IMAGING ECTOPIC PARATHYROID ADENOMAS. A LITERATURE REVIEW

Imágenes de adenomas paratiroideos ectópicos. Una revisión de la literatura

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Abbreviations

CT = computed tomography; 4DCT = 4-dimensional CT; EPA = ectopic parathyroid adenoma; EPG = ectopic parathyroid gland; PHPT = primary hyperparathyroidism; RLN = recurrent laryngeal nerve; SPECT = single-photon emission computed tomography; TE = tracheo-esophageal

Summary

Objective: (1) To review the anatomy and epidemiology of ectopic parathyroid adenomas (EPAs), (2) summarize the role of relevant imaging modalities in the localization of EPAs, and (3) briefly review surgical approaches for EPAs. ***Methods:*** Literature review of published English-language articles from 1984 through August 2017. ***Results:*** Summary of the literature indicates that the prevalence of EPA is approximately 20% in unexplored patients with primary hyperparathyroidism, but it is as high as 66% in re-operative patients. EPAs may be located anywhere from the carotid bifurcation to the aortopulmonary window. Ultrasound has limited accuracy in identifying EPAs except near the thyroid and thyrothymic ligament and requires expert experience from the user. Among dual-phase 99mTc sestamibi scintigraphy techniques, hybrid imaging with both single-photon emission computed tomography (SPECT) and computed tomography (CT), (SPECT/CT) is superior to planar scintigraphy or SPECT alone at localizing EPAs. Four-dimensional computed tomography (4DCT) precisely delineates important anatomic relationships and is highly sensitive in localizing EPAs. Although 4DCT requires radiation, intravenous iodinated contrast, and reader experience, it is well-equipped to detect lesions at various ectopic sites and guide the surgical approach. EPAs frequently require alternative surgical approaches. Re-operative parathyroidectomy may be attempted in patients having previously undergone bilateral neck exploration by an experienced surgeon once the lesion is colocalized by 2 repeat imaging modalities. Removal of nonlocalized disease requires a careful and systematic exploration of superior and inferior gland locations. ***Conclusion:*** EPAs pose challenges during both localization and surgical removal. High-volume experience and multidisciplinary care are necessary for optimal outcomes.

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Resumen

Objetivos: 1) Revisar la anatomía y epidemiología de los adenomas paratiroideos ectópicos (APE); 2) resumir el papel de las modalidades de imagen relevantes en su localización; y 3) revisar brevemente los enfoques quirúrgicos para los mismos. ***Métodos***: Reseña literaria de artículos publicados en inglés desde 1984 hasta agosto de 2017. ***Resultados***: El resumen de la literatura indica que la prevalencia de APE es de, aproximadamente, el 20 % en pacientes con hiperparatiroidismo primario que no han sido intervenidos quirúrgicamente, pero en pacientes reintervenidos es tan alta que alcanza el 66 %. Los APE pueden estar localizados en cualquier lugar, desde la bifurcación de la carótida hasta la ventana aortopulmonar. El ultrasonido tiene una agudeza diagnóstica limitada en su identificación, excepto para los que están localizados cerca de la glándula tiroides y al ligamento tirotímico. Requiere gran experiencia del operador. Si se comparan las técnicas de gammagrafía Sestamibi-99mTc de fase dual, la imagen híbrida con tomografía computarizada de emisión de fotón simple (SPECT) y con tomografía computarizada (TC), la técnica SPECT/TC es superior a la gammagrafía planar o SPECT en la localización de los APE. La TC en cuatro dimensiones (4DTC) delinea con precisión las relaciones anatómicas importantes y es altamente sensible para la localización de los APE. Aunque la 4DTC requiere radiación, medio de contraste intravenoso yodado y experiencia del lector, provee buena información para detectar lesiones en varios sitios ectópicos y guiar el abordaje quirúrgico. Los APE frecuentemente requieren enfoques quirúrgicos alternativos. Se puede intentar una nueva paratiroidectomía en pacientes que han sido previamente sometidos a una exploración bilateral del cuello, por un cirujano experimentado, una vez que la lesión se localice mediante dos modalidades de imágenes. La remoción de la enfermedad no localizada requiere una exploración cuidadosa y sistemática de las localizaciones superiores e inferiores de las glándulas. ***Conclusión***: Los APE plantean desafíos tanto para su localización como para la extirpación quirúrgica. Con el fin de obtener resultados óptimos se requiere contar con la experiencia de un alto número de pacientes y una atención multidisciplinaria.

Introduction

Ectopic parathyroid adenomas (EPAs) pose unique challenges in the management of patients with primary hyperparathyroidism (PHPT). These lesions can be difficult to identify on imaging studies, as well as challenging to remove. Nearly 20% of unexplored patients with PHPT have an EPA, and this prevalence can be as high as 66% in re-operative patients (1-6). Imaging modalities such as ultrasound, sestamibi scintigraphy, and 4-dimensional computed tomography (4DCT) are widely used for pre-operative localization, and are particularly important in the setting of ectopic glands. In addition, EPAs are the most common cause for failed initial surgical exploration, and may require alternative surgical approaches (1,4-8). In this article, we review the anatomy, epidemiology, and role of imaging in the management of EPAs. We present images of both common and uncommon ectopic locations that radiologists and surgeons should recognize.

1. Anatomy and incidence of ectopic parathyroid glands

Understanding the anatomy and relative frequency of EPAs is essential for both identifying and removing ectopic disease. The embryologic development of parathyroid glands provides a useful framework for radiologists and surgeons alike to appreciate possible ectopic sites and their likelihood of occurrence.

1.1 Orthotopic Parathyroid Glands

Inferior parathyroid glands arise from the third pharyngeal pouch and descend alongside the developing thymus. Orthotopic inferior glands lie inferior, posterior, or lateral to the lower pole of the thyroid gland, and are anterior to the recurrent laryngeal nerve (RLN). Meanwhile, superior parathyroid glands arise and descend from the fourth pharyngeal pouch. Orthotopic superior glands lie posterior to the body of the thyroid gland, and are posterior to the RLN. For both inferior and superior glands, the relationship of the gland to the RLN is preserved even in ectopia

1.2 Ectopic Parathyroid Glands

Ectopic parathyroid gland (EPG) refers to a gland that is located outside of its orthotopic site. An EPG can arise from abnormal migration during embryogenesis, or can be acquired. In the latter case, enlarged glands can become displaced from their orthotopic locations due to their size, under the influence of gravity, or by mass effect from an associated enlarged thyroid; or can be iatrogenic from surgical auto-transplantation (figure 1). Ectopic adenomas deserve a high index of suspicion in both unexplored and re-operative patients. The prevalence of EPA is between 17.5 and 22% in unexplored patients with PHPT (1-3). In re-operative patients, however, ectopic glands may comprise up to 66% of missed adenomas, making EPAs much more common in the re-operative setting than in the unexplored setting (1,4-6,8,9).

