Case Report

A Case Report on Persistent Primary Hyperparathyroidism in a Post-Total Thyroidectomy Patient

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ABSTRACT: We report a patient with papillary thyroid carcinoma, status post total thyroidectomy and radioactive iodine therapy, who presents with symptoms of primary hyperparathyroidism – uncommon in post-thyroid surgery patients. The patient was suspected to have a parathyroid adenoma but no lesion was localized on ultrasound and SPECT/CT – the current gold standard for parathyroid adenoma detection. Four-dimensional computed tomography (4D CT) was performed, an innovation for parathyroid adenoma detection, which yielded positive results. Patient underwent minimally-invasive parathyroidectomy and histopathology confirmed that the lesion was indeed a parathyroid adenoma. Though 4D CT alone is superior in sensitivity and comparable in specificity with the current gold standard, multi-modality assessment increases the confidence of the diagnosis.

Keywords: *4D computed tomography; 4D CT; Four-dimensional computed tomography; Parathyroid adenoma; Primary hyperparathyroidism*

INTRODUCTION

Patients who undergo total thyroidectomy are at risk of developing hypoparathyroidism due to the inadvertent removal or devascularization of the parathyroid glands during surgery. This is the most common complication in post-thyroidectomy patients. Thus, the development of hyperparathyroidism is unexpected in these patients and should raise suspicion for other endocrine disorders, such as multiple endocrine neoplasm (MEN). Case reports on post-thyroid surgery patients developing hyperparathyroidism are associated with irradiation procedures leading to the development of parathyroid neoplasms. Hyperparathyroidism also develops in patients with auto-transplanted parathyroid glands that became reactively hyperplastic and hyperfunctioning after a prolonged period of hypocalcemia.[1]

Parathyroid adenomas are benign hormone secreting tumors involving one or more parathyroid glands. A solitary parathyroid adenoma is the most common cause of primary hyperparathyroidism (approximately 80% of cases), as the hyperplastic tissues of the adenoma produce parathyroid hormones.[2]

Primary hyperparathyroidism secondary to parathyroid adenoma causes increased bone resorption, decreased phosphorus reabsorption, increased calcium absorption in the intestines, and increased calcium reabsorption in the kidneys. Patients may present with nephrolithiasis with or without urinary symptoms, muscle weakness, arthralgia, osteoporosis, as well as psychiatric and cognitive dysfunction (depression, anxiety, cognitive impairment, among others). However, in most cases, patients remain asymptomatic but with elevated parathyroid hormone and calcium levels. [2,5]

Detection of parathyroid adenomas traditionally utilizes ultrasonography and scintigraphy, both of which are considered first line modalities in the detection of adenomas. Recent imaging developments have led to the emergence of the single-photon emission computed tomography/computed tomography (SPECT/CT). SPECT. Much like scintigraphy, SPECT/CT utilizes radiotracers (most commonly, technetium-99m (^{99m}Tc) sestamibi) which aids in the localization of the adenoma by demonstrating the degree of tracer uptake of the nodule, reflective of its activity. SPECT/CT is the current gold standard in pre-operative detection of parathyroid adenomas because it provides functional information derived from SPECT with the anatomical information derived from plain CT.[3] However, several imaging pitfalls have been identified. In a study by Gotthardt et al, they found that the size, the location, and the number of adenomas matter. Smaller lesions were harder to detect using scintigraphy, and thyroid gland uptake masks multi-gland parathyroid adenomas. Superiorly located parathyroid adenomas are also likely missed due to their deeper location.[5] To address these pitfalls, new imaging techniques, such as the 4D computed tomography, have been developed, though still highly underutilized.

4D computed tomography is a contrast enhanced multiphasic imaging technique used in the detection and differentiation of adenomas from other mimics. It is a form of angiography with tracking and timing designed to localize parathyroid glands and detect pathologies. Proponents of the modality recommends its use as a second line modality if the first line modalities (ultrasound and scintigraphy/SPECT) fail to demonstrate a parathyroid lesion. It provides accurate anatomic localization of the adenoma, and allows surgeons to perform minimally invasive parathyroidectomies. 4D CT is also useful in in localizing ectopic and tiny adenomas, as well as in the evaluation of the parathyroid glands in post-surgical patients because of its superiority in providing greater anatomic detail.[2]

Parathyroid adenomas typically exhibit hypoattenuation in the non-enhanced CT images, with peak enhancement in the arterial phase, and subsequent washout in the following phases with complete washout noted in the delayed phase. To aid clinicians and surgeons, the following information are deemed essential in the radiologist's report: (1) number of gland involvement, (2) precise location, and (3) size.[2]

This is a known case or papillary thyroid carcinoma, status post-total thyroidectomy and post-radioactive iodine therapy patient, presenting with symptoms of primary hyperparathyroidism post-operatively. No identifiable parathyroid lesion was detected in the neck ultrasound and SPECT/CT. Patient was then advised to undergo 4D CT scan for further evaluation.

