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ACTUALITIES IN ENDOCRINOLOGY- PARATHYROID IMAGING

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Abstract

Parathyroid imaging modalities have been used to guide clinicians and surgeons in finding the source of hyperparathyroidism for over 40 years. Primary hyperparathyroidism (PHPT) is generally caused by a parathyroid gland(s) autonomous production of parathyroid hormone (PTH), associated by enlargement of one or more glands. Noninvasive imaging procedures that are used in the management of hyperparathyroidism are anatomical (ultrasound, computer tomography, magnetic resonance imaging) and/or functional (nuclear medicine techniques: planar scintigraphy, single photon emission tomography, positron emission imaging) and/or hybrid imaging.

Key words: primary hyperparathyroidism, echography, scintigraphy, hybrid imaging.

INTRODUCTION

The parathyroids are in most cases four small glands that regulate the phosphocalcemic metabolism through the secretion of the parathyroid hormone (PTH). They are normally situated posterior to the thyroid parenchyma, but in some cases they may be found intrathyroidal or in ectopic locations: in the superior pole of the thymus, upper mediastinum or somewhere between the angle of the jaw to the aortic arch. Parathyroid imaging techniques are used for the localization of the source of hyperparathyroidism when abnormal high PTH values are found. Primary hyperparathyroidism is associated by enlargement of one or more glands (hyperplasia, adenoma or parathyroid cancer) and can be associated with multiple endocrine neoplasia (like MEN type 1, type 2a, type 4) (1).

Imaging Methods

Noninvasive imaging procedures that are used in the management of hyperparathyroidism are anatomical: ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and/or functional using nuclear medicine techniques: planar scintigraphy, single photon emission tomography (SPECT), positron emission imaging (PET) and/or hybrid imaging (SPECT-CT, US-SPECT, PET-CT, PET-MR).

Ultrasound

Ultrasound is the first used imaging technique in evaluating hyperparathyroidism. Its advantages are the high availability, low cost and that is a non-invasive, non-ionizing procedure, with a drawback that it is operator dependent. It can neither visualize ectopic parathyroid glands nor glands located in the thyroid tissue. US sensitivity reaches the value of 89% (with a range of 27-89%) while specificity ranges from 87% to 94% (2). The US sensitivity dropped to 35% in cases with multiple hyperplasia, and even lower in double adenomas (1).

Neck ultrasound is performed using a linear high energy probe (5-15 MHz) with the patient in supine position, with the patients head tilted back (1). Normal parathyroid glands appear as round-oval, homogeneously hypoechoic masses posterior to the thyroid bed with an average size of 6x4x2mm. US can be performed multiple times in evaluating and monitoring anatomical alterations from the normal echographic appearance, such as: the size, shape, cystic degeneration or vascularity (3).

Computed Tomography

Cross-sectional imaging such as CT and MRI is used for the better localization of ectopic parathyroid adenomas. The radiation doses from CT varies a long range from low dose CT to 4D-CT, depending on the use of the study. Low dose CT (like 120kVp and 50mAs) is used for the PET-CT protocol in anatomical localization of the suspected hyper-functioning parathyroid gland. (4) 4D-CT requires higher radiation doses so it is used when traditional imaging techniques, such as US and planar scintigraphy/SPECT-CT, are negative or equivocal (5).

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Magnetic resonance imaging

MRI uses non-ionizing radiofrequency pulses and is used usually when the initial imaging is negative (4). It is preferred to CT in children, young adults, pregnancy due to the lack of radiation and in patients with persistent or recurrent hyperparathyroidism after surgery, due to the metal artifacts seen on CT (5).

Nuclear medicine and Hybrid imaging

Parathyroid scintigraphy uses radio-pharmaceuticals to evaluate the function of the gland. Various radiotracers or radiopharmaceuticals are used in different image acquisition protocols. The first radiotracer used to successfully image the parathyroid glands was ^{201}Thallium in the 1980s. Now ^{99m}Tc-sestamibi (MIBI) is the preferred functional imaging agent with the dual phase image acquisition protocol. According to Maublant (1993), MIBI passes through cell membranes by diffusion and is retained within cell mitochondria. Images are acquired at an early phase (5-15minutes) and at a late phase (2-3h)(6). Different wash-out times from the thyroid parenchyma and parathyroid glands make it that only the abnormal parathyroid glands are seen on the later images. Similar to MIBI is ^{99m}Tc-tetrofosmin. 201Tl and MIBI washes out of the thyroid similarly in the first 20 minutes. Diagnostic accuracy is higher in lonely adenomas with the predominance of oxyphilic cells and lower in multiglandular involvement. False negative imaging can be found in association with hyperplastic glands, cystic degeneration of the parathyroid, high body mass index, small glandular size and upper glands (7). False positive images can be found in benign or malignant thyroid nodules, ultrasound can be used to differentiate them. One meta-analysis determined a pooled sensitivity for scintigraphy of 83% (99% confidence interval (CI) 96.358 -97.412) with similar specificity values (8).

