGeorge syndrome, is extraordinarily uncommon and should be considered a diagnosis of exclusion only after exhaustive evaluation for ectopic or supernumerary gland locations. A thorough understanding of parathyroid embryology, migration patterns, and ectopic anatomy is therefore critical to avoid unnecessary dissection, reduce operative morbidity, and optimize surgical outcomes during thyroid and parathyroid surgery [1] [2] [4] [5].

For the purposes of this review, a missing parathyroid gland is defined as a gland that cannot be identified in its expected anatomic location during surgical

exploration. Importantly, a missing gland is not synonymous with gland absence or agenesis; rather, it most commonly reflects an ectopic location, concealment within surrounding adipose or thymic tissue, intrathyroidal incorporation, or displacement resulting from embryologic migration. The clinical significance of a missing parathyroid gland varies according to the operative setting. During thyroidectomy, the primary objective is the identification and preservation of normally functioning glands to prevent postoperative hypoparathyroidism. During initial parathyroidectomy for primary hyperparathyroidism, failure to identify a parathyroid gland may indicate ectopic localization and can contribute to persistent disease if an abnormal parathyroid gland remains *in situ*.

In contrast, during reoperative exploration for persistent or recurrent hyperparathyroidism, a missing gland frequently represents a previously overlooked ectopic gland and poses a substantially greater technical challenge because of scar formation and distorted anatomy. Accordingly, this review addresses the embryologic basis, anatomic patterns, and operative strategies for the localization of the missing parathyroid gland across each of these distinct clinical scenarios.

Modern endocrine and head and neck surgery, therefore, emphasizes a structured, embryology-based exploration strategy rather than indiscriminate dissection. Understanding the migration patterns of the superior and inferior parathyroid glands is critical to minimizing operative failure, reducing morbidity, and improving success rates during both primary and reoperative surgery.

2. Embryology and Surgical Anatomy

During the fifth to sixth week of intrauterine development, the embryonic pharynx is organized into the pharyngeal/branchial apparatus, marked externally by four branchial clefts of ectoderm origin and internally by five branchial pouches of endoderm origin (**Figure 1**). The branchial apparatus is made up of the branchial clefts and branchial pouches together with the branchial arches of mesoderm origin found in between them [3] [6]. This apparatus undergoes normal involution, leaving behind some derivatives which include the thyroid gland, parathyroid glands, thymus, the C-cells of the thyroid gland via the ultimobranchial body, Eustachian tube, middle ear, and external auditory canal [3] [6].

The parathyroid glands develop as epithelial thickenings of the dorsal endoderm of the third and fourth branchial pouches [3]. The superior parathyroid glands are derived from the fourth branchial pouch, which also gives rise to the ultimobranchial bodies. The ventral aspect of these pouches is believed to fuse with the rudimentary fifth branchial pouches, forming the ultimobranchial bodies [3] [6] [7]. The superior parathyroid glands follow the migration of the ultimobranchial bodies, which descend a relatively limited path toward the lateral thyroid region, ultimately giving rise to the parafollicular cells of the thyroid gland. The superior parathyroid glands separate from the ultimobranchial bodies as the median and lateral thyroid anlagen fuse and incorporate the ultimobranchial bodies; this separation determines the final anatomic position of the superior para-

thyroid glands relative to the thyroid [3] [6] [7]. The inferior parathyroid glands are derived from the third branchial pouch (dorsal aspect) along with the thymus (derived from the ventral aspect of the third branchial pouch). The parathyroid glands remain intimately connected with their respective branchial pouch derivatives.

Embryonic Pharynx and Branchial Apparatus (5–6 Weeks)

The pharynx develops into the branchial apparatus consisting of branchial clefts (ectoderm), branchial pouches (endoderm), and branchial arches (mesoderm).

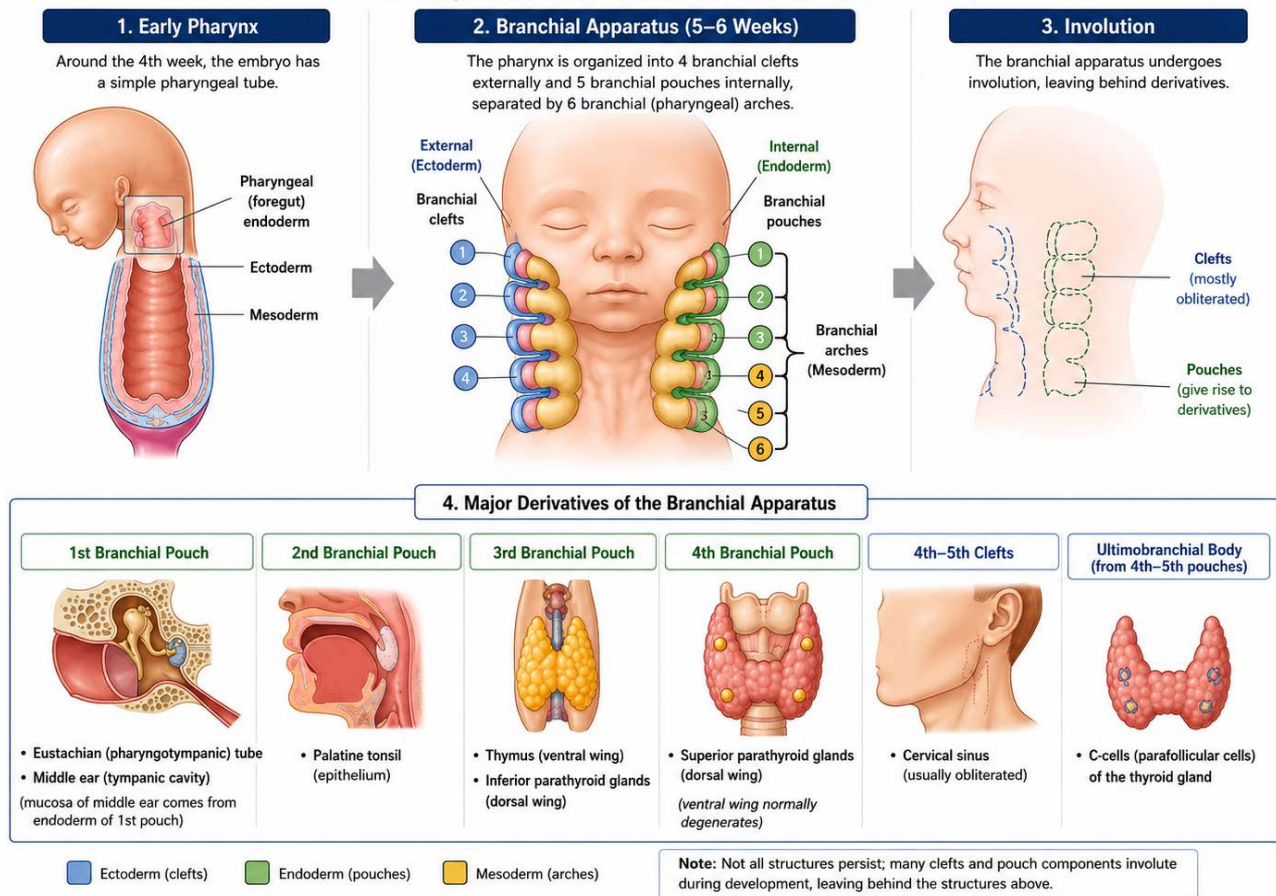


Figure 1. Embryonic pharynx and the branchial apparatus.

