Avoiding Complications of Thyroidectomy

Preservation of Parathyroid Glands

Elizabeth E. Cottrill, MD

KEYWORDS

- Parathyroid preservation • Hypoparathyroidism • Autofluorescence

KEY POINTS

- Knowledge of embryology and anatomy is foundational to parathyroid preservation without devascularization.
- Anticipatory dissection immediately on the thyroid capsule medial and ventral to the parathyroids allows for their identification and preservation of their blood supply.
- When avulsion or devascularization occurs, autotransplantation should be undertaken.
- Technologies harnessing autofluorescent properties of parathyroid tissue can aid in identification of parathyroid glands intraoperatively, but do not assess for viable tissue.
- Indocyanine green angiography can assess the adequacy of vascular supply to parathyroids intraoperatively.

INTRODUCTION

Preservation of the parathyroid glands during thyroid surgery and/or central neck dissection is a critical aspect of the procedure that must be performed deliberately to minimize the risk of postoperative hypoparathyroidism (hypoPT), a common and potentially life-threatening complication. HypoPT can occur due to removal or devascularization of the parathyroid glands during surgery. Herein, we discuss techniques that can be used to preserve the parathyroid glands during surgery, factors that influence the success of these techniques, and new technologies that may be used to aid in recognition and potentially preservation of parathyroid tissue.

Background

hypoPT is one of the most common complications of total thyroidectomy, completion thyroidectomy, and surgeries involving bilateral central compartment neck dissection.[1–5] The incidence of postsurgical hypoPT is difficult to know definitively because

Department of Otolaryngology Head and Neck Surgery, Thomas Jefferson University Hospital, 925 Chestnut Street. 6th Floor, Philadelphia, PA 19107, USA
E-mail address: Elizabeth.cottrill@jefferson.edu

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of the variety and extent of the procedures performed, various postoperative supplementation protocols, and varying clinical and biochemical criteria used to evaluate or define it.[1,6–8] A 2018 position statement from the American Thyroid Association defined temporary hypoPT, as an intact parathyroid hormone (PTH) level less than the lower limit of the laboratory standard (usually 12 pg/mL) concurrent with resultant hypocalcemia for less than 6 months after surgery and defined permanent hypoPT as this condition lasting beyond 6 months.[1] A 2014 systematic review and meta-analysis of 116 studies estimated the median incidence of temporary hypoPT ranges from 19% to 38% and permanent hypoPT 0% to 3%.[8] Risk factors for postoperative hypoPT have been evaluated by many authors and are summarized in **Box 1**.[8–10]

Embryology and Anatomy

The first step in the recognition and preservation of parathyroid glands during central neck surgery is development of a solid foundational knowledge of parathyroid embryology and anatomy. The development of the parathyroid glands starts during the fourth week of embryonic development. They arise from the third and fourth pharyngeal pouches, which also give rise to other structures. The third pharyngeal pouch gives rise to the inferior parathyroid glands as well as the thymus, whereas the fourth pharyngeal pouch gives rise to the superior parathyroid glands, thus the parathyroid pairs are occasionally referenced as PIII and PIV, respectively. The migration of the parathyroid cells to their final location occurs during the seventh week of embryonic development.[11,12]

The parathyroid glands are highly vascularized. Although classic teaching is that parathyroids are dominantly supplied by the inferior thyroid artery, Halstead and Evans[13] and more recently Nobori and colleagues have described superior thyroid artery contributions to parathyroid vascularity[14] (**Fig. 1**). Parathyroid glands are innervated by sympathetic and parasympathetic fibers.[15]

Owing to embryologic migration, the parathyroid glands may have variable final anatomic location (**Table 1**). The superior parathyroid glands (PIV) are most often located at the level of the cricoid cartilage or the lower border of the thyroid cartilage, whereas the inferior parathyroid glands (PIII) are often located at the level of the junction between the inferior and middle thirds of the thyroid gland.[11] Because of the longer migration tract of the PIII glands, from the level of the mandible to the pericardium, their normal location includes a wider area and they are also more likely to be ectopic. Undescended PIIIs can be located high in the neck above the thyroid along the carotid sheath often along with a remnant of thymic tissue.[16,19,26] Contrary to their

Box 1
Risk factors for permanent hypoparathyroidism following central neck operations:

- Bilateral thyroid procedures (total thyroidectomy or completion)
- Central Neck Dissection
- Autoimmune thyroiditis (Graves' disease, chronic lymphocytic thyroiditis)
- Substernal goiter
- Low-volume thyroid surgeon
- Prior gastric bypass or malabsorptive state
- Simultaneous thyroidectomy and parathyroidectomy
- Prior central neck surgery/revision central neck surgery

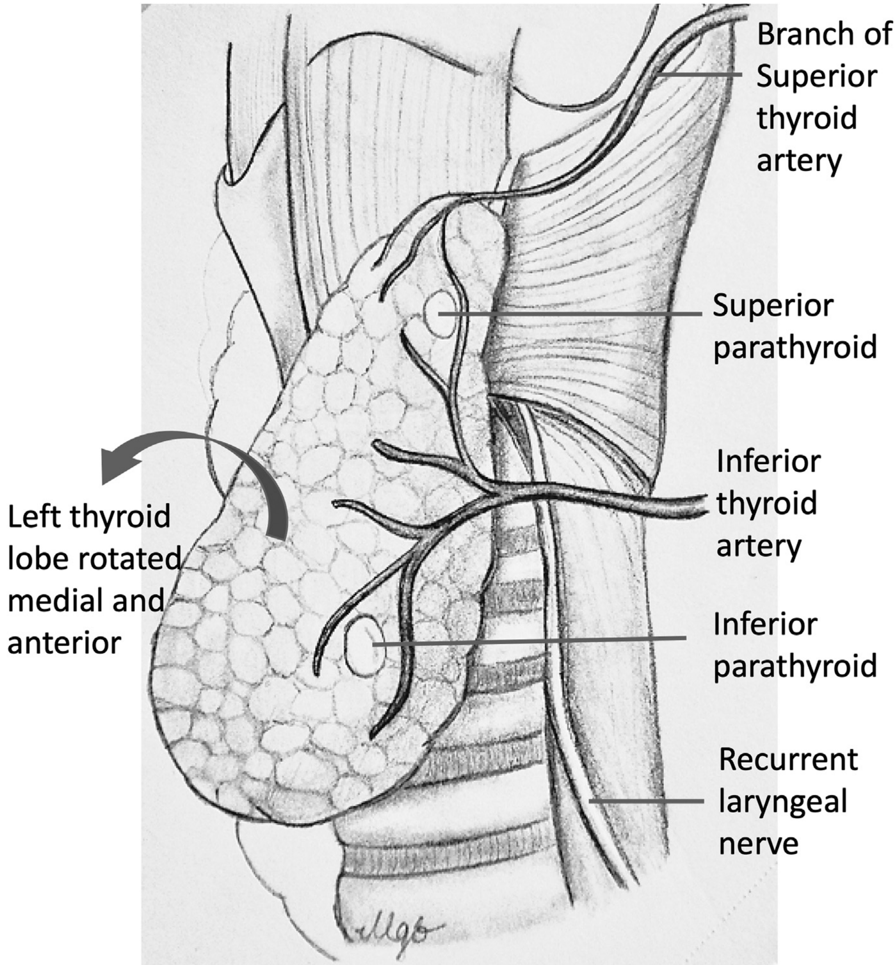

Fig. 1. Parathyroid vascularization with branches from both inferior and superior thyroid arteries depicted. Preservation of viable parathyroid glands requires maintaining an adequate blood supply through the distal branches which supply them. (Image courtesy: Isabella Boon.)

naming, the superior parathyroid glands are not always found cephalad to the inferior glands, but the pairs do maintain a consistent anatomic relationship to each other as they relate to the course of the recurrent laryngeal nerve: the superior glands (PIV) being located *posterior or dorsal* to the trajectory of the nerve and the inferior glands (PIII) being *anteriorly or ventrally* located.