CASE

This is the case of a 61-year-old, Filipino, female, from Cainta, Rizal, status post total thyroidectomy and radioactive iodine therapy for papillary thyroid carcinoma 12 years prior to consult. Her other co-morbids include hypertension, diabetes mellitus, and dyslipidemia. The patient initially presented with low back pain in the same year that she underwent the thyroid surgery. Initial diagnostics revealed microscopic hematuria (RBC 10-12/hpf; Normal range: 0-2 /hpf) and pyuria (WBC 15-18/hpf; Normal range: 0-3/hpf) on urinalysis. Bilateral nephrolithiases were also detected on ultrasound of the kidneys and urinary bladder (KUB). The patient was prescribed Co-amoxiclav 625 mg/tab to treat the suspected infection for 1 week and Sambong and potassium citrate three times a day as supplements for the nephrolithiases.

Eleven years and ten months after the initial consult, repeat urinalysis and KUB ultrasound revealed persistent microscopic hematuria and unchanged nephrolithiasis on the right. At this point, her medications were continued, save for the antibiotics, and patient underwent extracorporeal shockwave lithotripsy (ESWL) for the right-sided nephrolithiasis. On follow up eleven years and nine months prior, there was resolution of microscopic hematuria on urinalysis, hence current medications were discontinued and replaced with calcium carbonate supplementation.

Six years prior, there was noted recurrence of microscopic hematuria on routine urinalysis. She now complained of vague bone pains, dysuria, and palpitations. These symptoms were suggestive of a hypercalcemic state. Initial diagnostics confirmed this as the ionized (iCa) was found to be at the upper normal limit (Patient iCa: 1.26 mmol/L; Normal range of iCa: 1.12 – 1.32 mmol/L) and total calcium (TCa) levels were found to be elevated (Patient TCa: 2.51 mmol/L; Normal range of TCa: 2.23 – 2.5 mmol/L). Parathyroid hormone (PTH) levels were normal (Patient PTH: 60.4 pg/mL; Normal range of PTH: 15-68.3 pg/mL).

Since the patient was taking calcium carbonate supplements, this was halted as it may have been causing the hypercalcemia. Serial serum calcium levels were re-measured after halting the supplements, and the parameters were still at the upper normal limit or elevated (iCa: 1.25 mmol/L; TCa: 2.44-2.66 mmol/L). Repeat PTH levels were now borderline elevated (PTH: 67.62 pg/mL; Normal range of PTH: 15-68.3 pg/mL). A hyperparathyroid state was then suspected. The patient was advised to undergo SPECT/CT and neck ultrasound for possible detection of a parathyroid adenoma - the most common cause of primary hyperparathyroidism. Both the ultrasound and SPECT/CT revealed no parathyroid focus. On follow-up, the serum calcium levels and parathyroid hormone levels were persistently elevated. Patient experienced occasional back pain and dysuria in the interim, but was reported to be tolerable.

One year prior, she experienced hypogastric pain, and there was recurrence of the microscopic hematuria on routine urinalysis. CT stonogram was done which revealed an obstructing distal ureterolithiasis. The patient underwent three sessions of ESWL within that year. After the ESWL, repeat CT stonogram was done which showed resolution of the obstructing ureterolithiasis.

Four months prior, there was persistence of symptoms. The patient was advised a repeat neck ultrasound and SPECT/CT which still yielded negative results (Figure 1). Vitamin D levels were found to be normal (Patient 25OH Vit D: 75.8 ng/dL; Normal 25OH Vit D: > 30 ng/dL). The normal vitamin D levels pointed toward a primary hyperparathyroid state (usually presenting as normal to high vitamin D), rather than a familial hypocalciuric hypercalcemia, which presents with low vitamin D levels.

On review of systems, the patient complained of weight loss, dry mouth, nausea, insomnia, and difficulty concentrating, symptoms characteristic of a hyperparathyroid state. Patient denied family history of thyroid or parathyroid disorders. The patient denied smoking or use of illicit drugs, or regular consumption of alcoholic beverages.