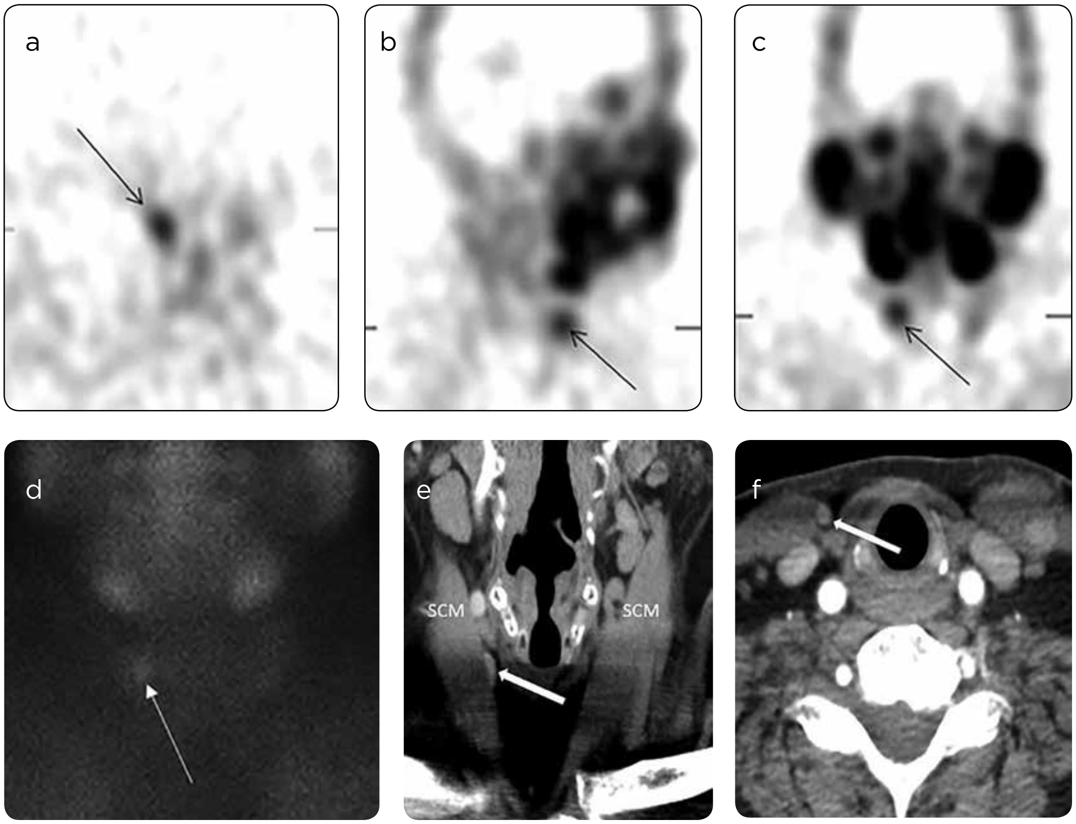


Figure 1. Auto-transplanted parathyroid adenoma. Axial (A), sagittal (B), coronal (C), and delayed coronal (D) single-photon emission computed tomography (99mTc Sestamibi scan) planar images localize an auto-transplanted ("acquired ectopic") hyperfunctioning parathyroid gland (thin arrows) after remote thyroidectomy. Axial (E) and coronal (F) arterial computed tomography images confirm parathyroid adenoma (thick arrows) medial to the sternocleidomastoid muscle.

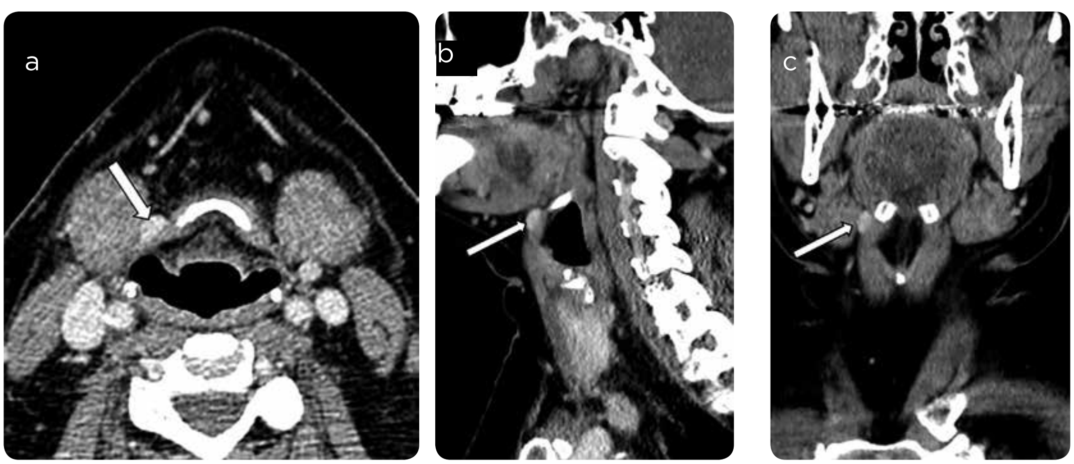


Figure 2. Undescended inferior parathyroid adenoma. Axial (A), coronal (B), and sagittal (C) postcontrast computed tomography show an undescended right inferior parathyroid adenoma to the right of the hyoid bone, located anteriorly in the neck.

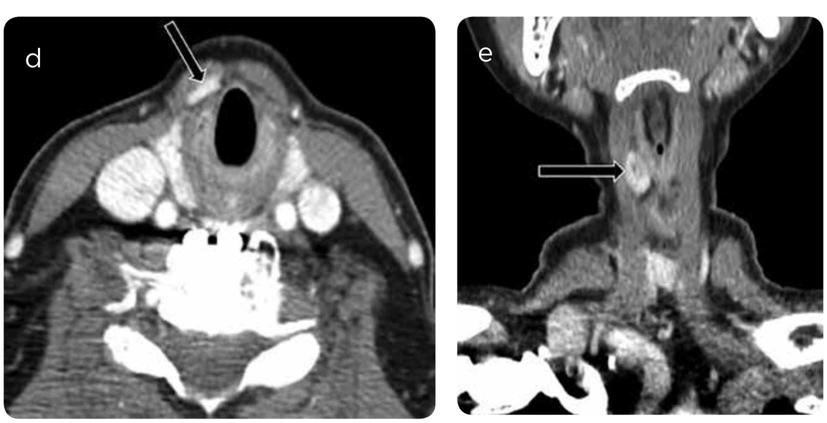


Figure 3. Parathyroid adenoma within strap muscles. Axial (A) and coronal (B) postcontrast computed tomography show a right parathyroid adenoma within the strap muscles, located ventrally, and likely an inferior gland in origin. Central hypoattenuation is a common feature of parathyroid adenoma seen on computed tomography.

1.3 Inferior EPGs

Inferior EPGs are more common than superior EPGs because inferior glands have a longer and more variable embryologic descent. As a result, inferior EPGs can be located anywhere from the carotid bifurcation to the aortopulmonary window. Submandibular or undescended glands are located above the upper pole of the thyroid near the carotid bifurcation. Undescended glands arise when inferior glands fail to migrate with the thymus (figures 2 and 3). The prevalence of undescended parathyroid glands ranges from 0.08 to 2% in patients undergoing parathyroidectomy and from 5 to 9% in re-operative cases (10-15). Inferior EPGs may also be found inside the thyroid parenchyma (figure 4), in the thyrothymic ligament, or within the thymus itself (figure 5). Another common location for inferior EPGs is the anterior mediastinum (figure 6). Anterior mediastinal glands occur when glands are engulfed during thymic development and descend posterior to the sternum. Lastly, inferior EPGs can be found inferior to the thymus in the mediastinum, including in the aortopulmonary window or adjacent to the aorta (5,8,16,17). Such glands may arise due to an association with the left RLN.

1.4 Superior EPGs

Superior EPGs are not as common as inferior EPGs but can similarly arise from abnormal descent or be acquired due to enlargement and displacement from their normal location. Superior EPGs can be located within the carotid sheath (figure 7), in the retropharyngeal space (figure 8), in retro- or para-esophageal regions, in the hypopharynx (figure 9), and even in the oral cavity. Another common location for superior EPGs is the tracheo-esophageal (TE) groove (figure 10). As in most existing literature, we will consider the TE groove to be an ectopic site, although some consider it to be a posterior extension of the normal superior gland location, particularly when the gland is enlarged and heavy. Like inferior EPGs, superior EPGs can also be located within the thyroid parenchyma. Lastly, superior EPGs can be overly descended, located below the inferior pole of the thyroid gland (figures 11 and 12). These glands are often mistaken for orthotopic inferior glands because of their inferior location. However, overly descended superior glands remain posterior to the RLN. In a study of 270 patients with single-gland PHPT, Duke and colleagues found that overly descended superior adenomas were the most common EPA type in both unexplored and re-operative patients (1).