The superior parathyroid glands demonstrate a remarkably constant embryologic migration pattern when compared with the inferior parathyroid glands. Since they arise from the fourth branchial pouch and undergo only limited caudal migration, they are usually identified in a predictable location along the posterior aspect of the junction of the upper and middle thyroid lobe near the cricothyroid junction (in roughly 80% of the cases) [3] [6] [7], each superior parathyroid gland with its own capsule of connective tissue. Nevertheless, approximately 1% of superior parathyroid glands may occupy ectopic positions, most commonly within the paraesophageal or retroesophageal space, retrolaryngeal region, high lateral pharyngeal area, or carotid sheath [4] [8]–[10]. These ectopic superior parathyroid

glands are clinically important because they account for a subset of missed glands during thyroidectomy and failed cervical explorations for primary hyperparathyroidism.

Enlarged superior parathyroid glands may descend inferiorly along the tracheoesophageal groove because of gravity, progressive superior parathyroid gland enlargement, and the path of least resistance created by loose visceral fascial planes within the neck. As a result, a pathologic superior parathyroid gland may ultimately come to rest inferior to the normal location of the inferior parathyroid glands, creating potential confusion during cervical exploration. In these situations, the embryologic origin of the gland can often still be inferred by its posterior relationship to the recurrent laryngeal nerve and its location within the retrovisceral compartment.

Unlike inferior parathyroid glands, which frequently migrate with the thymus into the anterior mediastinum, descended superior parathyroid glands characteristically remain posterior, most commonly within the tracheoesophageal groove or retroesophageal space [4] [8] [11] [12]. This phenomenon is of major surgical importance because enlarged, descended superior parathyroid glands are a well-recognized cause of failed initial parathyroid exploration. During reoperative surgery, the surgeon must therefore carefully evaluate the posterior cervical compartment, particularly the retroesophageal plane extending toward the thoracic inlet. A superior adenoma descending along the tracheoesophageal groove may appear radiographically and intraoperatively to represent an inferior gland unless embryologic anatomy is fully appreciated. The distinction is clinically relevant because superior glands are generally located dorsal to the recurrent laryngeal nerve, whereas inferior glands are usually ventral to the nerve [4] [13].

Truly ectopic superior parathyroid glands are exceedingly rare. When present, they may be localized within the middle or posterior mediastinum or, less commonly, within the aortopulmonary window [8] [11] [14]. Superior mediastinal ectopia likely results from excessive caudal migration during embryogenesis or secondary displacement caused by progressive adenomatous enlargement. Unlike inferior glands associated with thymic descent into the anterior mediastinum, ectopic superior glands that migrate into the chest generally maintain a posterior mediastinal relationship because of their origin from the fourth pharyngeal pouch [11] [12]. These lesions may descend behind the great vessels, esophagus, or trachea and can occasionally require transthoracic or thoracoscopic approaches for resection if inaccessible through a transcervical exploration.

Parathyroid adenomas within the aortopulmonary window represent one of the rarest ectopic locations encountered in endocrine/head and neck surgery. These glands are usually situated between the aortic arch and pulmonary artery near the ligamentum arteriosum and vagus nerve, or recurrent laryngeal nerve. Because of their deep mediastinal location, localization frequently requires advanced imaging such as Sestamibi SPECT/CT, 4D-CT, MRI, or selective venous sampling [14] [15]. Recognition of this embryologic and anatomic possibility is critical in patients with persistent or recurrent primary hyperparathyroidism after failed cer-

vical exploration.

During embryologic development, the inferior parathyroid glands arise from the dorsal endoderm of the third branchial pouch together with the thymus. As fetal development progresses, both structures migrate caudally from the pharynx into the lower neck and superior mediastinum.

Because the inferior parathyroid glands accompany the thymus during this relatively long and complex migratory descent, their final position is considerably more variable than that of the superior parathyroid glands. This embryologic relationship explains the broad spectrum of ectopic locations encountered during thyroidectomy and parathyroidectomy procedures [3] [4] [8] [16] [17].

The most common location of the inferior parathyroid glands is near the inferior pole of the thyroid gland, typically roughly 1 cm from the point where the recurrent laryngeal nerve (RLN) crosses the inferior thyroid artery. In nearly 50% of individuals, the inferior gland lies anterior to the posterolateral surface of the lower thyroid pole, frequently within a delicate pocket of thymic-derived adipose tissue closely associated with the thyroid capsule [4] [11] [12]. In many cases, the gland is loosely attached to the thyrothymic ligament, a key surgical landmark that should routinely be examined during cervical exploration.

Due to their embryologic descent with the thymus, inferior parathyroid glands are frequently identified along the thyrothymic tract. Approximately 15% to 50% of inferior glands are located within the thyrothymic ligament or embedded within cervical thymic tissue [4] [14] [17]. This variability is clinically important because inferior parathyroid glands situated within the thymus or thyrothymic ligament are among the most common causes of failed initial parathyroid exploration and persistent primary hyperparathyroidism. For this reason, careful examination of the cervical thymus and thyrothymic tract is essential when an inferior parathyroid gland is not immediately identified in its expected orthotopic position [14] [15] [17].

The inferior parathyroid glands demonstrate substantially greater positional variability than the superior parathyroid glands because of their longer migratory pathway. Ectopic inferior glands may remain undescended and be identified high in the neck near the carotid bifurcation, angle of the mandible, or skull base, often associated with an undescended thymus [8] [16] [17]. Conversely, excessive caudal migration may result in glands located deep within the superior or anterior mediastinum, frequently within thymic tissue. Less commonly, inferior glands may also be identified in retroesophageal, paraesophageal, or carotid sheath locations [4] [14] [16].