On physical examination, the patient had stable vital signs (BP 110/80, HR 95 bpm, RR 20 cpm, and T 37C). No masses noted on palpation of the neck region.

A 4D CT scan was done to rule out any ectopic or tiny parathyroid adenomas which may not have been detected by the neck ultrasound and SPECT/CT. Images were obtained by a multidetector Siemens 236 Somatom Definition AS 64092 CT machine. The images obtained were 3mm and 1 mm axial images with coronal and sagittal reconstructions. The scan revealed a tiny, low-attenuating, nodular focus in the left paratracheal region at the level of the C6 vertebra, at least 0.9 cm inferior to the hyoid bone and exhibiting peak enhancement in the arterial phase and subsequent washout in the delayed phases. The focus measured approximately 0.6 x 0.3 x 0.5 cm (craniocaudal x width x anteroposterior measurements). (Figure 2). The patient underwent minimally-invasive parathyroidectomy and histopathology confirmed that the lesion localized on 4D CT was indeed a parathyroid adenoma. Immediate post-surgical blood tests show that her parathyroid hormone and calcium levels went down to normal levels after the resection (See Figure 3). The patient has since been clinically well and her serum calcium and parathyroid hormone levels have remained normal after six months of follow up.

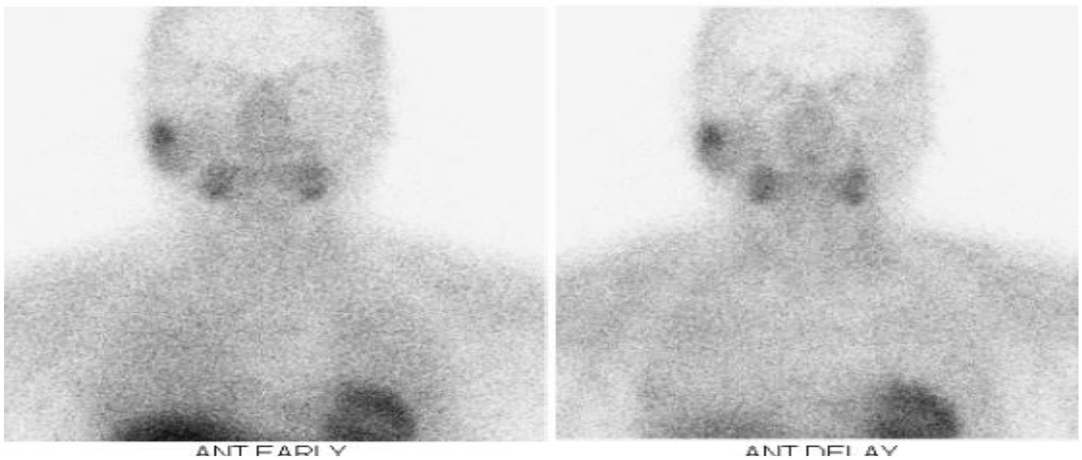

Figure 1. Representative images of the SPECT study dated December 2018. The image shows the early and delayed phases of the scintigraphy study. Findings were negative for a parathyroid lesion.