The distribution of EPAs by ectopic site and patient type is provided in table 1.

2. Imaging modalities

The diagnosis of hyperparathyroidism is made using a combination of clinical and laboratory findings (18). Imaging is used to localize adenomatous glands, identify their relationship to nearby structures, and plan the operative approach. Accordingly, pre-operative imaging provides anatomical localization of the gland and helps identify patients who are candidates for minimally invasive parathyroidectomy. In addition, pre-operative imaging is particularly important in guiding re-operation for recurrent or persistent hyperparathyroidism after a failed initial surgery. In this section, we list the imaging modalities frequently used to localize parathyroid adenomas, and discuss their strengths and weaknesses in localizing EPAs. Specifically, we address the application of ultrasound, sestamibi scintgraphy, and 4DCT as they are the most commonly utilized modalities. Although magnetic resonance imaging and positron emission tomography are occasionally used to localize parathyroid lesions, they are less widely available and not discussed in the present review.

2.1 Ultrasound

Ultrasound is a commonly used modality for localizing parathyroid adenomas. On ultrasound, adenomas appear as oval-shaped, homogenous, and hypo-echoic masses (figures 11 a and b). Doppler interrogation allows visualization of a polar vessel with a peripheral rim of vascularity surrounding the adenomatous gland (figures 4 a and b; and 11 c and d). However, parathyroid adenomas can occasionally be heterogeneous or complex (i.e., solid and cystic) and do not always exhibit the characteristic vascular features. Ultrasound is inexpensive, widely available, radiation-free, and well-suited to evaluate concomitant thyroid pathology. For detecting EPAs, ultrasound has a reported sensitivity between 11 and 59%, and a specificity as high as 100% in previously unexplored patients with PHPT (2,19). Ultrasound is particularly accurate for identifying adenomas adjacent to the inferior poles of the thyroid gland, in the thyrothymic ligament, and just posterior to the thyroid gland (8,20). Ultrasound has moderate accuracy in identifying undescended or submandibular EPAs (2). However, many ectopic locations are sonographically inaccessible; ultrasound has no role in identifying EPAs in the carotid sheath, retro-esophageal region, thymus (2), TE groove, and mediastinum (8,20), as well as overly descended superior glands, and glands behind overlying structures (e.g., sternum, trachea, esophagus, clavicle). Consequently, failure to localize an EPA in sonographically accessible locations should raise suspicion for an EPA in an inaccessible location. In experienced hands, ultrasound can distinguish between intrathyroidal adenomas and thyroid nodules (21). False positives in ultrasound are generally caused by thyroid nodules and lymph nodes that are mistaken for parathyroid lesions. As a result, it can be challenging to distinguish parathyroid adenomas using ultrasonography in patients with multinodular goiter or reactive adenopathy, such as in Hashimoto thyroiditis. Although ultrasound enables fine-needle aspiration of suspected parathyroid lesions, it results in significant fibrosis of the adenoma and surrounding tissues (thus complicating surgical removal) and is therefore only performed in unusual locations once all other etiologies have been ruled out. Lastly, ultrasound does not accurately identify multigland disease (22,23). In general, ultrasound can greatly contribute to the localization of parathyroid lesions but requires expert experience from the user.

2.2 Sestamibi Scintigraphy

Sestamibi scintigraphy has historically been the most commonly used imaging modality to localize parathyroid adenomas. This modality uses 99mTc sestamibi radiotracer that concentrates in the mitochondria of tissues with high metabolic activity, such as the mitochondria-rich oxyphil cells of hyperfunctioning parathyroid glands (24). There are 2 phases for the detection of radioactivity. The early phase (15 minutes after injection) demonstrates uptake in both the thyroid and parathyroid glands, whereas the delayed phase (120 minutes after injection) demonstrates washout of the radiotracer from normal thyroid tissue but retention in hyperfunctioning parathyroid glands.

Table 1. EPA Distribution by Site and Patient Type

Ectopic site	Primary or unexplored patients		Re-operative patients	
	Percentage of all EPAs	Reference	Percentage of all EPAs	Reference
Inferior				
Submandibular, undescended, carotid bifurcation	4 % 5 %	Roy et al. (2) Phitayakorn et al. (24)	8 % 11 %	Shin et al. (9) Jaskowiak et al. (5)
Thyrothymic ligament	12 %	Phitayakorn et al. (24)	5 %	Shin et al. (9)
Intrathymic	19 % 38 %	Phitakayorn et al. (24) Roy et al. (2)	<1 % 19 %	Jaskowiak et al. (5) Shin et al. (9)
Anterior mediastinum	14 %	Phitayakorn et al. (24)	2 % 23 %	Shin et al. (9) Jaskowiak et al. (5)
Inferior to thymus in mediastinum	6 %	Roy et al. (2)	1 % 6 %	Jaskowiak et al. (5) Shin et al. (9)
Superior				
Carotid sheath	3 % 3 %	Phitayakorn et al. (24) Roy et al. (2)	5 % 11 %	Jaskowiak, et al. (5) Shin et al. (9)
Retropharyngeal			7 %	Shin et al. (9)
Retro-esophageal	8 % 31 %	Phitayakorn et al. (24) Roy et al. (2)	4 % 7 %	Jaskowiak et al. (5) Shin et al. (9)
TE groove or para-esophageal	16 %	Phitakayorn et al. (24)	5 % 36 % 37 %	Shin et al. (9) Silberfein et al. (6) Jaskowiak et al. (5)
Posterosuperior mediastinal	5 %	Phitayakorn et al. (24)	4 %	Shin et al. (9)
Overly descended	52 %	Duke et al. (1)	13 % 33 %	Shin et al. (9) Duke et al. (1)
Intrathyroidal				
Inferior origin only	14 %	Phitayakorn et al. (24)		
Superior origin only	3 %	Phitayakorn et al. (24)		
Both included	18 % 18 %	Roy et al. (2) Phitakayorn et al. (24)	4 % 10 % 14 %	Silberfein et al. (6) Shin et al. (9) Jaskowiak et al. (5)

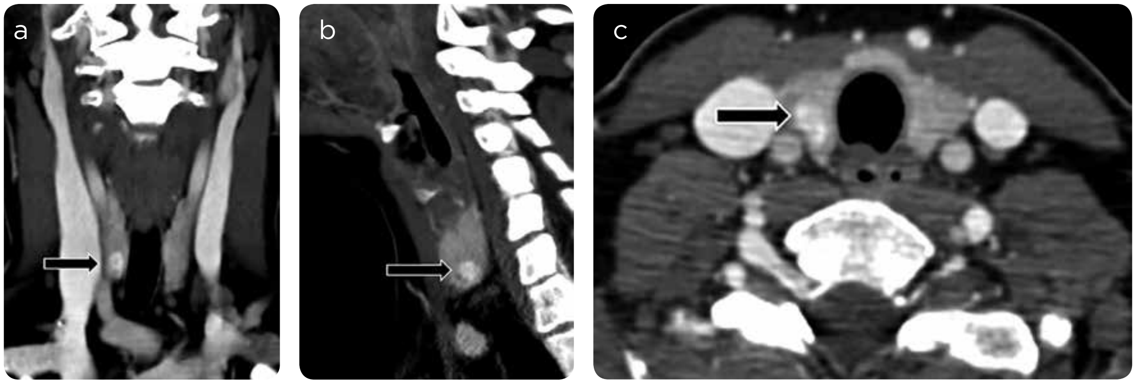
Abbreviations: EPA = ectopic parathyroid adenoma; TE = tracheo-esophageal.