Intrathyroidal inferior parathyroid glands represent another important anatomic variant. These glands are estimated to occur in approximately 1% to 3% of patients and are more commonly associated with inferior rather than superior parathyroid glands [16] [18].

Intrathyroidal glands may be partially embedded within the thyroid capsule or completely surrounded by thyroid parenchyma, making intraoperative identifica-

tion particularly challenging. Failure to recognize this possibility may contribute to persistent hyperparathyroidism after an apparently adequate cervical exploration. In selected cases, partial thyroid lobectomy or targeted thyroidotomy may be required when imaging or intraoperative findings strongly suggest an intrathyroidal parathyroid adenoma [16] [18] [19].

Knowledge of the embryology and migratory anatomy of the inferior parathyroid glands is fundamental for endocrine and head and neck surgeons. A systematic understanding of both orthotopic and ectopic locations significantly improves gland identification during thyroidectomy, facilitates successful parathyroid exploration, minimizes operative failure, and reduces the risk of inadvertent parathyroid devascularization or excision.

3. Prevalence and Clinical Impact of Ectopic Parathyroid Glands

Among ectopic parathyroid glands found within the neck, 51.7% are in the retroesophageal/paraesophageal space or intrathyroidal [1]. The prevalence of ectopic parathyroid adenomas is approximately 15% to 22% in previously unexplored patients with primary hyperparathyroidism, but rises to as high as 66% in reoperative cases [14] [20]. Ectopic parathyroid glands account for 16% to 31% of failed parathyroidectomies, with the thymus being the single most common missed location (41% of failures) [21]. The AHNS/BAETS consensus guidelines emphasize the clinical adage: “if looking for a missed superior parathyroid gland, look low; if looking for a missed inferior gland, look high” [22].

Supernumerary Glands

Approximately 81% of individuals have exactly four parathyroid glands, while 13% to 15% harbor supernumerary glands (most commonly a fifth gland, typically within the thymus) [3] [4] [23]. Supernumerary glands are clinically relevant in secondary hyperparathyroidism and MEN syndromes, where wide excision of perithyroidal fat and transcervical thymectomy is recommended [4].

4. Imaging for Ectopic Localization

When ectopic location is suspected, imaging modality selection matters:

- Ultrasound has limited sensitivity for ectopic glands (~46% for ectopic adenomas) but is superior for intrathyroidal glands (96%). A novel ultrasonographic technique using the cranial angle between the adenoma long axis and strap muscles can help distinguish superior from inferior parathyroid gland origin (sensitivity 72%, specificity 74%) [24] [25].
- Sestamibi SPECT/CT retains value for retrosternal and mediastinal glands (identifying 81% of retrosternal lesions) and performs comparably to 4D CT for thymic/mediastinal ectopia [14] [25].
- 4D CT demonstrates superior sensitivity (~81%) compared to sestamibi SPECT/CT (~65%) for overall parathyroid localization, with particular advantage for ec-

topic glands, detecting 96% of ectopic adenomas in one series. 4D CT precisely delineates anatomic relationships critical for surgical planning [20] [25] [26].

- 18F-Choline PET/CT is emerging as a valuable modality, particularly for multigland disease and cases with equivocal conventional imaging [27] [28].

5. General Intraoperative Principles for Identifying the Parathyroid Glands

Before declaring a gland ectopic, meticulous evaluation of the orthotopic field is mandatory; approximately 80% to 90% of parathyroid glands are located within a few millimeters of the posterior thyroid capsule [1]. Therefore, careful subcapsular dissection along the posterior thyroid surface should be completed prior to extending exploration. Excessive or indiscriminate dissection should be avoided because it increases the risk of recurrent laryngeal nerve injury, parathyroid devascularization, bleeding, and fibrosis complicating future surgery.

Intrathyroidal parathyroid glands represent another important consideration. These account for approximately 2% to 3% of all parathyroid glands and up to 20% to 22% of ectopic inferior glands [14]. For this reason, inspection and palpation of the thyroid specimen following lobectomy or thyroidectomy is considered standard practice in experienced endocrine surgery centers [29].

Reoperative series further demonstrate that most “missing” glands are ultimately identified in standard embryologic locations rather than truly aberrant sites.

The AHNS/BAETS guidelines recommend that reoperative surgery should only proceed after colocalization by at least two concordant imaging modalities and should be performed by experienced surgeons, given the increased morbidity of revision exploration [22].

Silberfein *et al.* reported that missed glands during failed parathyroidectomy were most commonly located in the tracheoesophageal groove, thyrothymic ligament, and superior mediastinum [30]. These findings reinforce the importance of systematic exploration guided by embryology.

6. Recommendations for Intraoperative Identification of the Parathyroid Glands

Successful identification and preservation of the parathyroid glands during thyroidectomy and parathyroidectomy requires not only a thorough understanding of embryology and anatomy, but also recognition of several subtle intraoperative morphological characteristics. Although normal parathyroid glands are classically described as having a yellow-brown or “London tan” coloration and measuring approximately $6 \times 4 \times 2$ mm in size, experienced endocrine and head and neck surgeons rely on additional operative cues to distinguish parathyroid tissue from adjacent lymph nodes, adipose tissue, or thyroid nodules [3]. These surgical “pearls” are particularly important in difficult dissections, reoperative surgery, inflammatory conditions, and oncologic resections where normal anatomy may be distorted [13] [16] [31].

One of the most important principles in identifying parathyroid glands is the maintenance of a meticulous bloodless surgical field.

Even minimal blood staining significantly obscures the characteristic surface features and coloration of parathyroid tissue, thereby impairing visual identification. Careful hemostasis with fine bipolar cautery and gentle tissue handling are therefore critical during capsular dissection of the thyroid gland [13] [32].

Normal parathyroid glands are typically soft, flattened, and highly compressible structures that are generally not palpable unless enlarged or pathologic. This tactile characteristic may help distinguish a normal gland from a cervical lymph node, which is usually firmer, rubbery, and more discrete on palpation. Preservation of this tactile awareness remains valuable even in the modern era of magnification and fluorescence imaging technologies [16] [31].

Parathyroid glands are frequently surrounded by a delicate adipose envelope or “fat pad”, which itself serves as an important anatomic landmark.

Inferior parathyroid glands are commonly embedded within thymic-associated fatty tissue near the thyrothymic ligament, whereas superior glands are usually located posterior to the recurrent laryngeal nerve and superior to the crossing point of the inferior thyroid artery and RLN. Recognition of these characteristic fat compartments often facilitates rapid identification of otherwise inconspicuous glands [13] [32].