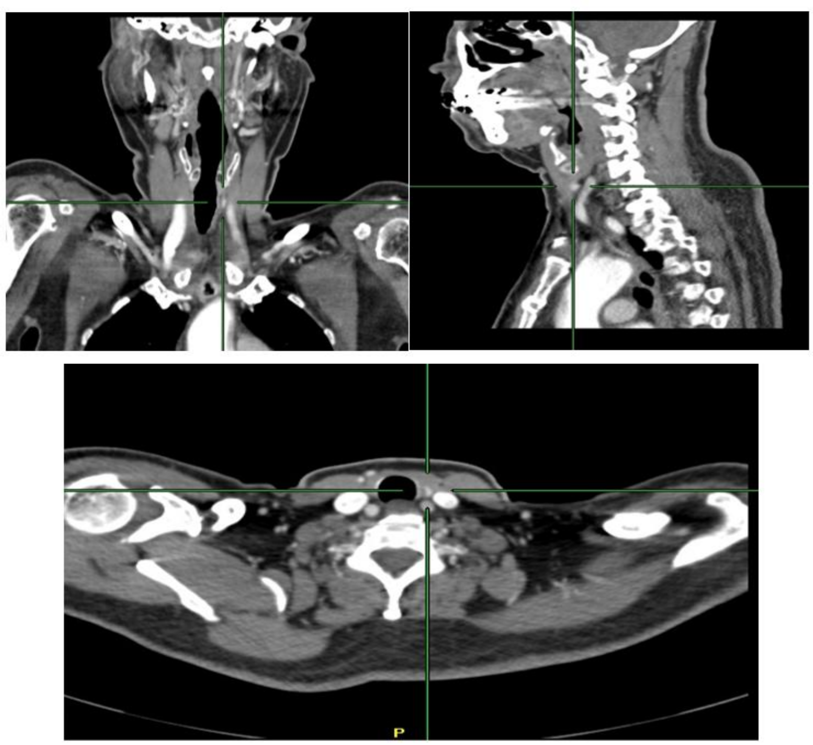

Figure 2. Representative images of the 4D CT study dated April 2019 (Upper left – coronal; Upper right – sagittal; Lower – axial). The images show a tiny low attenuating nodular focus in the left paratracheal region at the level of the C6 vertebra at least 0.9 cm inferior to the hyoid bone exhibiting peak enhancement in the arterial phase, measuring approximately 0.6 x 0.3 x 0.5 cm (CC x W x AP).

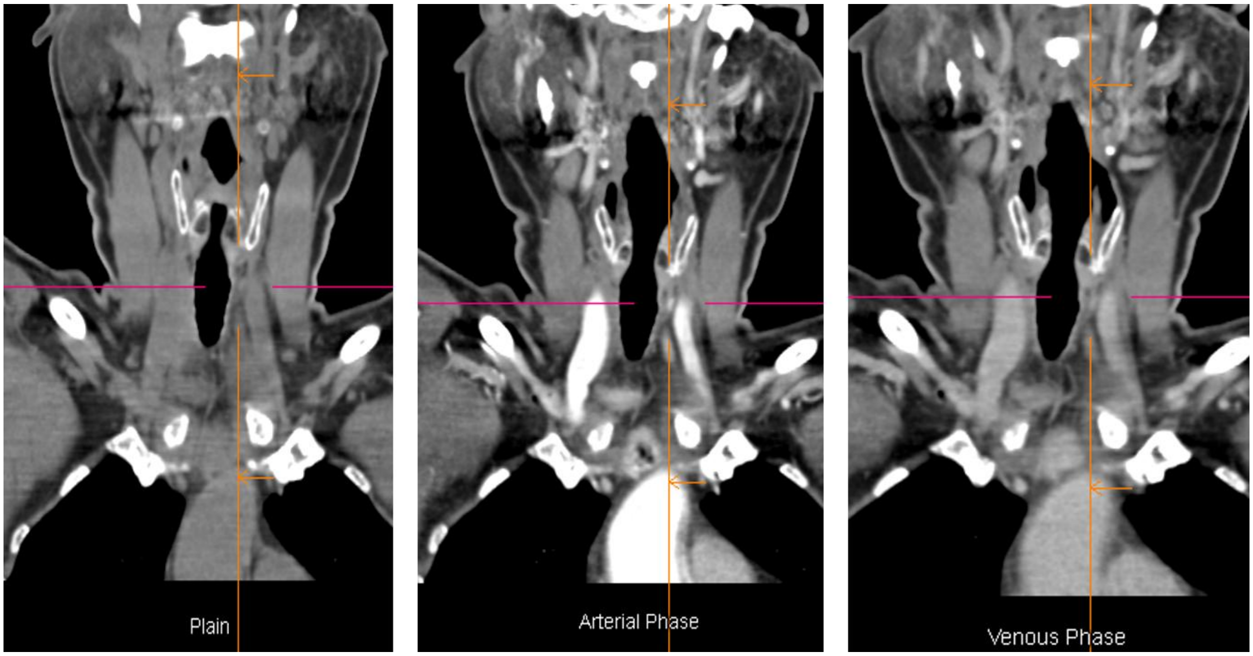

Figure 3. Representative images of the 4D CT study dated April 2019 (RIGHT TO LEFT: Plain, arterial phase, and venous phase). The images show a tiny low attenuating nodular focus in the left paratracheal region at the level of the C6 vertebra at least 0.9 cm inferior to the hyoid bone exhibiting peak enhancement in the arterial phase and subsequent washout in the venous phase, measuring approximately 0.6 x 0.3 x 0.5 cm (CC x W x AP).