The parathyroid glands may be located within the fibrofatty tissue in the thyroid bed, adherent to the thyroid capsule, *within* the thyroid capsule, or rarely intrathyroidal. A true intrathyroidal parathyroid, fully embedded in thyroid parenchyma, is extremely rare and should be distinguished from a parathyroid which is located just beneath the thyroid capsule (subcapsular) and is less rare. The historically reported incidence of a true intrathyroidal parathyroid is between 0.5% and 4%.[16,18,24,27] More recent studies have reported the prevalence of intrathyroidal parathyroids to be more common on the right side and within the inferior portion of the thyroid lobe, and their

Table 1
Parathyroid gland location

Superior Parathyroid (PIII)	References	Inferior Parathyroid (PIV)	References
80% posterior aspect of thyroid lobe, 1 cm cephalad to the intersection of the inferior thyroid artery and the recurrent laryngeal nerve, close to the cricothyroid joint	Refs[16–18]	42%–61% along the anterior, lateral, or posterior aspect of the inferior thyroid pole	Refs[18,19]
15% posterolateral surface of the superior thyroid pole	Refs[16,18,20,21]	25% thyrothymic ligament or within the cervical thymus	Ref[18]
3%–4% retropharyngeal or retroesophageal	Refs[16,18]	5% anterior mediastinum or intrathoracic	Refs[16,18,22]
<1% cephalad to the superior pole of the thyroid: adjacent to carotid, pyriform sinus, and so forth	Refs[18,23,24]	2% cephalad ectopic position above superior pole (easily confused with PIVs) <4% intrathyroidal (most common right inferior pole)	Refs[16,18,19,22,25]

frequency is reportedly higher in cases of hyperfunctioning parathyroid glands.[28,29] Although there is considerable variability in the final location of the parathyroid glands, there is often mirror symmetry from right to left with symmetry of the PIV seen in approximately 80% of cases and of the PIII in approximately 70% of cases. The most common asymmetry identified is when one PIII is located within the thymus. The awareness of parathyroid symmetry may facilitate parathyroid gland identification during surgical neck exploration.

Supernumerary and subnumerary parathyroid glands are also possible. Autopsy series have reported less than four glands in up to 6% of the population,[4,21] potentially an overestimate given the frequency of ectopic glands which may not have been identified. More than four glands have been reported in 5% to 13% of autopsies with up to 11 distinct parathyroids being reported in a single individual.[18,30,31] In patients with renally induced hyperparathyroidism (HPT) reports are higher. A study of 300 renal-HPT patients reported 30% of patients having more than four parathyroids identified at the time of initial surgery with 80% of these being located in the cervical thymus.[30] These supernumerary parathyroid glands develop from accessory parathyroid fragments arising from the pharyngobranchial duct when the pharyngeal pouches separate from the pharynx.[26] Microscopic ectopic rests are also somewhat common. These are derived from embryologic parathyroid debris and weigh less than 5 mg as compared with true supernumerary parathyroids which weigh 24 g on average.[18] A 1992 study of surgical patients without renal HPT reported finding microscopic embryonic parathyroid rests in less than 30% of patients.[32] In the case of HPT, the presence of continuous growth stimulation may stimulate microscopic rests to grow and thus reaches a size comparable to true supernumerary glands.[18,31]

Intraoperative Technique

The perspicacious surgeon builds on a solid foundational anatomic and embryologic knowledge with the practice of meticulous surgical technique. Avoiding damage to the parathyroid glands first requires that a surgeon can recognize parathyroid tissue to avoid avulsing it from its blood supply. Unfortunately, parathyroid glands can appear deceptively similar to fibroadipose tissue, lymph nodes, and even thyroid tissue due to their small size, coloration, and the classic presence of a fat-cap. Therefore, using anatomic and embryologic foundational knowledge as a basic map, one is able to identify landmarks and use a “proactive anticipatory visual approach,”[1] in the words of Orloff and colleagues to identify parathyroid tissue.

The technique of gentle capsular dissection, immediately on the surface of the thyroid, reflecting the perithyroidal fatty tissues serially as one works from medial to lateral and from ventral to dorsal along the capsule of the thyroid allows for identification and preservation of the parathyroid blood supply in the majority of cases. There is evidence that utilization of loupe magnification (2.5x) significantly reduces the rate of inadvertent parathyroidectomy (3.8% vs 7.8%) and both postoperative clinical and biochemical hypocalcemia.[33] It should be emphasized that surgical technique requires dissection immediately on the surface of the thyroid gland medial or anterior to the parathyroids and therefore distal to their fine network of blood supply (see **Fig. 1**). One should anticipate the possible arterial contribution of the superior thyroid artery via a small branch to the superior parathyroid as well as anastomotic branches and care should be taken to preserve these contributions during dissection of the superior thyroid pole. Once identified, the parathyroids are carefully freed from their medial attachments and reflected off the thyroid gland along with their laterally based vascular pedicle while ligating only the distal-most branches of the inferior thyroid artery at the level of the thyroid capsule.[34] Vessels spanning the medial border of the parathyroid and the adjacent lateral thyroid capsule are generally believed to be insufficient to vascularize the parathyroid gland and it has been suggested that distal arterial segments may be supplied by anastomotic vessels from the trachea and esophagus.[34,35] Nevertheless, a classic 1982 study by Delattre and colleagues of 100 cadaveric dissections of the neck injected with latex to study the vascular supply of the parathyroids reported that standard capsular dissection would likely have been insufficient to maintain vascular supply to all four parathyroids in 5.5% of specimens.[36]