Another useful intraoperative feature is the presence of a small vascular pedicle entering the gland. In most cases, the blood supply arises from terminal branches of the inferior thyroid artery [3]. Careful preservation of this delicate vascular arcade is essential to maintain postoperative gland viability and reduce the risk of hypoparathyroidism [16] [32].

A classic operative finding described by Cope is the tendency of parathyroid glands to develop superficial ecchymosis or discoloration following gentle manipulation, commonly referred to as “Cope’s sign”. This subtle bruising phenomenon may assist in confirming parathyroid tissue during difficult dissections, although excessive manipulation should obviously be avoided to preserve vascular integrity [4] [31].

Occasionally, two parathyroid glands may lie immediately adjacent to one another, creating the appearance of a single bilobed structure. These so-called “kissing glands” represent two separate glands enclosed within closely approximated capsules rather than a truly bilobed gland. Identification of a cleavage plane between the capsules confirms the diagnosis. Awareness of this uncommon configuration is important when a “missing” gland cannot otherwise be identified during cervical exploration [8] [13].

Finally, normal parathyroid glands characteristically reside within the visceral compartment of the neck beneath the pretracheal fascia but are usually not densely adherent to the thyroid capsule itself. As a result, they often demonstrate a subtle mobility and may be gently rolled or displaced beneath the fascial layer using a fine dissecting instrument. This “sliding” characteristic can help differentiate par-

athyroid tissue from lymph nodes or fibrotic tissue that are more fixed to surrounding structures [16].

Collectively, these anatomical and morphological features remain fundamental surgical principles for safe endocrine/head and neck surgery. Although adjunctive technologies such as near-infrared autofluorescence and indocyanine green angiography continue to evolve, meticulous surgical technique and detailed anatomical knowledge remain the cornerstone of successful parathyroid gland identification and preservation.

7. Superior Parathyroid Gland: Evidence-Based Search Strategy

7.1. Typical Orthotopic Location

Because superior parathyroid glands originate from the fourth branchial pouch and migrate minimally, their position is relatively constant. They are typically located on the posterior aspect of the junction of the upper and middle third of the thyroid lobe, approximately 1 cm above the intersection of the recurrent laryngeal nerve (RLN) and inferior thyroid artery, frequently within the tracheoesophageal groove posterior to the RLN [7]. The superior parathyroid gland is classically situated dorsal to the RLN, an important operative landmark that helps distinguish it from inferior glands [3].

Identification of the superior parathyroid gland begins with meticulous exposure of the posterior aspect of the thyroid lobe and recognition of the inferior thyroid artery (ITA), which serves as the most reliable anatomic landmark for localization of the superior gland. In most cases, the superior parathyroid gland is located approximately 1 cm cranial to the ITA along the posterior surface of the thyroid gland (**Figure 2**). After the ITA has been identified, careful blunt dissection is carried posteriorly and cranially toward the shiny prevertebral fascia, which defines the posterior limit of safe dissection and represents the deepest potential location of a superior parathyroid gland. A bloodless surgical field is essential because even minor bleeding may obscure the subtle morphologic characteristics that distinguish parathyroid tissue from surrounding fat, lymph nodes, or thyroid tissue.

Careful visual inspection should precede aggressive dissection. Rather than immediately manipulating tissue that appears suspicious for parathyroid tissue, the surgeon should first confirm the relevant anatomic landmarks and systematically inspect the region extending 1 to 2 cm cranial to the ITA on the posterior surface of the thyroid lobe. Superior parathyroid glands are commonly associated with derivatives of the fourth branchial pouch and may therefore occupy paraesophageal, retroesophageal, retropharyngeal, or high cervical locations adjacent to the hyoid bone. In contrast to inferior parathyroid glands, superior parathyroid glands demonstrate a relatively constant embryologic migration pattern; however, enlarged superior glands frequently descend in a posterior and caudal direction and may migrate behind the ITA into the tracheoesophageal groove, occasionally lying

inferior to the inferior parathyroid gland.

IDENTIFICATION OF THE SUPERIOR PARATHYROID GLAND

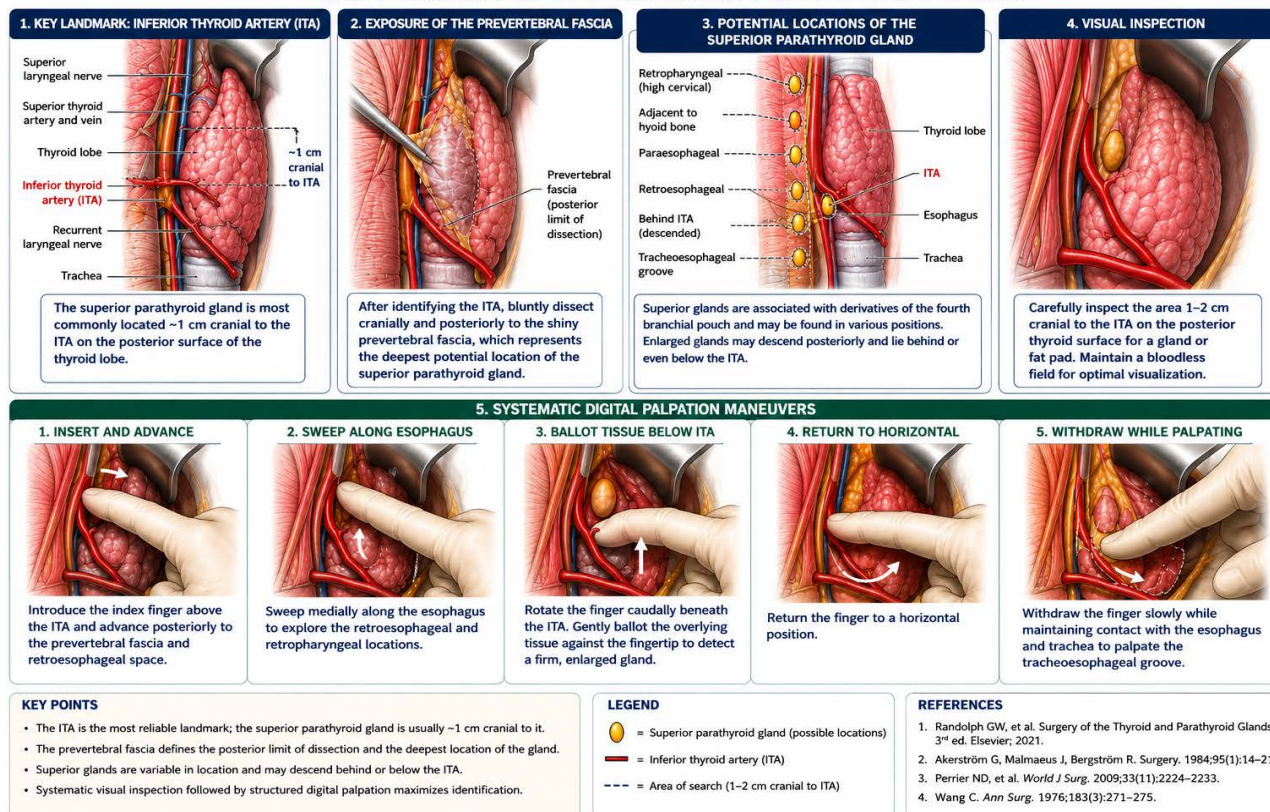


Figure 2. Identification of the superior parathyroid gland.