DISCUSSION

The patient presented with a myriad of symptoms consistent with primary hyperparathyroidism. Since this is uncommon in post-thyroidectomy patients, it is important to consider other possible causes of hyperparathyroidism and hypercalcemia.

In all patients presenting with hypercalcemia, any form of calcium supplementation must be halted to rule out an iatrogenic cause of hypercalcemia. In this case, the hypercalcemia persisted even after calcium supplementation was halted. Chronic kidney disease (CKD) must also be ruled out in patients with hypercalcemia, but as the patient had normal creatinine levels and normal-sized kidneys with no sonographic signs of parenchymal disease, CKD was ruled out as well. It is then more likely that the etiology is PTH-dependent.[6]

Between the two causes of PTH-dependent hypercalcemia, the cause is most likely primary hyperparathyroidism due to the normal vitamin D levels, as compared to familial hypocalciuric hypercalcemia (FHH) which presents with low vitamin D levels. Primary hyperparathyroidism is commonly caused by a single adenoma, but the absence of an identifiable adenoma or hyperplasia on initial neck ultrasound and the gold standard SPECT/CT makes this diagnosis less likely. Clinical syndromes associated with hyperparathyroidism must also be ruled out. MEN 2A and 2B are possible differentials as the patient has history of thyroid cancer. However, these can be ruled out since the patient had a history of papillary thyroid carcinoma, and not the medullary type seen in MEN 2A and MEN 2B.[6, 7] The absence of adrenal or pancreatic masses on CT scan also rule out the aforementioned diagnoses.

The 4D CT scan was done to rule out any tiny or ectopic parathyroid adenomas which may not have been detected by the neck ultrasound and SPECT/CT. There is no standard protocol regarding use of the 4D CT scan, and this varies from institution to institution. The variations in the protocol takes into consideration the CT machine used, the radiation dose, the scope of the study, and the amount of contrast administered. Rodgers et al was among the first proponents of the 4D CT in 2006. They recommended a triphasic scan comprised of a pre-contrast, arterial, and delayed phases, with an area of coverage from the lower margin of the mandible down to the upper mediastinum. Approximately 120 mL of iodinated contrast (Optiray 300) was administered through a gauge 18 antecubital vein catheter, and phasic images were taken in 25 second intervals.[8]

Wojtczak et al and Kelly et al both suggested the use of four phases, comprised of a pre-constrast, early arterial, venous, and a delayed phase for the former and pre-contrast, arterial, early delayed, and late delayed for the latter.[9, 10] The area of coverage of Kelly et al's protocol spans from the maxillary teeth down to the carina. They administered a contrast dose of 100mL via an 18-gauge catheter and with each phase taken in 30 second intervals, save for the late delayed phase which was taken 45 seconds after the early delayed phase. Zeina et al has a similar protocol, but with an area of coverage from the external auditory meatus to the carina, and with contrast phases taken at 25, 60, and 90 seconds post-contrast bolus.[11] The rationale of the additional phases is to better evaluate the attenuation of the parathyroid adenoma overtime and differentiate it from other surrounding structures. Vu et al evaluated the attenuation of the different neck structures when compared to parathyroid adenomas. They found that parathyroid adenomas appear more hypodense in non-contrast images, shows greater increase in density in the early arterial phase, and exhibits faster contrast washout relative to the thyroid gland. Thyroid nodules, on the other hand, minimally enhance in the arterial phase and persistently enhance in the venous phase, exhibiting gradual washout in the late delayed phases. Tortuous vessels are often mistaken for adenomas, and this may be avoided by identifying and tracking the vasculature during the early arterial phase. Likewise, normal lymph nodes appear isoenhancing relative to the surrounding muscles.[12] With the increasing knowledge on the attenuation of the different neck structures, other protocols have abandoned the need to do the late delayed phase, with some only performing the early arterial phase to reduce the risk of iatrogenic cancers (especially in the thyroid) from the radiation.

In deciding on the most suitable protocol for The Medical City, the team was guided by the ALARA principle – as low as reasonably achievable; thus, the radiation dose, contrast dose, and area of coverage were decided upon with this in mind. The Medical City's 4D CT protocol was referenced from Hoang et al and modified based on the functions of the institution's CT scan machine.[2] The area of coverage is from the angle of the mandible down to the carina, which is similar to the institution's neck CT coverage, but extended down to the carina to cover for any ectopic parathyroid adenomas which are commonly found in the superior mediastinum. Plain, early arterial, and venous/delayed phases were performed to better evaluate the adenoma by characterizing its attenuation in the aforementioned phases. The contrast dose was set at 75 mL and delivered through a gauge 20 right antecubital venous access. The early arterial phase images were taken 2 seconds after the full contrast dose, while the delayed images were taken 25 seconds after.