The use of energy devices for vessel sealing during thyroidectomy is another relevant surgical technical factor. These energy devices generate a zone of collateral thermal spread within the tissues and necessitate an optimal 3 to 5 mm distance of separation between the instrument and the parathyroid gland to avoid thermal injury to adjacent tissues.[37,38] After removal of the specimen, it should be critically inspected for evidence of adherent parathyroid tissue before handing off the specimen for pathology. Any avulsed parathyroid tissue should be immediately placed in cold saline for preservation and consideration of confirmation of parathyroid tissue via frozen section or other modality (see next section discussing technologies) before preparing it for auto transplantation.

Visual inspection of the parathyroid glands in vivo after extirpation of the thyroid or central lymph node packet should be undertaken critically to assess for devascularization or venous congestion. Venous disruption can often be perceived visually by classic darkening and implies the high potential for dysfunction of that gland. A parathyroid which is found to have apparent blood supply, but dark blue–purple discoloration may have vascular congestion which can often be alleviated by sharp scoring of the parathyroid gland capsule resulting in normalization of color. Care should be taken not to disrupt the blood supply in performing this maneuver and a fresh blade or sharp scissor which has not been in contact with cancerous tissue should be used. In turn, the blade or scissor used for scoring should then be either cleaned or retired for the duration of the case to avoid the risk of inadvertent parathyroid auto transplantation. Arterial ischemia of the parathyroid may be subtle or without any perceptible color change. indocyanine green (ICG) angiography, discussed later, is a newer technology which may be used to evaluate parathyroid tissue more clearly for appropriate vascular function. Although frank avulsion from blood supply is a clear indication for autotransplantation, some studies suggest that discolored parathyroids have only transiently impaired function,[39,40] recommending autotransplantation only if the evidence of arterial insufficiency is clearly seen or confirmed by angiography.

Preservation of intrathyroidal parathyroids as well as those located within the thyroid capsule is incredibly difficult and, especially in the case of the former, would likely require high suspicion on preoperative ultrasonographic imaging. If a subcapsular parathyroid is identified after removal of the thyroid gland, consideration of the proximity of the parathyroid to a potentially cancerous thyroid nodule should be made before incising the thyroid capsule to remove the parathyroid for reimplantation. Generally, a small intraoperative biopsy should be undertaken to confirm parathyroid tissue before morselization and reimplantation.

Although preservation of all parathyroid glands during total thyroidectomy with or without central neck dissection is a critically important operative goal, this objective is not always attainable due to potential variations in location or blood supply of the glands or due to the extent of thyroid disease such as in the case of thyroid cancer with a high burden of central neck metastases. During central neck dissection, superior parathyroid glands are at lower risk of devascularization or inadvertent removal than the inferior glands, owing to the bulk of nodal metastases being in the more caudal paratracheal and pre-tracheal areas. If central neck dissection is to be undertaken, this author recommends using a 5 to 0 Prolene to mark the parathyroids opposite their vascular pedicle at the time of their initial identification to help identify them clearly during dissection of level VI. If autofluorescent technology (discussed later) is available, then this technology along with surgeon visualization to confirm parathyroid tissue can be used. If avulsed or devascularized parathyroid glands are not overtly involved with cancer, then morselization and autotransplantation in the sternocleidomastoid muscle should be undertaken. Consideration should be given to staged or less aggressive contralateral surgery if there is evidence of devascularization of both parathyroids on one side requiring autotransplantation.