Parathyroid dual-tracer scintigraphy technique uses a subtraction protocol in which first there is administered a radiotracer that is fixed in the thyroid parenchyma (^{99m}Tc - pertechnetate/ ^{1231}I) and secondly a metabolic radiopharmaceutical (^{99m}Tc-MIBI/ ^{99m}Tc-tetrofosmin/^{201}Tl-chloride). Regions of interest (ROI) are defined for the first acquisition contouring the thyroid gland and from the second set the ROI for the thyroid and parathyroids. The subtraction of the gamma counts of the first ROI from the second ROI leaves on the subtracted image the counts from the overactive parathyroids. Variants of dual-tracer parathyroid scintigraphy: ^{99m}Tc-pertechnetate/ ^{201}Tl-Cloride, ^{123}I/^{201}Tl- Cloride, ^{123}I/^{99m}Tc-MIBI, ^{99m}Tc-pertechnetate/^{99m}Tc-MIBI.

In hybrid imaging the addition of two localizing imaging techniques provides an additional increase in sensitivity and positive predictive value, giving a three-dimensional functional nuclear medicine (SPECT/PET) and anatomical detail imaging, thus helping the surgeons better prepare for the surgical procedure or even change the course of action from bilateral neck exploration to minimal invasive surgeries (9). The pooled detection rate of MIBI SPECT/CT in the preoperative planning of patients with PHPT and the 95% confidence intervals can rise up to 88% on the per patient-based statistics (95% CI=84% to 92%), and respectively 88% (95% CI=82% to 92%) on a per lesion-based analysis (10).

PET-CT has proved its usefulness in staging, restaging and postsurgey evaluation of various neoplasia and can be used in the diagnosis of parathyroid adenomas and cancer. The most available radiotracer is six 2-deoxy-2-(18F) fluoro-D-glucose (18F-FDG). The glucose metabolism is quantified by using a parameter named standard uptake value (SUV) which has been validated as a semi-quantitative parameter of malignancy. High SUV values correlate with poor prognosis and tumor aggressiveness (11).

Parathyroid carcinoma is a rare endocrine malignancy (<1% cases of hyperparathyroidism). There is no typical imaging method that can truly differentiate parathyroid carcinoma from the benign pathology. MIBI scintigraphy and US are the most frequent modalities used to characterize the primary lesion. The CT with low contrast enhancement and MRI are used for the assessment of loco-regional extent in the soft tissue and lymph node status in the central compartment. 18F-FDG PET-CT can be used in the work-up of parathyroid adenomas and cancer, although false positive results can be found in brown tumors. The primary parathyroid carcinoma and its metastatic sites show significant avidity for 18F-FDG, with a SUVmax value that can reach 10.78 in the primary lesion (11).

Beyond 18F-FDG, several tracers have been used to image hyperfunctional parathyroid glands, like L-(11C)Methionine (11C-MET), (11C)2-hydroxy-N,N,N-trimethylethanaminium (11C-CH), N-((18F) Fluoromethyl)-2-hydroxy-N,N-dimethylethanaminium (18F-FCH) and 6-(18F) fluoro-L-DOPA (18F-DOPA). In a recent study, sensitivity for the detection of a lesion in the correct quadrant had a pooled estimate of 69% (95% CI 60-78%), pooled PPV ranged from 91 to 100% with a pooled estimate of 98% (95% CI 96-100%)

(12). 18F-FCH PET imaging in hyperparathyroidism demonstrates higher lesion-to-background ratios being expected in patients with high PTH, using both low-dose CT and MRI for anatomical correlation. PET/MR is accurate in estimating the volume of parathyroid adenomas (13). 11C-MET PET may be considered a reliable second-line imaging modality to enable minimally invasive parathyroidectomy (12).

Several integrated US-nuclear medicine systems were developed for different pathologies. From the functional techniques the SPECT modality is the best candidate that could work in tandem with US. Software algorithms are used for fusing the complementary imaging techniques that can be acquired independently or simultaneous. US- small field of view single photon emission probe systems are being developed to guide surgeons intraoperative, and in converting an extensive surgery to a minimal invasive - targeted procedure (14).

Using a multidisciplinary team every center can improve the diagnostic accuracy of abnormal parathyroid glands. Hybrid imaging is becoming the "new normal" in parathyroid imaging giving a better understanding of the functionality and form for this pathology.

Conflict of interest

The authors declare that they have no conflict of interest.

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