Due to its large anatomic coverage, sestamibi techniques can localize orthotopic and ectopic parathyroid adenomas in both the neck and thorax. The 3 most common sestamibi scintigraphy techniques are planar (2-dimensional) imaging, single-photon emission computed tomography (SPECT), and hybrid imaging with both SPECT and CT (SPECT/CT).

Existing studies on sestamibi scintigraphy are subject to a few limitations. For example, it is difficult to determine the specificity of the modality due to insufficient reporting of follow-up studies performed on patients with negative scintigraphy findings. Also, "true negatives" are often excluded from studies. Furthermore, most studies have a very limited sample size of patients with EPAs. Nevertheless, the existing literature on sestamibi scintigraphy enables us to measure its efficacy in localizing EPAs.

In unexplored patients, planar 99mTc sestamibi scintigraphy has a sensitivity between 70 and 89%, a positive predictive value between 90 and 100%, and a specificity between 88 and 100% for localizing EPAs (2,25,26). However, planar imaging is limited by its two-dimensionality. For example, superior EPGs that are overly descended or in the TE groove will resemble orthotopic inferior glands on planar scintigraphy. Meanwhile, oblique sestamibi projections, SPECT, and SPECT/CT will reveal such glands to be posterior to the plane of orthotopic inferior glands (1,24,27-29).

SPECT provides three-dimensional information about a gland's position (Fig. 1). SPECT/CT delivers better anatomic detail but requires additional radiation. As compared to planar and SPECT scintigraphy, SPECT/CT better elucidates the relationship between an adenoma and its adjacent structures (figures 11 h and k). SPECT/CT has a sensitivity between 75 and 100% in detecting EPAs (30-32). SPECT/CT accurately localizes undescended (30), retrotracheal (32,33), TE (29), intrathyroidal (20,30,31,33), overly descended (29), and mediastinal glands (20,30,31,33).



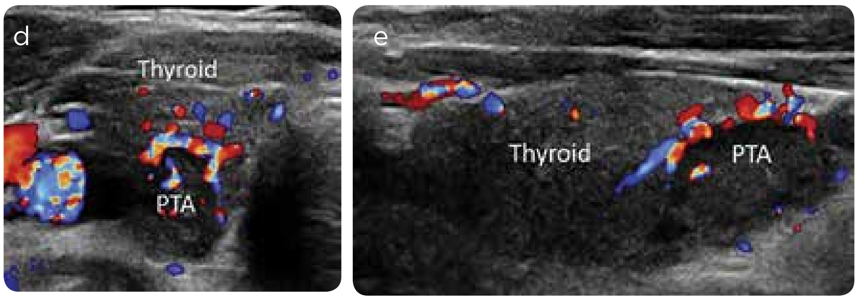


Figure 4. Intrathyroidal parathyroid adenoma. Axial (A), coronal (B), and sagittal (C) postcontrast computed tomography show a right intrathyroidal parathyroid adenoma (which may originate from either a superior or inferior gland). Transverse (D) and longitudinal (E) Doppler ultrasound confirms the hypoechoic intrathyroidal parathyroid adenoma, with a characteristic vascular rim.

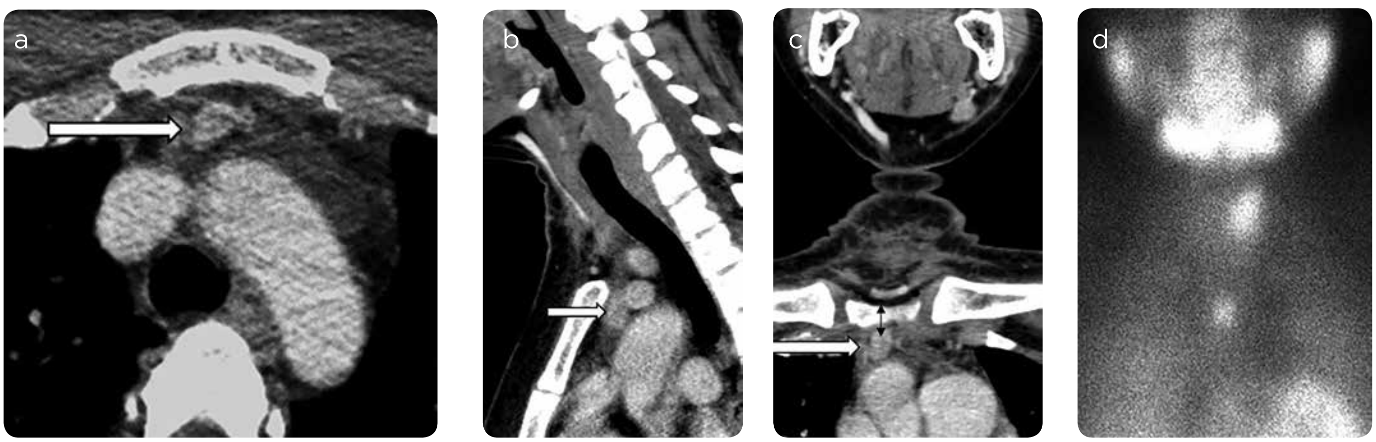


Figure 5. Intrathymic inferior parathyroid adenoma. Axial (A), coronal (B), and sagittal (C) computed tomography demonstrate an intrathymic right inferior parathyroid adenoma, located ventrally in the anterior-superior mediastinum, also visualized on the static delayed single-photon emission computed tomography image (D). The lesion is located <4 cm from the sternal notch (black arrow, B).

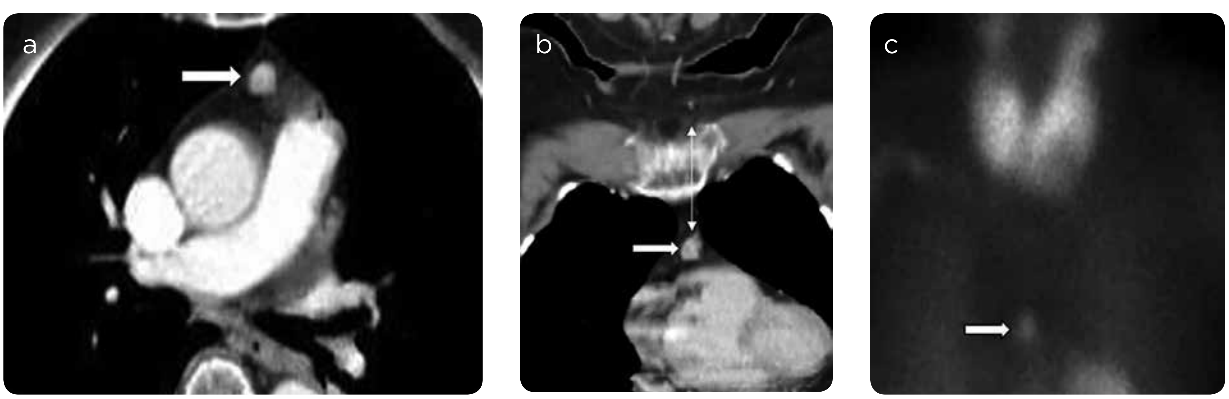


Figure 6. Anterior mediastinal parathyroid adenoma. Axial (A) and coronal (B) postcontrast computed tomography show an anterior mediastinal parathyroid adenoma (white arrow), confirmed on the static delayed single-photon emission computed tomography image (white arrow). Lesion located >4 cm (thin arrow, B) below the sternal notch, requiring thoracoscopy for resection.

