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WORD COUNT	2813	TIME SUBMITTED	15-FEB-2023 03:03PM
		PAPER ID	96629430

Name of Journal: *World Journal of Radiology*
Manuscript NO: 82638
Manuscript Type: MINIREVIEWS

Multi-modality Parathyroid Imaging: A shifting paradigm

Shrea Gulati, Sunil Chumber, Gopal Puri, Stanzin Spalkit, N A Damle, CJ Das

Abstract
The goal of parathyroid imaging in hyperparathyroidism is not diagnosis, rather it is the localization of the cause of hyperparathyroidism for the best therapeutic approach. Hence, the role of imaging to accurately and precisely localize the abnormal parathyroid tissue is more important than ever to facilitate minimally invasive parathyroidectomy over bilateral neck exploration. The common causes include solitary parathyroid adenoma, multiple parathyroid adenomas, parathyroid hyperplasia and parathyroid carcinoma. It is highly imperative for the radiologist to be cautious of the mimics of parathyroid lesions like thyroid nodules and lymph nodes and be able to differentiate them on imaging. The various imaging modalities available include high resolution ultrasound of the neck, nuclear imaging studies, four-dimensional computed tomography (4D CT) and magnetic resonance imaging (MRI). Contrast enhanced ultrasound (CEUS) is a novel technique which has been recently added to the armamentarium to differentiate between parathyroid adenomas and its mimics. Through this review article we wish to review the imaging features of parathyroid lesions on various imaging modalities and present an algorithm to guide their radiological differentiation from mimics.

INTRODUCTION

Primary hyperparathyroidism is the commonest cause of hypercalcemia resulting from pathologies intrinsic to the parathyroid glands.[1] It manifests biochemically as raised parathyroid hormone and calcium levels.[2] Primary hyperparathyroidism is most commonly due to a single benign parathyroid adenoma (approximately 80% of the patients), with multiglandular disease seen in approximately 15-20% of patients.[3] Primary hyperparathyroidism is due to multiglandular involvement consisting of either multiple adenomas or hyperplasia of all 4 glands (5-10%) and very rarely by parathyroid carcinoma (<1%).[4] The definitive management is achieved by surgical excision of the abnormal parathyroid tissue. Preoperative imaging is mandatory in deciding the surgical approach and improves localisation of the abnormal gland. The commonly accepted modalities to guide imaging include ultrasound, 4-dimensional computed tomography (4-D CT), magnetic resonance imaging (MRI) and nuclear medicine studies whereas CEUS is the new kid on the block. In this review, we would like to revisit the characteristic imaging findings on various modalities and will present an algorithm of differentiating parathyroid adenomas from their mimics.

ANATOMY:

The usual number of parathyroid glands is four, but this can vary. Some persons have more than four parathyroid glands. The normal shape of the parathyroid gland is ovoid or bean shaped and it measures 4-6 mm in length, 2-4 mm in width and 1-2 mm in thickness. The plane of the recurrent laryngeal nerve (RLN), identified by the trachea-oesophageal groove helps identify the superior and inferior parathyroid glands, the superior is posterior to the RLN while the inferior is anterior to the RLN.[5] In 16 % of the individuals the parathyroid glands are ectopically located.[6] The embryological origin of the inferior parathyroid glands is from the third pharyngeal pouch while the origin of the superior parathyroid gland is from the fourth pharyngeal pouch. The longer course of embryological migration of the superior parathyroid glands makes it more prone for ectopic location. Ectopic superior parathyroid glands are found in the retropharyngeal or retroesophageal locations, while ectopic inferior parathyroid may be seen within the carotid sheath or mediastinum (Figure 1).[7] Uncommonly, there may be failure of descent of the inferior parathyroid glands, which may be finally located cephalad to the superior parathyroid gland.[8]

ROLE OF IMAGING:

The diagnosis of primary hyperparathyroidism is made biochemically with demonstration of raised parathormone (PTH) levels. **The role of radiology in hyperparathyroidism is not diagnosis, rather it is accurate localisation and surgical planning.**[5] There are two approaches to surgical management of hyperparathyroidism - bilateral neck exploration (BNE) and minimally invasive parathyroidectomy (MIP). BNE is the conventional surgical approach which involves a large midline surgical incision, exploration and examination of all four parathyroid glands and excision of the abnormal tissue. Due to the large incision involved and meticulous exploration, it is associated with excellent long term cure rates.[9] The downside of this meticulousness is the associated higher risk of recurrent laryngeal nerve damage and poor cosmesis. MIP involves a unilateral small incision on the affected side and surgical removal of only the pathological gland identified precisely and accurately by preoperative imaging studies.[5] As per the European Society of Endocrine Surgeons (ESES), in experienced hands keeping in view the indications and contraindications of the surgery, MIP is a reliable and safe procedure with equivalent cure rates.[9] As compared to BNE, MIP is associated with shorter operative times, better cosmesis, shorter hospital stays and therefore lower costs.[10]

IMAGING:

The imaging techniques available for parathyroid imaging include high resolution ultrasound of the neck, Tc99m sestamibi scan, 4D CT and MRI.

HIGH RESOLUTION ULTRASONOGRAPHY:

Duplex ultrasound with a linear array transducer with 10 MHz or higher frequency is used for imaging of the parathyroid glands. With the patient in supine position and mild neck extension (using a pillow under the upper back), the neck is scanned in both transverse and longitudinal planes focussing on the region behind the thyroid gland. The normal location of parathyroid lesions is lateral to the trachea and oesophagus and medial to the carotid artery and the jugular vein. This knowledge helps to closely inspect the expected locations meanwhile differentiating it from close mimics. The small size and deep location of the normal parathyroid gland makes it non-identifiable on ultrasound. Parathyroid adenomas which are larger than 1 cm in size are readily visible on ultrasound. The sonographic detection of small parathyroid adenomas, especially those <1 cm in size can be enhanced by using graded compression technique.[11] Parathyroid adenomas are oval/ bean shaped, well circumscribed lesions which are homogenously hypoechoic as compared to the neighbouring thyroid gland (Figure 2). Color Doppler provides associate information of the origin and course of the feeding artery of the parathyroid adenoma.[12,13] This is attributed to the high vascularity of the parathyroid adenomas which are supplied by an enlarged feeding inferior thyroidal artery (Feeding vessel sign). Spectral Doppler can determine the blood flow velocity of the feeding artery and get information of a low resistive index. This polar vascularity sign helps in differentiation from a lymph node which typically shows central hilar vascularity on Doppler.[14] Along with hypervascularity of the affected parathyroid, the ipsilateral thyroid gland can also show hyperaemia in 85% of the cases and this may serve as a surrogate marker of underlying parathyroid adenoma.[11,14] In patients with known syndromes like MEN-1 (Figure 3), multiple adenomas can be seen and identification of a single adenoma should not lead to a false sense of satisfaction of search. Uncommonly, parathyroid adenomas can show atypical features such as ectopic location, completely intrathyroidal, internal areas of cystic degeneration, heterogenous internal echotexture rather than the homogenous hypoechoic echotexture which make prospective sonographic diagnosis difficult.[15–18]

High resolution ultrasound has the advantage of non-involvement of radiation, low cost and easy availability although it is highly operator dependant in the detection of parathyroid adenomas but has a sensitivity of 84% in the hands of an experienced sonologist.[19] The two most important differentials of parathyroid adenomas are thyroid nodules and lymph nodes, and ultrasound is a useful modality for their differentiation (Table 1). The oesophagus and the longus colli muscle can sometimes mimic parathyroid adenomas.[14]

CONTRAST-ENHANCED ULTRASOUND (CEUS):

CEUS is the new armamentarium added in the evaluation of parathyroid adenomas. The differentiation of parathyroid adenomas from parathyroid hyperplasia as well as non-parathyroid lesions like lymph nodes and thyroid nodules is difficult on conventional ultrasound. [7,20]Studies have demonstrated the use of contrast enhanced ultrasound as a novel technique in the differentiation of these entities.[21–23] On CEUS, parathyroid adenomas show early peripheral hyperenhancement with central washout in the later phases (Figure 4).[21] Parathyroid hyperplasia on the other hand shows more homogenous contrast uptake.[21] Physiological lymph nodes show homogenous and centrifugal pattern of enhancement.[24–26] Thyroid nodules tend to show homogenous hyperenhancement with a fast wash-in and slow washout pattern.[21]

SHEAR WAVE ELASTOGRAPHY:

This is a newer modality which has been explored for distinguishing parathyroid adenoma from the neighbouring thyroid tissue. Parathyroid adenomas show a significantly lower tissue elasticity than thyroid tissue. This may serve as an additional differentiating feature between the two entities.[27]

PARATHYROID SCINTIGRAPHY:

The most common radiotracer used for imaging parathyroid glands is sestamibi with ^{99m}Tc. Both thyroid and parathyroid glands take up sestamibi, however the differentiating point is that the uptake by hyperplastic or adenomatous parathyroid tissue is more intense, and also shows a delayed wash-out as compared to thyroid tissue which shows faster wash-out.[28] Therefore, foci of increased radiotracer uptake persisting on a delayed scan (variably acquired at 60-180 minutes after radio-tracer administration) represents parathyroid tissue. Subtracting images acquired by using two radio-tracer agents, the first one which is taken up by both thyroid and parathyroid tissue (like sestamibi) and a second which is taken up by only thyroid tissue (^{99m}Tc pertechnetate or ^{123}I) can help image the parathyroid. This was the basis of the famous Thallium- Technetium subtraction scan. However, this technique is less used these days due to the availability of more effective radiotracer, sestamibi.

FOUR DIMENSIONAL CT (4D CT):

4D CT is advantageous over both ultrasonography and nuclear imaging studies in the precise localisation of both orthotopic and ectopic glands and better differentiation of parathyroid adenomas from mimics like lymph nodes and thyroid nodules (Table 1).[29]
4D-CT demonstrated an accuracy of 93%. 4D-CT revealed a suboptimal 44% sensitivity, but 100% specificity, for multigland disease.[30]

The first three dimensions in 4D CT are the three planes of image interpretation - axial, sagittal and coronal, while the fourth dimension refers to the change in enhancement pattern with time in the non-contrast, arterial and delayed (venous) phases (Table 2).

Streak artifacts from hyperattenuating materials like high density contrast in neck vessels and surgical clips can hamper evaluation. The streak artifact caused by venous pooling may be prevented by using a saline chase after contrast injection.[29] The beam hardening artifact caused by clavicles and the shoulder girdle can interfere with interpretation of imaging findings which may be reduced by neck elevation achieved by putting a rolled towel under the shoulders.[29] In addition, patients are advised to avoid speaking, swallowing or coughing during image acquisition to avoid motion artifacts.

In order to felicitate the precise detection of parathyroid adenomas, Hoang *et al* described a systematic five step approach : (1) Search for potential eutopic lesions in the arterial phase (2) Search for potential ectopic lesions in the arterial phase (3) Review the pattern of enhancement on other phases (4) Evaluate the morphological appearance and (5) Correlate the CT findings with other imaging modalities and clinical history.[29] The characteristic imaging findings of a parathyroid adenoma are low attenuation on the non-contrast image, intense arterial enhancement (138-180 HU) and wash-out in the venous phase (Figure 5,6). [31,32] The low attenuation on non-contrast images is important to differentiate from thyroid lesions, which are hyperdense on non-contrast CT owing to the iodine content. The typical search should start from the most common location of parathyroid adenoma i.e., around the thyroid gland. This should be followed by a keen search along the expected path of migration of parathyroid glands i.e., superiorly extending from the level of carotid bifurcation to the carina inferiorly. Rarer sites of ectopic parathyroid adenomas like the retropharyngeal space and intrathyroidal locations should also be screened (Figure 7-10).

Since the ultimate goal of imaging is to facilitate precise operative planning, it is important to provide the surgeon with relevant information while reporting parathyroid adenomas preferably using a predefined cartoon (Figure 1). This includes number of candidate lesions, size of the lesions, location of the lesion with respect to standard surgical landmarks (superior and inferior thyroid poles, suprasternal notch and trachea-oesophageal groove), ectopic or supernumerary parathyroid glands, underlying thyroid pathology and arterial anomalies associated with non-recurrent laryngeal nerve (aberrant right subclavian artery) which may increase risk of operative injury to the nerve.[5]

Exophytic thyroid nodules and level VI cervical lymph nodes can mimic parathyroid adenomas as they have similar shape and locations. The differentiation may be done on the basis of contrast enhancement patterns. Thyroid nodules show high attenuation on the non-contrast image owing to their high iodine content and show delayed enhancement as compared to adenoma. Lymph nodes although similar in shape to parathyroid adenomas can be differentiated from the latter based on contrast kinetics.