When visual identification is unsuccessful, systematic digital palpation can aid localization. The index finger is gently introduced into the previously developed plane above the ITA and advanced posteriorly to the prevertebral fascia and retroesophageal space.

The finger is then swept medially along the esophagus to assess the retroesophageal and retropharyngeal regions. Subsequently, the finger is rotated caudally beneath the ITA, and the overlying tissue is gently balloted against the fingertip to detect a firm, enlarged gland. Finally, the finger is slowly withdrawn while maintaining contact with the esophagus and trachea in order to carefully palpate the tracheoesophageal groove, another common location for descended superior glands. This methodical approach allows identification of the majority of superior parathyroid glands while minimizing unnecessary tissue dissection and reducing the risk of devascularization or recurrent laryngeal nerve injury [4] [8] [13] [16].

7.2. Common Ectopic Locations of Superior Parathyroid Glands

When ectopic, the superior parathyroid glands tend to migrate posteriorly rather than inferiorly. The tracheoesophageal or paraesophageal groove represents the most frequent ectopic location for superior parathyroid glands and should be sys-

tematically explored when the gland is not identified in its orthotopic position [1] [29]. Undescended superior parathyroid glands may remain posteriorly located high in the neck within the retroesophageal or retropharyngeal region [7]. Superior glands may also descend along the esophagus into the posterior mediastinum while maintaining a posterior relationship to the RLN [14].

7.3. Stepwise Surgical Approach for a Missing Superior Parathyroid Gland

When a superior parathyroid gland is not immediately identified, a methodical sequence should be followed:

- Complete subcapsular dissection along the posterior upper and middle thyroid of the thyroid lobe.
- Explore the tracheoesophageal groove along the course of the RLN.
- Perform blunt dissection of the paraesophageal and retroesophageal spaces.
- Evaluate the high posterior neck for undescended glands.
- Inspect the thyroid specimen for intrathyroidal parathyroid tissue.

This systematic approach minimizes unnecessary dissection while maximizing identification rates [29] [30].

8. Inferior Parathyroid Gland: Evidence-Based Search Strategy

8.1. Typical Orthotopic Location

Inferior parathyroid glands arise from the third branchial pouch and descend with the thymus, resulting in greater variability. Orthotopically, they are usually located near the lower thyroid lobe, anterior to the RLN, within or adjacent to the thyrothymic ligament [7]. Because of their prolonged embryologic migration, inferior glands account for the majority of ectopic parathyroid glands encountered during surgery [14].

Identification of the inferior parathyroid glands begins with meticulous exposure and medial mobilization of the thyroid lobe, which alone may allow visualization of the gland in its expected location. Inferior parathyroid glands are embryologically derived from the third branchial pouch together with the thymus and therefore descend along a longer and more variable migratory pathway than the superior glands, explaining their less predictable anatomy and frequent association with thymic tissue [8] [13] [14].

A useful intraoperative landmark is the “tongue” of cervical thymic tissue that frequently extends superiorly toward the inferior pole of the thyroid gland. The inferior parathyroid gland is commonly identified along this trajectory, usually embedded within or attached to a fatty thymic pad located near the lower thyroid pole [4] [13]. Careful visual inspection should therefore proceed from the inferior thyroid pole toward the thyrothymic ligament and cervical thymus. In many cases, the gland is located on the posterior aspect of this thymic-associated fat pad [4].

When the gland cannot be readily identified, additional dissection maneuvers

may be necessary. Gentle blunt dissection of the inferior pole vessels may expose the gland; however, if this remains unsuccessful, the thymus should be mobilized by dividing the thyrothymic ligament and delivering the cervical thymus into the operative field with careful traction. Preservation of the thymic capsule is important to avoid tissue fragmentation and bleeding that may obscure identification of parathyroid tissue [13] [33].

Because of their embryologic descent, inferior parathyroid glands may occupy ectopic locations, including within the thymus, thyrothymic ligament, carotid sheath, retroesophageal space, or superior anterior mediastinum [8] [13] [14]. Consequently, persistent failure to identify the parathyroid gland should prompt systematic exploration of the accessible superior mediastinum and inspection of the carotid sheath up to the level of the carotid bifurcation.