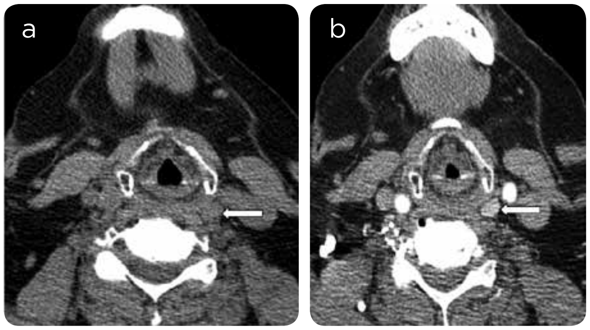


Figure 7. Parathyroid adenoma in the carotid sheath. Axial precontrast (A) and postcontrast (B) computed tomography show an enhancing left superior parathyroid adenoma deep-dorsal in the neck, intraoperatively found to be in the carotid sheath.

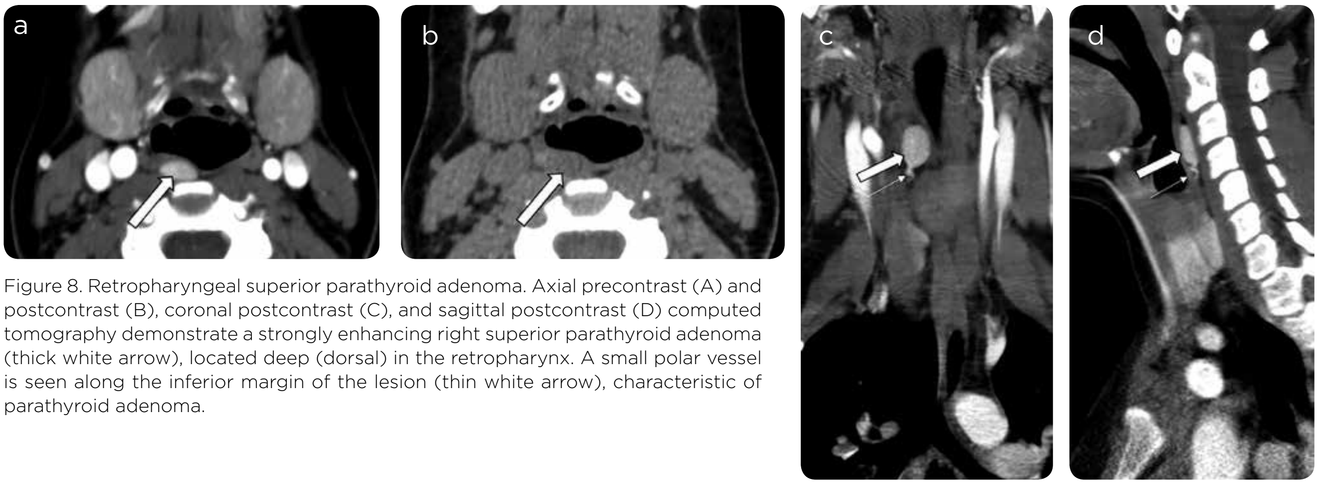


Figure 8. Retropharyngeal superior parathyroid adenoma. Axial precontrast (A) and postcontrast (B), coronal postcontrast (C), and sagittal postcontrast (D) computed tomography demonstrate a strongly enhancing right superior parathyroid adenoma (thick white arrow), located deep (dorsal) in the retropharynx. A small polar vessel is seen along the inferior margin of the lesion (thin white arrow), characteristic of parathyroid adenoma.

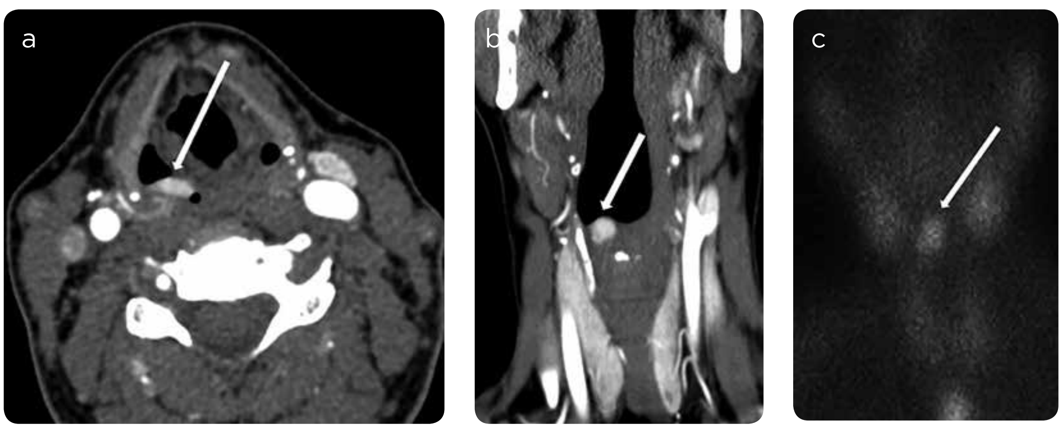


Figure 9. Parathyroid adenoma in the pyriform sinus. Axial (A) and coronal (B) postcontrast computed tomography show an ectopic parathyroid adenoma located in the right pyriform sinus, confirmed on the delayed coronal static single-photon emission computed tomography image (C).

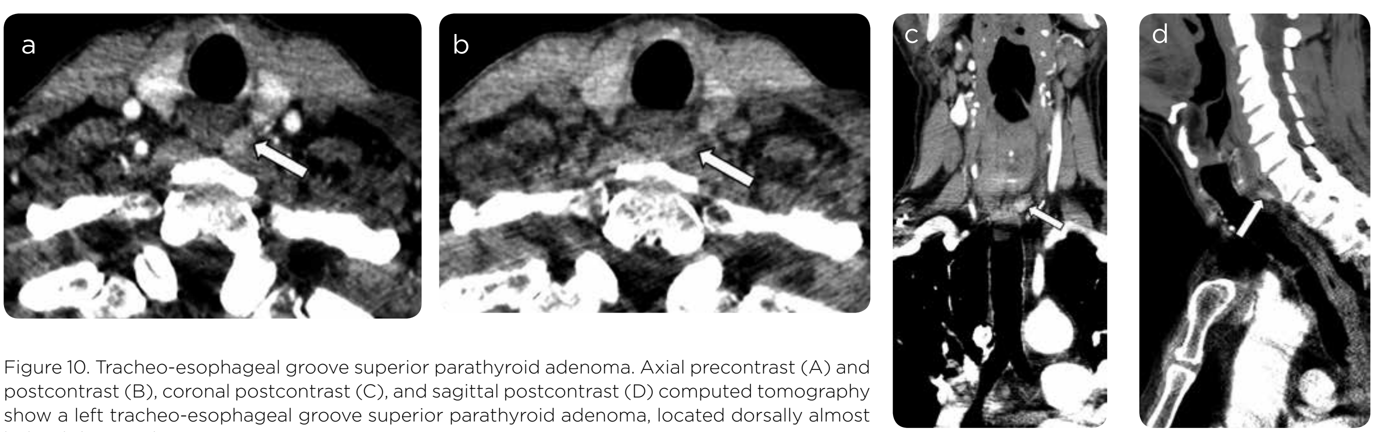


Figure 10. Tracheo-esophageal groove superior parathyroid adenoma. Axial precontrast (A) and postcontrast (B), coronal postcontrast (C), and sagittal postcontrast (D) computed tomography show a left tracheo-esophageal groove superior parathyroid adenoma, located dorsally almost behind the esophagus.