Lymph nodes show progressive enhancement on the delayed phase as compared to parathyroid adenomas which show washout of contrast.

The detection of one lesion should not give a false sense of satisfaction to the radiologist since multiglandular disease can occur in 10 % of the cases.[33] Hence, a relook is always suggested.

While 4D CT is an excellent modality for detection of parathyroid adenomas, it does involve considerable radiation exposure. The effective dose is 10.4 mSv for 4D CT as compared to 7.8 mSv for nuclear scintigraphy, however 4D CT is associated with 50 times higher organ dose to the thyroid gland which becomes a cause of concern in young females since it increases the life time risk of development of thyroid cancer.[34]

MRI:

MRI is often not used as a first line modality. It is more commonly used as problem solving modality in patients with recurrent or residual disease. The non-involvement of ionising radiation makes it a safer modality as compared to 4D CT and nuclear imaging studies; however, the modality is time consuming and isn't readily available. On a 1.5 T MRI machine, the sensitivity is 80%.[35–37] Benign parathyroid lesions are seen as well-circumscribed ovoid lesions with a cleavage plane with the thyroid tissue which is best seen on out of phase images.[37] The signal characteristics of parathyroid adenomas vary on MRI, but most commonly they tend to show homogenously hyperintense signal on T2 weighted images (Figure 11).[37] On post gadolinium scan, they show rapid enhancement in the arterial phase. Solid parathyroid lesions show higher signal on diffusion weighted images as compared to the other anatomically neighbouring structures in the neck thus helping in differentiation from the former.[38] 4D MRI is a novel method which has been explored in the imaging of parathyroid adenomas. The sensitivity of 4 D MRI was 90 % and after optimisation, 100% and the specificity was 90 %.[39] 4DMRI has similar accuracy to 4 D CT for the detection of parathyroid lesions. However, 4DMRI has the advantage of lack of exposure to ionizing radiation, which can be beneficial in younger patients.[40] The protocol used is the acquisition of fast T1

VIBE sequences in the axial plane prior to and after administration of gadolinium acquiring the images every 13 s for 10 sequential scans.[39] Parathyroid adenomas showed fast enhancement after 26-30 s similar to their pattern on 4D CT.[39]

CHOLINE PET:

PET is a non-invasive nuclear imaging study which provides both anatomical and functional information post intravenous injection of a radio-tracer agent. Choline labelled with positron emitters like carbon-11 or fluorine-18 are used for parathyroid imaging.[41] Increased choline uptake can be seen in parathyroid adenomas owing to the parathormone induced upregulation of choline kinase.[42] The image acquisition is done with the patient in a supine position about 45 to 60 minutes post intravenous injection of 18-fluoro choline.[43] Eyeballing is used to detect lesions in the eutopic or ectopic locations with parathyroid tissue being identified as maximum standardised uptake value (SUV max) four times greater than thyroid tissue.[44] Fluoro-choline PET can identify abnormal parathyroid gland in 92% patients in whom ultrasound and other nuclear imaging studies are negative.[45] It has excellent ability to detect small adenomas. The radiation dose is around 6 mSv which is lesser than that involved in MIBI scan and 4D CT. The scan involves a single acquisition as compared to the MIBI scan which involves imaging at two time points.[46] Choline has high sensitivity in the detection of parathyroid adenomas especially in multi-glandular disease. The high lesion to thyroid ratio improves the ability to detect smaller lesions. There are however several limitations with choline PET which include limited availability, high cost and the absence of a standardised protocol for imaging.

CONCLUSION

The primary goal of imaging in a clinically diagnosed case of hyperparathyroidism is precise localisation of the presence of parathyroid lesions which permits accurate surgical planning. The first line imaging modalities are ultrasound of the neck and scintigraphy. The inability to localise on these modalities or disconcordant findings on these modalities necessitates the use of 4D CT, MRI or F-Choline PET. Novel modalities such as contrast enhanced ultrasound and shear wave elastography of the neck should be coming up in a big way as it is free of radiation as well as safe for the kidneys. The various imaging modalities may also be used to differentiate parathyroid hyperplasia, parathyroid adenoma and parathyroid carcinoma (Table 3, Figure 12), though this may not always be possible and histopathological examination is the gold standard.

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