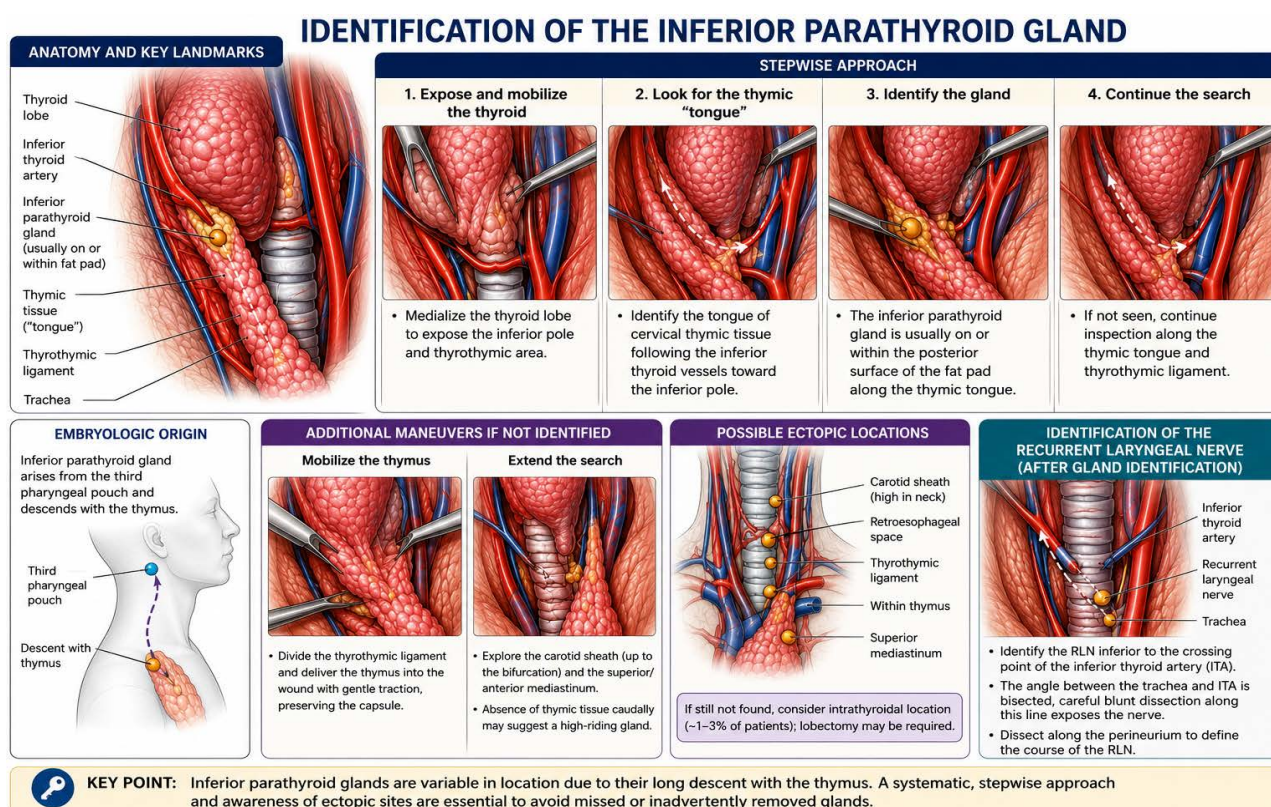


Figure 3. Identification of the inferior parathyroid gland.

Absence of thymic tissue inferior to the thyroid gland may suggest a non-descended third branchial pouch derivative and should raise suspicion for a high cervical ectopic inferior gland [13]. If exhaustive cervical exploration remains unsuccessful, intrathyroidal location must be considered. Intrathyroidal parathyroid glands have been reported in approximately 1% to 3% of patients and may occasionally correspond to thyroid nodules identified on preoperative ultrasonography [13] [18]. In selected cases, thyroid lobectomy may therefore be required to identify a missing abnormal gland.

To minimize tissue distortion and bleeding during parathyroid gland identification, the recurrent laryngeal nerve (RLN) is preferably identified only after the parathyroid glands have been exposed and the target gland selected for excision. The RLN is typically identified inferior to the crossing point of the inferior thyroid artery (ITA). Careful blunt dissection along the angle formed between the trachea and the ITA facilitates safe localization of the nerve and definition of its trajectory (**Figure 3**) [13] [33].

8.2. Common Ectopic Locations of Inferior Parathyroid Glands

Approximately 30% of ectopic inferior glands are intrathymic [14]. This explains why limited cervical thymectomy is frequently necessary during parathyroid exploration. Inferior parathyroid glands may also descend with thymic tissue into the anterosuperior mediastinum [14]. Intrathyroidal inferior glands account for approximately 20% to 22% of ectopic inferior glands [14]. Failed embryologic descent may leave inferior parathyroid glands high in the neck, including within the carotid sheath [29].

8.3. Stepwise Surgical Approach for a Missing Inferior Parathyroid Gland

If the inferior parathyroid gland is not identified near the lower pole of the thyroid lobe, the following strategy is recommended:

- Follow the thyrothymic ligament inferiorly toward the thymus.
- Mobilize and inspect cervical thymic tissue.
- Perform a limited cervical thymectomy when clinically indicated.
- Inspect the lower pole of the thyroid lobe and thyroid specimen for intrathyroidal tissue.
- Explore the carotid sheath and high cervical region in cases suspicious for undescended glands.

This sequence reflects the predictable embryologic descent of inferior parathyroid glands and avoids unnecessary random exploration [14] [30].

9. Management of Identified Parathyroid Glands during Thyroidectomy

Once a parathyroid gland has been identified during thyroidectomy, the primary objective is preservation of the gland and its vascular supply *in situ* whenever possible. Careful capsular dissection of the thyroid gland helps maintain the delicate arterial branches arising predominantly from the inferior thyroid artery and minimizes the risk of postoperative hypoparathyroidism. Visual assessment of gland viability is based on preservation of normal color, turgor, and an intact vascular pedicle. A well-perfused gland typically maintains its characteristic tan-yellow appearance, whereas a gland that appears dark, dusky, cyanotic, or obviously devascularized should be considered at risk for postoperative dysfunction [32] [34].

When the vascularity of a gland is questionable, several methods may assist viability assessment, including inspection for capillary bleeding after gentle gland incision, intraoperative indocyanine green (ICG) fluorescence angiography, or near-infrared autofluorescence imaging, although routine use varies among institutions [35]-[38]. If a gland is inadvertently removed with the thyroid specimen or is clearly devascularized, immediate autotransplantation is recommended. The gland is typically confirmed by frozen section when uncertainty exists, minced into 1 to 2 mm fragments, and implanted into a pocket within the sternocleidomastoid muscle or the nondominant forearm brachioradialis muscle, where it can regain function through revascularization [32] [39]-[41].

Current evidence suggests that preservation of at least one well-vascularized parathyroid gland *in situ* is the most important factor in preventing permanent hypoparathyroidism following thyroid surgery [32] [40].

10. Lessons from Reoperative Parathyroid Surgery

Reoperative parathyroidectomy provides valuable insight into the causes of failed initial exploration. Contemporary series consistently demonstrate that previously missed glands are usually located in predictable embryologic sites rather than truly aberrant positions.

Silberfein *et al.* reported that the most common locations of missed parathyroid glands included the tracheoesophageal groove, thyrothymic ligament, and superior mediastinum [30]. Similarly, Phitayakorn and McHenry demonstrated that ectopic abnormal parathyroid glands overwhelmingly follow embryologic migration pathways [14]. These findings strongly support systematic exploration strategies rooted in embryologic anatomy.

11. Surgical Adjuncts and Modern Considerations

Several adjunctive techniques may facilitate the localization of difficult parathyroid glands intraoperatively.