Figure 11. Multimodality localization of overly descended ectopic parathyroid adenoma. Ultrasound longitudinal (A) and transverse (B) images with corresponding color Doppler ultrasound (C, D) show a large hypo-echoic mass posterior and inferior to the left lobe of the thyroid gland with a surrounding arc of vascularity. The anterosuperior margin of the lesion is irregular (white arrow, A) and perhaps infiltrating the thyroid gland (possible carcinoma). Contrast CT axial (E, F) and sagittal (G) images confirm irregularity of the anterior superior margin of the lesion, which is inseparable from the thyroid gland (white arrow, E) but clearly separable inferiorly (black arrow, F). The lesion is large and posteriorly located in the tracheo-esophageal groove, indicative of an overly descended left superior parathyroid adenoma. Further characterization and staging with single-photon emission computed tomography/CT shows in the noncontrast axial CT image (H) a hypodense parathyroid adenoma (thick arrow) located behind the normal hyperdense thyroid gland (thin arrow). Fused axial (I), coronal (J), and sagittal (K) images demonstrate focal radiotracer uptake in the mass posterior to the inferior left thyroid lobe, posterior to the trachea, and to the left of the esophagus. No other areas of abnormal radiotracer uptake are seen. CT = computed tomography.

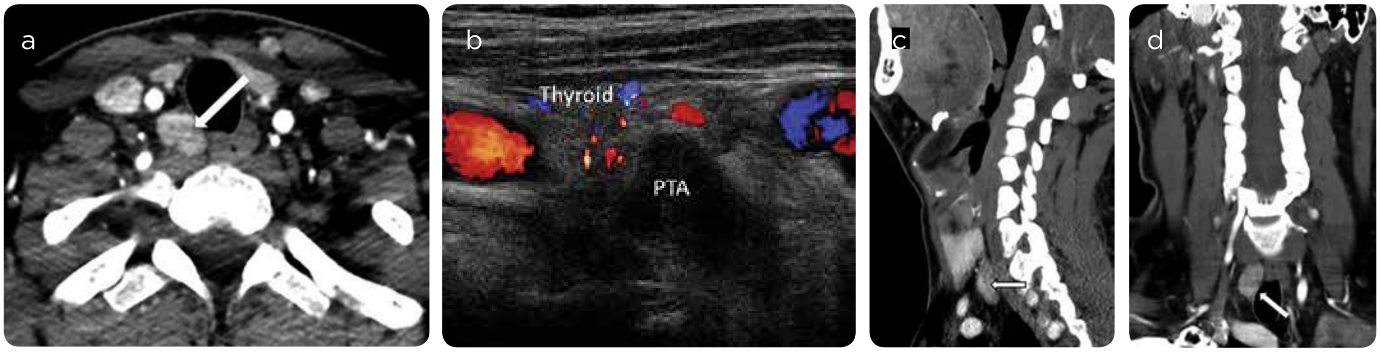


Figure 12. Overly descended superior parathyroid adenoma. Axial (A), coronal (B), and sagittal (C) postcontrast computed tomography show a large overly descended right superior parathyroid adenoma (white arrow) located inferior and dorsal to the inferior margin of the thyroid gland. Doppler ultrasound longitudinal plane (D) shows the overly descended right superior parathyroid adenoma located inferior to the thyroid gland.

In addition, SPECT/CT can better differentiate between thyroidal and nonthyroidal tissue and is significantly better at detecting smaller parathyroid glands than planar imaging (31). Finally, a meta-analysis of 24 studies demonstrated that SPECT/CT is superior to planar and SPECT techniques in localizing EPAs (30).

In general, dual-phase 99mTc sestamibi scintigraphy techniques accurately identify EPAs in the retro-esophageal space, thymus, and mediastinum (2,34,35). In addition, this modality has moderate or limited accuracy in detecting intrathyroidal or submandibular/undescended glands. Despite their availability and high sensitivity/specificity for ectopic localization, scintigraphy techniques are subject to multiple limitations. Sestamibi imaging has poor accuracy in detecting retropharyngeal glands and glands in the carotid sheath (because salivary glands uptake the radiotracer and can obscure findings) (2,3). Even combined protocols that perform planar scintigraphy followed by SPECT/CT report sensitivities that vary from 50 to 100% in detecting EPAs (3,8,19). Scintigraphy requires long imaging times (2 hours) and a modest radiation dose. Lastly, sestamibi scintigraphy has a low spatial resolution and has limited success for small glands and multigland disease (36,37). Although pinhole collimators can increase spatial resolution and help distinguish parathyroid lesions from thyroid tissue, their use can be time consuming when added to SPECT/CT protocols (38-41). Among scintigraphy techniques, we recommend the use of SPECT/CT because it provides both anatomic detail and functional information that enable precise localization and better surgical planning, particularly in cases of ectopia or when considering minimally invasive parathyroidectomy.

2.3 4DCT

In 4DCT, images are acquired in 4 phases: noncontrast, early arterial, late arterial, and delayed (venous). Parathyroid adenoma corresponds to an avidly enhancing (hyperdense) rounded lesion during the arterial phase. Modifications of the CT protocol to reduce the radiation dose include 1 to 3 phases, either a single arterial phase (42), or a combination of a noncontrast phase and a single contrast enhanced phase or 2 contrast enhanced phases (34). More so than the preceding modalities, 4DCT possesses a very high spatial resolution that delineates important anatomic landmarks and reveals the relationship of the adenoma to surrounding structures. For example, CT localizes the lesion superior versus inferior to the inferior thyroid artery and ventral versus dorsal to the TE groove (figure 10). In addition, CT accurately measures the distances from mediastinal or thyrothymic ligament lesions to the inferior margin of the thyroid gland and the superior margin of the manubrium (figures 5 b and 6 b). As a result, CT is well-equipped to guide the surgical approach. In a study of 40 patients with PHPT undergoing parathyroidectomy, 4DCT correctly localized 100% of ectopic lesions (3). 4DCT is particularly accurate for detecting EPAs in the carotid sheath (figure 7), retro-esophageal space (figure 8), and mediastinum (figures 6 a and b). 4DCT also distinguishes overly descended superior glands (figure 11 e and g) from orthotopic inferior glands by revealing their posterior-deep location and relation to the RLN. However, this modality has a limited ability to distinguish intrathyroidal adenomas and thyroid nodules, as both enhance similarly on 4DCT (34). The recommended anatomical coverage for 4DCT in the setting of parathyroid adenoma is from the level of the carina up to the base of the skull. This modality is commonly used to detect suspected EPAs in the setting of failed initial parathyroidectomy but is also becoming the index imaging modality of choice in many centers. Although 4DCT is rapid (2 min), not user dependent, and has a high sensitivity and positive predictive value in detecting EPAs, it has its disadvantages. 4DCT is relatively new and requires reader experience. This modality has limited success in identifying small glands, glands that may be obscured or confounded by co-existing posterior thyroid nodules, or multigland disease. Lastly, 4DCT requires the use of both ionizing radiation and intravenous iodinated contrast. The radiation dose to the thyroid from 4DCT is 6.02 mSv, as compared to 0.45 mSv from combined planar and SPECT/CT scintigraphy (43). The lifetime attributable risk of thyroid cancer from 4DCT in a standard 55-year-old female patient is 3 cases per 100,000 patients, as compared to 1 case per 100,000 patients from sestamibi scintigraphy (43). Although 4DCT confers more than twice the whole-body effective dose of radiation than combined planar and SPECT/CT scintigraphy (28 mSv versus 12 mSv), 4DCT does not meaningfully increase the lifetime risk of cancer (43).