Several studies have compared the sensitivities and specificities of the different modalities in detecting parathyroid lesions, as summarized in Table 1.[2] Rodgers et al determined that the sensitivity of 4D CT in localization of parathyroid adenomas was at 70%, much higher compared to the sensitivity of ultrasound and scintigraphy which are at 29% and 33%, respectively.[8] Similarly, Eichihorn-Wharry also found that 4D CT was superior, with 70% sensitivity compared to scintigraphy which was 62% sensitive.[13] Galvin et al compared the sensitivities of the different modalities in accurately diagnosing single gland and multi glandular disease; 4D CT was the most sensitive, with 88% sensitivity in single gland detection and 53% sensitivity in detecting multi glandular involvement. They identified factors contributing to missed lesions in scintigraphy, namely: multi-gland disease, poor tracer uptake, and masking by adjacent structures such as the thyroid and the submandibular glands. As for 4D CT, factors include: multinodular goiter, noisy images in patients with large habitus, and unsuspected multi-gland disease.[14]

Table 1. Summary table of multi-modality sensitivity and specificity studies in the detection of parathyroid adenomas. The cited studies exhibit the superiority of 4D CT in the determination and lateralization of parathyroid adenomas compared to ultrasound and SPECT (Referenced and adapted from a Radiopedia article by Hoang JK).

	Ultrasound		**SPECT**		**4D CT**	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Rodgers et al [a]	29 %		33 %		70 %	
Eicchorn-Wharry et al [a]			62 %		73 %	
Galvin et al [a]						
Single gland			50 %		88 %	
Multi-gland			24 %		53 %	
Kukar et al [a]						
Single gland	55 %		61 %		93 %	
Multi-gland	13 %		0 %		32 %	
Chazen et al [b]						
Single gland					85.7%	100%
Multi-gland					42.9 %	100%
Yeh et al [a]			65%	98%	85%	92%
Minhas et al [a]					92.3 %	80%
Beland et al [a]					92%	82%

a – Determined laterality

b – Determined specific quadrant localization

Prior to the advent of 4D CT, a negative ultrasound and SPECT/CT study warrants a highly-invasive radical neck exploration to identify a possible parathyroid adenoma. The ability of 4D CT to localize parathyroid adenomas in ultrasound and SPECT/CT-negative cases spares patients from undergoing highly-invasive exploration procedures. 4D CT's accuracy in localizing the specific quadrant of the parathyroid adenoma also minimizes the need for radical parathyroidectomy in favor of minimally-invasive parathyroidectomy.

The American Association of Endocrine Surgeons still recommends ultrasound and SPECT/CT as first-line modalities before considering 4D CT.[20] A paper by Kedarisetty et al argues that 4D CT must be reserved for SPECT/CT negative cases that are still being suspected to have an adenoma because of cost, radiation dose, and availability of technology. Ultrasound has a sensitivity, specificity, and accuracy of 44%, 86%, and 49%, respectively. SPECT/CT alone has a sensitivity, specificity, and accuracy of 77%, 71%, and 77%, respectively. On the other hand, 4D CT alone has a sensitivity, specificity, and accuracy of 80%, 75%, and 79%. Combined ultrasound and SPECT/CT are 85% sensitive, 83% specific, and 85% accurate. They also found that combined SPECT/CT and 4D CT had a sensitivity of 88%, specificity of 100%, and accuracy of 89%.[21]

Conclusion

The use of 4D CT was beneficial for the patient who presented with persistent primary hyperparathyroidism with seemingly no identifiable focus based on neck ultrasound and the current gold standard for parathyroid adenoma imaging, SPECT/CT.

The 4D CT gives the radiologist a better understanding of the patient's anatomy and guides the surgeons in their surgical planning as it is superior in specific quadrant localization. Accurate localization reduced the need to perform invasive radical neck dissections in favor of localized parathyroidectomies, which affected the patient's post-operative outcomes and hospitalization costs.

Our case report shows that the 4D CT is an effective additional diagnostic tool for parathyroid adenoma detection. Multi-modality assessment increases the over-all sensitivity, specificity, and accuracy in detecting parathyroid adenomas, increasing the radiologists' confidence in the diagnosis.

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