- Rapid intraoperative parathyroid hormone (ioPTH) monitoring assists in confirming biochemical cure and may reduce unnecessary exploration.
- Near-infrared autofluorescence technology has emerged as a promising adjunct for identification and preservation of parathyroid tissue during thyroid and parathyroid surgery [42].
- Radioguided parathyroidectomy using technetium-99m sestamibi may aid localization, particularly in reoperative settings or minimally invasive approaches [43] [44].
- Frozen section analysis may occasionally help distinguish parathyroid tissue from lymph nodes, thyroid tissue, or fat, although it should not substitute for careful anatomic identification.

12. Classification System for Parathyroid Adenomas

In 2009, Perrier *et al.* proposed a standardized nomenclature for parathyroid ad-

enoma localization based on anatomic relationship to the thyroid gland, recurrent laryngeal nerve (RLN), and embryologic migration pathways [17].

Although originally designed for hyperfunctioning adenomas, this classification is highly applicable to the broader concept of the missing parathyroid gland encountered during thyroidectomy and cervical exploration. This classification system classifies glands into Types A through G (Figure 4).

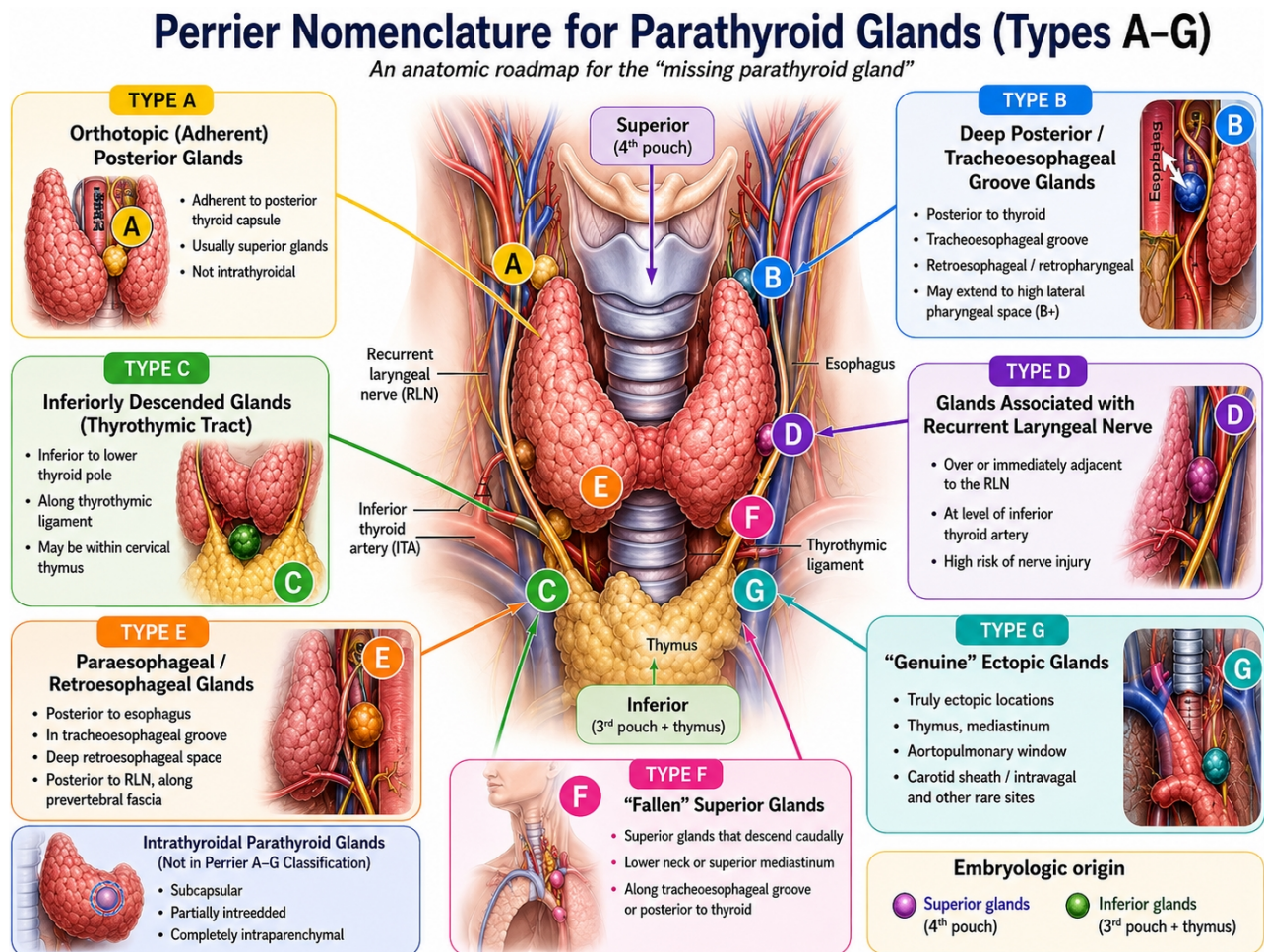


Figure 4. Classification system for parathyroid adenomas [17].

The Perrier A to G classification was originally developed to describe the embryologically predictable locations of ectopic hyperfunctioning parathyroid adenomas encountered during surgery for primary hyperparathyroidism [13] [17]. In the present review, this nomenclature is extended beyond adenomatous disease and applied as an anatomical framework for the broader problem of the “missing” parathyroid gland encountered during thyroidectomy, initial parathyroidectomy, and reoperative cervical exploration. The classification is used as a systematic guide to locations that should be evaluated when a gland cannot be readily identified, regardless of whether the gland is normal, hyperplastic, or adenomatous. Orthotopic glands correspond primarily to Type A locations, whereas ectopic glands

are categorized according to their relationship to embryologic migration pathways (Types B to G). Normal parathyroid glands may be found within any of these locations, although most reside in orthotopic positions.

Intrathyroidal glands represent a special consideration because they are not explicitly emphasized in the original Perrier nomenclature; in this review, they are discussed separately as an important cause of a missing gland, particularly during thyroidectomy and failed parathyroid exploration. Furthermore, the Perrier system was designed primarily as a localization scheme rather than a comprehensive classification of all possible parathyroid locations and therefore does not fully account for rare supernumerary glands, acquired displacement from prior surgery, or unusual anatomic variants. Despite these limitations, the classification provides a practical embryologic roadmap that can facilitate a structured and reproducible search strategy for the missing parathyroid gland.

12.1. Type A: Adherent Posterior Glands

Type A glands are located in the expected orthotopic position and are adherent to the posterior thyroid capsule, typically near the superior pole of the thyroid gland [17]. Characteristics include:

- Posterior to the upper thyroid pole.
- Closely adherent to thyroid parenchyma.
- Not intrathyroidal.
- Usually corresponding to orthotopic superior glands.