2.4 Imaging in the Re-Operative Setting

Re-operative patients often suffer from recurrent or persistent hyperparathyroidism after a failed initial exploration. In multiple studies investigating the detection of parathyroid adenomas in re-operative patients, sestamibi scintigraphy performed better than ultrasound and plain CT with contrast (4,5). Sestamibi scintigraphy has a sensitivity between 65 and 67% and has a specificity of 100% (i.e., no false positives) in detecting adenomas in re-operative patients. Although ultrasound can assess for causes of failed initial exploration such as thyroid nodules or intrathyroidal lesions, it has a sensitivity between 41 and 48% in detecting adenomas in the re-operative setting (4,5). Meanwhile, plain CT with contrast has a sensitivity between 42 and 52% in detecting adenomas in the re-operative setting (4,5). It is important to note that although EPGs are not the only cause of recurrent or persistent hyperparathyroidism, they are the most common cause (1,4,5). Most surgeons will only perform re-operative parathyroidectomy after a failed bilateral neck exploration by an experienced surgeon if 2 imaging modalities colocalize the same lesion. Sestamibi scintigraphy and 4DCT constitute the preferred two-modality combination in this setting (3,7,34).

3. Surgical removal of ectopic parathyroid neoplasia

Surgical removal of parathyroid adenomas is the only definitive treatment for PHPT. In patients needing surgical treatment, diseased glands—whether orthotopic or ectopic—should be removed. In a study of 271 patients with PHPT, Moreno and colleagues found no significant differences in operative success rates between single adenomas at different locations (44). Nevertheless, the removal of EPAs routinely requires alternative surgical approaches from the removal of orthotopic adenomas.

3.1 Surgical Approach by Ectopic Site

Undescended and submandibular adenomas can be removed using a high oblique neck incision (5,36,45). EPGs in the carotid sheath can be identified through careful dissection of carotid sheath structures. Retroesophageal glands often lie flattened between the anterior surface of the prevertebral fascia of the cervical vertebrae and the posterior aspect of the esophagus. EPGs in the TE groove can be missed by surgeons who are reluctant to dissect near the RLN, or because such glands drift posteriorly to the prevertebral fascia. Adenomas located within the thymus or thyrothymic ligament often require transcervical delivery of the thyrothymic ligament and superior thymus (36,45,46). Such adenomas were found to have significantly longer mean operative times than adenomas at other sites (44). Anterior mediastinal glands can be removed using a transcervical approach, partial sternotomy, or mediastinoscopy. Middle and posterior mediastinal glands can be removed using a thoracoscopic left lateral approach or are occasionally amenable to angio-embolization. For thoracic glands, selective approaches such as anterior mediastinoscopy, robotic approaches, and standard thoracoscopic approaches produce less morbidity with associated faster recovery times than traditional sternotomy or open anterior lateral thoracotomy (19).

3.2 Surgical Approach in the Re-Operative Setting

The most common cause of persistent PHPT is surgeon inexperience in locating and adequately excising parathyroid neoplasia (7). As a result, ectopic adenomas can comprise up to 66% of missed adenomas in failed initial parathyroidectomies and are 4 times more common in the re-operative setting than in the primary setting (1,6). If a patient has persistent disease after having undergone exploration by an experienced surgeon, then EPA can be suspected. Repeat cervical exploration should only be attempted in cases that are definitively localized on repeat imaging, especially if the patient has undergone bilateral neck exploration. Blind repeat exploration after a comprehensive bilateral neck exploration has a high rate of failure alongside an increased risk of bleeding and nerve injury complications (5,47). As in the primary setting, the use of a cervical approach, median sternotomy, anterior mediastinotomy, or video-assisted thoracoscopic resection can be appropriate for the removal of mediastinal glands in the re-operative setting. As with index cases, we recommend routine use of intra-operative parathyroid hormone (PTH) monitoring in the re-operative setting, as it rapidly and accurately confirms the removal of hyperfunctioning lesions, and has been shown to increase the success rate of re-operative parathyroidectomy (48,49). A difficult exploration may warrant PTH sampling, extensive bilateral cervical exploration, blind thyroid lobectomy, cervical thymectomy, retro-esophageal or carotid sheath exploration, or ligation of the ipsilateral inferior thyroid artery (7,45,47). Pre-operative venous sampling may be helpful but requires the expertise of interventional radiology (50).

3.3 Surgical Approach for Nonlocalized Disease

For cases in which the lesion is not definitively localized before resection, we recommend an even higher index of suspicion for multigland disease as well as a careful and systematic surgical exploration. Superior parathyroid glands can be identified by exploring the orthotopic superior gland location, visceral central neck compartment posteriorly to the prevertebral fascia, superior pole of the thyroid, carotid sheath, TE groove, and retroesophageal space (6,45,48). Inferior parathyroid glands can be identified by exploring the orthotopic inferior gland location, inferior thyroid lobe, thyrothymic ligament, and any tongue of cervical thymus that is identified (45,48). If the enlarged parathyroid gland(s) is still not identified, consider performing cervical thymectomy on the side of the missing gland, as well as examining the thyroid lobe on the side of the missing gland, taking care to use intra-operative ultrasound if needed to assess for intrathyroidal lesions (6,45,48).