Technological Advances: Autofluorescence and Parathyroid Angiography

New technology, aimed at improving identification of parathyroid glands intraoperatively, has arisen over the past 10 to 15 years. Researchers at Vanderbilt University discovered that when excited in the near-infrared (NIR) spectrum (785 nm), the resulting autofluorescence (AF) wavelength of parathyroid tissue (820–830 nm) was consistently greater than that of surrounding tissue types (thyroid, fat, and muscle).[41] Technologies which harness this natural phenomenon rely on the *difference* between emitted wavelengths of tissues in the central neck. The technologies use either a camera with visual comparison of exposed tissues by the surgeon in real time, or a disposable probe which measures the AF wavelength of the tissue being touched. NIR-AF technology is noninvasive and real time. It requires no drugs or injections, thus avoiding side-effects. The two kinds of NIR-AF systems which currently exist are detailed in **Table 2** and these include both a probe-based system (PTEye, Medtronic) and an optical-based system (Fluobeam, Fluoptics). Other commercially available optical systems exist and can also be used for parathyroid detection, although not FDA approved for this use specifically.[42]

Because the technology relies on the difference in AF wavelengths between tissues, it is important to realize several limitations.

- AF intensity may differ between patients.
- Diseased parathyroids (hyperplasia, adenomas) may have weaker AF than normal glands.
- Thyroid tissue can have abnormally high AF, especially in the case of thyroiditis
- False-positive signals have been reported from colloid nodules, brown fat, and metastatic lymph nodes.[43]
- The fluorophore intrinsic to parathyroid tissue is present in vivo and ex vivo and is resistant to heat, freezing, and formalin fixation,[44–46] therefore, these technologies do not assess viability or vascular supply of the tissue.

Table 2
Comparison of near-infrared autofluorescence systems available in the United States

Probe-Based Spectroscopy	Optical Camera-Based
• Surgeon holds a sterile probe • Background level is calibrated from five separate locations on the thyroid or trachea • System analyzes optical properties of the tissue being touched and gives a distinct numeric reading as well as audio/visual feedback • FDA-approved device (2018): PTEye (MedTronic)	• Surgeon looks at operative field with special camera within a sterile sheath • Surgeon visually searches for foci of high autofluorescence as compared with background • Imaging is limited to superficial layers of tissue • FDA-approved device (2018): Fluobeam (Fluoptics)

Despite these limitations, many studies over the past 8 years have shown the high accuracy and clinical usefulness of this technology.[44,45,47–65] Most of these studies report that the identification of parathyroid glands is more accurate with AF-based systems than with the naked eye only and allow for identification of parathyroid glands which would otherwise have been missed. Several studies also report better postoperative outcomes regarding hypoPT when using NIR-AF modalities.[50,57,64,66,67]

As mentioned previously, visual detection of ischemic parathyroid glands is imperfect and given the persistence of AF properties in devascularized and even formalin fixed parathyroid tissue, viability of parathyroids cannot be confirmed with NIR-AF technologies. Angiography with the fluorescent dye ICG has therefore been developed to confirm perfusion of parathyroid glands in vivo. ICG is an albumin-bound, water-soluble fluorescent dye with a half-life of 2 to 3 minutes and is FDA-approved. It was initially used to evaluate liver function and currently is used for retinochoroidal angiography. It has a peak absorption at 800 nm and peak emission at 830 nm, in the NIR spectrum, and can penetrate tissues up to 1 cm in depth allowing excellent visualization of vascularity. Owing to its short half-life and a toxic dose of 5 mg/kg, it can theoretically be injected many times throughout a procedure. The technology necessary to perform intraoperative ICG angiography is often readily available as most modern institutions in the United States will be equipped with an ICG fluorescence endoscopic camera in their operating suites. Its limitations are inherent in the lack of standardization and subjective nature of the assessment with currently available devices lacking numerical evaluation. It is therefore difficult to concretely compare data between groups or assess differences between devices used.[68,69]

Several studies have reported that ICG angiography is superior to “naked eye” visualization alone in determining vascular supply to the parathyroid glands and the correlation between vascularization and parathyroid function postoperatively has a very high positive predictive value.[70–73] ICG angiography can be used to evaluate parathyroid vasculature after thyroidectomy or paratracheal dissection, but it can also be used to identify the parathyroid vessel before thyroid resection allowing the surgeon to spare vessels which would otherwise have been ligated. This method of vessel mapping is an area of ongoing research.[57,74,75] Some studies have suggested that if at least one parathyroid gland is well-vascularized, the patient may be managed without measuring calcium and PTH postoperatively.[70]

DISCLOSURE

E.E. Cottrill does not have any commercial or financial relationships or conflicts of interest to disclose.

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