These glands may be difficult to identify during thyroidectomy because they blend with the posterior thyroid capsule and surrounding fat. Careful capsular dissection and preservation of the posterior vascular supply are essential.

12.2. Type B: Deep Tracheoesophageal Groove Glands

Type B glands are posteriorly displaced behind the thyroid gland and commonly lie within the tracheoesophageal groove [17]. This category includes glands located in:

- Retroesophageal space.
- Retropharyngeal region.
- High lateral pharyngeal space.
- Carotid sheath.

A “B+” subclassification describes glands located superior to the hyoid bone, reflecting excessive cranial migration [17]. These lesions are usually derived from the superior parathyroid glands and may descend posteriorly along the tracheoesophageal groove. In reoperative surgery, these glands are a common cause of failed exploration.

12.3. Type C: Inferior Descended Glands

Type C glands are located caudal to the thyroid gland, often along the thyrothymic tract [17]. Typical locations include:

- Inferior to the lower thyroid pole.
- Along the thyrothymic ligament.
- Near the clavicle.
- Within cervical thymic tissue.

These glands generally represent inferior parathyroid glands that have descended with the thymus during embryogenesis. Inferior parathyroid glands are found within the thyrothymic ligament or thymus in approximately 15% to 50% of cases [8] [9] [45].

12.4. Type D: Glands Adjacent to the Recurrent Laryngeal Nerve

Type D glands lie directly over or immediately adjacent to the RLN at the level of the inferior thyroid artery [17]. These glands are surgically important because:

- Dissection places the RLN at increased risk.
- They may mimic lymph nodes or fibrofatty tissue.
- Preservation of vascular supply is technically challenging.

Identification of the RLN before aggressive dissection in this region is strongly recommended.

12.5. Type E: Paraesophageal/Retroesophageal Glands

Type E glands are located within the paraesophageal or retroesophageal space posterior to the thyroid gland and esophagus [17]. These glands are usually derived from the superior parathyroid glands and represent posteriorly displaced lesions along the tracheoesophageal groove. Because of their deep location, Type E glands are an important cause of failed initial cervical exploration and persistent primary hyperparathyroidism. These glands may be found:

- Posterior to the recurrent laryngeal nerve.
- Within the tracheoesophageal groove.
- In the retroesophageal space.
- Adjacent to the prevertebral fascia.

Careful medial rotation of the thyroid lobe with identification of the RLN and blunt dissection along the prevertebral fascia are often required for identification.

12.6. Type F: “Fallen” Superior Parathyroid Glands

Type F (“fallen”) glands are embryologically superior parathyroid glands that descend inferiorly into the lower neck or superior mediastinum [17]. These glands often travel:

- Along the tracheoesophageal groove.
- Posterior to the thyroid gland.
- Into the superior mediastinum.

Enlarged superior adenomas may descend below the level of the inferior glands, creating confusion regarding embryologic origin [8] [15].

12.7. Type G: “Genuine” Ectopic Mediastinal Glands

Type G glands are truly ectopic mediastinal glands [17]. Locations include:

- Anterior mediastinum.
- Posterior mediastinum.
- Aortopulmonary window.
- Deep thymic tissue.

These lesions are uncommon but represent an important cause of persistent or recurrent hyperparathyroidism. Most mediastinal inferior glands remain accessible through a cervical approach, although deeply seated lesions occasionally require thoracoscopic or sternotomy approaches [9] [45].

13. Application of the Perrier Classification to the Missing Parathyroid Gland

The Perrier nomenclature provides a systematic framework for approaching the missing parathyroid gland during thyroidectomy and parathyroidectomy. Rather than performing random exploration, surgeons can sequentially evaluate embryologically predictable locations. A practical operative strategy includes:

- Identification of the RLN and inferior thyroid artery.
- Inspection of orthotopic superior parathyroid gland locations adherent to the posterior thyroid capsule (Type A).
- Exploration of posteriorly displaced glands within the tracheoesophageal groove (Type B).
- Examination of inferiorly descended glands along the thyrothymic ligament and cervical thymus (Type C).
- Assessment of parathyroid glands intimately associated with the RLN at the level of the inferior thyroid vessels (Type D).
- Exploration of the paraesophageal and retroesophageal space posterior to the esophagus and prevertebral fascia (Type E).
- Evaluation for “fallen” superior parathyroid glands that have descended caudally into the lower neck or superior mediastinum (Type F).
- Mediastinal assessment for truly ectopic glands when cervical exploration is negative (Type G).

Intrathyroidal parathyroid glands are not specifically categorized within the original Perrier A to G nomenclature and should instead be considered a separate anatomic entity. Nevertheless, they remain an important cause of failed cervical exploration and persistent primary hyperparathyroidism [18]. This systematic approach minimizes unnecessary dissection and reduces the risk of injury to the RLN and postoperative hypoparathyroidism.

Several of the anatomic location estimates, frequency data, and operative “pearls” discussed in this review are derived from a combination of classic cadaveric studies, surgical series, reoperative experiences, and expert consensus rather than prospective, high-level evidence. The embryologic migration patterns of the parathyroid glands are well established; however, reported frequencies of ectopic and su-

pernumerary gland locations vary among studies because of differences in patient populations, operative indications, definitions of ectopy, and methods of anatomic assessment.

In addition, many technical recommendations for identifying a missing parathyroid gland during thyroidectomy or parathyroidectomy reflect accumulated surgical experience from high-volume endocrine surgery centers and may not have been validated in randomized or prospective studies. Accordingly, the anatomic distributions and operative strategies presented herein should be viewed as practical, evidence-informed guidance intended to facilitate systematic exploration rather than absolute predictors of gland location in every patient.

14. Conclusions

A “missing” parathyroid gland during thyroid or parathyroid surgery is most commonly ectopic rather than absent. Because ectopic glands follow highly predictable embryologic migration pathways, systematic exploration guided by embryology and surgical anatomy remains the cornerstone of successful identification.

Superior parathyroid glands typically migrate posteriorly into the tracheoesophageal or retroesophageal space, whereas inferior glands most commonly localize within the thyrothymic ligament, thymus, or superior mediastinum.

Reoperative series confirm that most failed explorations result from incomplete evaluation of these predictable locations rather than truly aberrant anatomy [30].

Consequently, careful orthotopic inspection, methodical stepwise exploration, and knowledge of embryologic migration patterns are essential principles for endocrine and head and neck surgeons managing difficult parathyroid localization.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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