4. Conclusion

Ectopic parathyroid adenomas can be difficult to identify on imaging studies and difficult to remove during parathyroidectomies. Such glands are prevalent enough to merit a high index of suspicion among both radiologists and surgeons. Selecting the most appropriate preoperative imaging modality and correct surgical approach is essential for the successful management of EPAs. Understanding the relevant anatomy, incidence of ectopic disease, capabilities of various imaging modalities, and indications for different surgical approaches will help guide the management of patients with PHPT, whether caused by orthotopic or ectopic adenomas. Both high-volume experience and multidisciplinary care on the part of the surgeon, neuroradiologist, nuclear medicine physician, and imaging technician are critical for optimal outcomes.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Duke WS, Vernon HM, Terris DJ. Reoperative parathyroidectomy: Overly descended superior adenoma. Otolaryngol-Head Neck Surg. 2016;154:268-71.
2. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg. 2013;37:102-6.
3. Galvin L, Oldan JD, Bahl M, Eastwood JD, Sosa JA, Hoang JK. Parathyroid 4D CT and scintigraphy: What factors contribute to missed parathyroid lesions? Otolaryngol Head Neck Surg. 2016;154:847-53.
4. Gough I. Reoperative parathyroid surgery: The importance of ectopic location and multigland disease. ANZ J Surg. 2006;76:1048-50.
5. Jaskowiak N, Norton JA, Alexander HR, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. Ann Surg. 1996;224:308-20; discussion 320-321.
6. Silberfein EJ. Reoperative parathyroidectomy: Location of missed glands based on a contemporary nomenclature system. Arch Surg. 2010;145:1065.
7. Udelsman R. Approach to the patient with persistent or recurrent primary hyperparathyroidism. J Clin Endocrinol Metab. 2011;96:2950-8.
8. Noussios G, Anagnostis P, Natsis K. Ectopic parathyroid glands and their anatomical, clinical and surgical implications. Exp Clin Endocrinol Diabetes. 2012;120:604-10.
9. Shin JJ, Milas M, Mitchell J, Berber E, Ross L, Siperstein A. Impact of localization studies and clinical scenario in patients with hyperparathyroidism being evaluated for reoperative neck surgery. Arch Surg. 2011;146:1397-403.
10. Simeone DM, Sandelin K, Thompson NW. Undescended superior parathyroid gland: a potential cause of failed cervical exploration for hyperparathyroidism. Surgery. 1995;118:949-56.
11. Rioja P, Mateu G, Lorente-Poch L, Sancho JJ, Sitges-Serra A. Undescended parathyroid adenomas as cause of persistent hyperparathyroidism. Gland Surg. 2015;4:295-300.
12. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery. 1984;95:14-21.
13. Shen W, Düren M, Morita E, et al. Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg. 1996;131:861-7; discussion 867-9.
14. Fraker DL, Doppman JL, Shawker TH, et al. Undescended parathyroid adenoma: an important etiology for failed operations for primary hyperparathyroidism. World J Surg. 1990;14:342-8.
15. Billingsley KG, Fraker DL, Doppman JL, et al. Localization and operative management of undescended parathyroid adenomas in patients with persistent primary hyperparathyroidism. Surgery. 1994;116:982-9.
16. Okuda I, Nakajima Y, Miura D, Maruno H, Kohno T, Hirata K. Diagnostic localization of ectopic parathyroid lesions: developmental consideration. Jpn J Radiol. 2010;28:707-13.
17. Lappas D, Noussios G, Anagnostis P, Adamidou F, Chatzigeorgiou A, Skandalakis P. Location, number and morphology of parathyroid glands: results from a large anatomical series. Anat Sci Int. 2012;87:160-4.
18. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016;151:959.
19. Zerizer I, Parsaï A, Win Z, Al-Nahhas A. Anatomical and functional localization of ectopic parathyroid adenomas: 6-year institutional experience. Nucl Med Commun. 2011;32:496-502.
20. Chien D, Jacene H. Imaging of Parathyroid Glands. Otolaryngol Clin North Am. 2010;43:399-415.
21. Yeh MW, Barraclough BM, Sidhu SB, Sywak MS, Barraclough BH, Delbridge LW. Two hundred consecutive parathyroid ultrasound studies by a single clinician: the impact of experience. Endocr Pract. 2006;12:257-63.
22. Haciyanli M, Lal G, Morita E, Duh Q-Y, Kebebew E, Clark OH. Accuracy of preoperative localization studies and intraoperative parathyroid hormone assay in patients with primary hyperparathyroidism and double adenoma. J Am Coll Surg. 2003;197:739-46.
23. Sugg SL, Krzywda EA, Demeure MJ, Wilson SD. Detection of multiple gland primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. Surgery. 2004;136:1303-9.
24. Eslamy HK, Ziessman HA. Parathyroid scintigraphy in patients with primary hyperparathyroidism: 99mTc sestamibi SPECT and SPECT/CT. Radiographics. 2008;28:1461-76.
25. Ishibashi M, Nishida H, Hiromatsu Y, Kojima K, Uchida M, Hayabuchi N. Localization of ectopic parathyroid glands using technetium-99m sestamibi imaging: comparison with magnetic resonance and computed tomographic imaging. Eur J Nucl Med. 1997;24:197-201.
26. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. Am J Surg. 2006;191:418-23.
27. Krausz Y, Bettman L, Guralnik L, et al. Technetium-99m-MIBI SPECT/CT in primary hyperparathyroidism. World J Surg. 2006;30:76-83.
28. Kim SC, Kim S, Inabnet WB, Krynyckyi BR, Machac J, Kim CK. Appearance of descended superior parathyroid adenoma on SPECT parathyroid imaging. Clin Nucl Med. 2007;32:90-3.
29. Lavely WC, Goetze S, Friedman KP, et al. Comparison of SPECT/CT, SPECT, and planar imaging with single-and dual-phase 99mTc-Sestamibi parathyroid scintigraphy. J Nucl Med. 2007;48:1084-9.
30. Wong KK, Fig LM, Gross MD, Dwamena BA. Parathyroid adenoma localization with 99mTc-sestamibi SPECT/CT: a meta-analysis. Nucl Med Commun. 2015;36:363-75.
31. Zhen L, Li H, Liu X, Ge BH, Yan J, Yang J. The application of SPECT/CT for preoperative planning in patients with secondary hyperparathyroidism. Nucl Med Commun. 2013;34:439-44.
32. Serra A, Bolasco P, Satta L, Nicolosi A, Uccheddu A, Piga M. Role of SPECT/CT in the preoperative assessment of hyperparathyroid patients. Radiol Med. 2006;111:999-1008.
33. Ciappuccini R, Morera J, Pascal P, et al. Dual-phase 99mTc sestamibi scintigraphy with neck and thorax SPECT/CT in primary hyperparathyroidism: a single-institution experience. Clin Nucl Med. 2012;37:223-8.
34. Hoang JK, Sung W, Bahl M, Phillips CD. How to perform parathyroid 4D CT: Tips and traps for technique and interpretation. Radiology. 2014;270:15-24.
35. Johnson NA, Tublin ME, Ogilvie JB. Parathyroid imaging: technique and role in the preoperative evaluation of primary hyperparathyroidism. AJR Am J Roentgenol. 2007;188:1706-15.
36. Stack BC Jr, Moore ER, Belcher RH, Spencer HJ, Bodenner DL. Hormone, Relationships of parathyroid gamma counts, and adenoma mass in minimally invasive parathyroidectomy. Otolaryngol Head Neck Surg. 2012;147:1035-40.
37. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg. 2005;132:359-72.
38. Ho Shon IA, Yan W, Roach PJ, et al. Comparison of pinhole and SPECT 99mTc-MIBI imaging in primary hyperparathyroidism. Nucl Med Commun. 2008;29:949-55.
39. Tomas MB, Pugliese PV, Tronco GG, Love C, Palestro CJ, Nichols KJ. Pinhole Versus Parallel-Hole Collimators for Parathyroid Imaging: An Intraindividual Comparison. J Nucl Med Technol. 2008;36:189-194.
40. Bhatt PR, Klingensmith WC 3rd, Bagrosky BM, et al. Parathyroid imaging with simultaneous acquisition of 99mTc-Sestamibi and 123I: The relative merits of pinhole collimation and SPECT/CT. J Nucl Med Technol. 2015;43:275-81.
41. Klingensmith WC 3rd, Koo PJ, Summerlin A, et al. Parathyroid imaging: the importance of pinhole collimation with both single- and dual-tracer acquisition. J Nucl Med Technol. 2013;41:99-104.
42. Morón F, Delumpa A, Chetta J, Guffey D, Dunaway D. Single phase computed tomography is equivalent to dual phase method for localizing hyperfunctioning parathyroid glands in patients with primary hyperparathyroidism: a retrospective review. PeerJ. 2017;5:e3586.
43. Hoang JK, Reiman RE, Nguyen GB, et al. Lifetime attributable risk of cancer from radiation exposure during parathyroid imaging: Comparison of 4D CT and parathyroid scintigraphy. AJR Am J Roentgenol. 2015;204:W579-W85.
44. Moreno MA, Callender GG, Woodburn K, et al. Common locations of parathyroid adenomas. Ann Surg Oncol. 2011;18:1047-51.
45. Clark OH, Duh Q-Y, Kebebew E, eds. Atlas of endocrine surgical techniques. Philadelphia, PA: Saunders/Elsevier; 2010.
46. Perrier ND, Edeiken B, Nunez R, et al. A novel nomenclature to classify parathyroid adenomas. World J Surg. 2009;33:412-6.
47. Morris LF, Lee S, Warneke CL, et al. Fewer adverse events after reoperative parathyroidectomy associated with initial minimally invasive parathyroidectomy. Am J Surg. 2014;208:850-5.
48. Stack, BC, Bodenner DL, eds. Medical and surgical treatment of parathyroid diseases. Cham, Switzerland: Springer International Publishing; 2017.
49. Irvin GL, Molinari AS, Figueroa C, Carneiro DM. Improved success rate in reoperative parathyroidectomy with intraoperative PTH assay. Ann Surg. 1999;229(6):874-8; discussion 878-9.
50. McIntyre CJ, Allen JL, Constantinides VA, Jackson JE, Tolley NS, Palazzo FF. Patterns of disease in patients at a tertiary referral centre requiring reoperative parathyroidectomy. Ann R Coll Surg Engl. 2015;97:598-602.

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