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Review

Preoperative Localization Studies in Primary Hyperparathyroidism

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Abstract

Primary hyperparathyroidism (pHPT) is the third most frequently seen endocrine disease and it is the most common cause of hypercalcemia seen in ambulatory patients. PHPT is most often (80%-85%) caused by a single parathyroid adenoma, followed by double adenoma (4%-5%), multiple gland hyperplasia (10%-15%), and parathyroid carcinoma (<1%). The diagnosis of pHPT is biochemically established and the only curative treatment is surgery. Since the cause of pHPT is typically single-gland disease, it is possible to determine the majority of pathological glands with preoperative localization methods and use the minimally invasive parathyroidectomy (MIP) approach. MIP has become the standard treatment for pHPT in selected patients. There are both noninvasive and invasive preoperative localization methods. Noninvasive methods currently used include ultrasonography (US), parathyroid scintigraphy, 4-dimensional computed tomography (CT), magnetic resonance imaging, and positron emission tomography-CT with 18F-fluoroquinolone and 11C-methionine. Preoperative invasive localization methods include parathyroid hormone (PTH) measurement with fine-needle aspiration biopsy, lateralization with PTH measurement via bilateral jugular vein sampling, selective venous sampling, and parathyroid arteriography. The aim of this study was to evaluate preoperative localization studies used in cases of pHPT.

Keywords: Localization methods; preoperative localization; primary hyperparathyroidism.

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Primary hyperparathyroidism (pHPT) is characterized by autonomic excessive parathyroid hormone (PTH) production, an increase in PTH and calcium (Ca) levels due to impaired regulation of Ca metabolism, or "inappropriately normal" levels of Ca or PTH.[1, 2] PHPT is the third most common endocrine disease and is the most common cause of hypercalcemia seen in outpatient departments.[3] Most often, (80%-85%) pHPT is caused by a single parathyroid adenoma, followed by double adenoma (4%-5%) multiglandular hyperplasia (10%-15%), and parathyroid cancer (<1%).[4] The diagnosis of pHPT is biochemically established and the only curative treatment is surgery.

Historically, many patients present with and are diagnosed based on obvious signs and symptoms of pHPT. In the early 1970s, the use of automatic blood analyzers became widespread and the number of patients diagnosed during routine blood tests for other purposes increased. Today, many patients may not have the classic signs or symptoms associated with pHPT at the time of diagnosis and are diagnosed as asymptomatic or minimally symptomatic. A parathyroidectomy is indicated for all symptomatic patients with renal and bone manifestations.[5] In the treatment of asymptomatic pHPT, there are criteria for a surgical indication, and they are revised periodically according to the evidence in the literature.[6]

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Surgery is always an option, even in patients with asymptomatic disease or those who do not meet the standard criteria for surgical indication, because surgery is the only definitive treatment for pHPT.[6] In addition, many authors believe that surgical treatment should be considered independently of chronological age in all patients with asymptomatic pHPT with minimal perioperative risk and adequate life expectancy.[7]

In the last quarter of the last century, ultrasonography (US) and scintigraphy began to be used as preoperative imaging modalities. As technology advanced, these methods evolved and new imaging modalities have been introduced. It is now possible to determine the majority of pathological glands using preoperative imaging methods in the majority of pHPT patients.

Intraoperative PTH measurements and other intraoperative methods are now being used to increase the success rates of parathyroidectomy procedures. Surgical treatment has shifted from bilateral neck exploration (BNE) to minimally invasive parathyroidectomy (MIP) with the help of imaging methods and intraoperative PTH measurements. Today, MIP has become the standard treatment for selected pHPT patients who have positive imaging. However, BNE is still the gold standard in the surgical treatment of pHPT.[8]

Basic Principles of Parathyroid Imaging in Primary

Parathyroid imaging should not be performed for all patients diagnosed or suspected of pHPT. The diagnosis of pHPT is established biochemically. Imaging modalities are not used to confirm or exclude the diagnosis of pHPT, or in the determination of any surgical indication. Furthermore, negative imaging has not been associated with the disease being asymptomatic or a mild clinical course. There is no place for imaging in pHPT patient, who does not have an indication for surgery or cannot be operated on.

After establishing a surgical indication, a patient is referred to surgery, preferably to an experienced surgeon. Parathyroid imaging should be performed according to the surgeon's preference to determine the operation plan at the surgical center. Negative imaging is not a contraindication for parathyroid surgery.[9, 10] However, 90% of endocrinologists request at least 1 or more imaging studies before referring the patient to the surgeon with the imaging results.[11]

Noninvasive Localization Studies

Ultrasound

A description of preoperative parathyroid US was first reported by Arima et al.[12] in 1975. Since then, experience in US technology and parathyroid imaging has increased tremendously. In parallel with this growth, the use of US has become increasingly widespread and has become the first imaging method to be applied, together with scintigraphy, in preoperative imaging. US is an inexpensive, widely available, portable, radiation-free imaging technique with good anatomical resolution and sufficient sensitivity for initial imaging.[9, 13, 14] Additional thyroid pathology is observed in 29% to 51% of the patients with pHPT, and US also allows for the evaluation of thyroid pathologies.[9]

A percutaneous biopsy can be performed if necessary. The need for simultaneous thyroid surgery can be reduced from 30% to 6% with a fine-needle aspiration biopsy (FNAB) sample obtained from thyroid nodules.[9]

Generally, a 5 to 15 MHz high-frequency linear probe should be used. For an US evaluation, the patients should be placed in the supine position with their neck extended and a pillow placed under the shoulder. Longitudinal and transverse images should be obtained and the entire neck should be examined.[9] Particular attention should be paid to the posterior and inferior border of the thyroid. Potential ectopic parathyroid pathologies should be investigated from the neck to the superior mediastinum.[9]

Normal parathyroid glands cannot be visualized with US.[9, 13, 14] Classic US findings of parathyroid adenoma include well-circumscribed, homogenous, ovoid, hypoechoic structures compared to the thyroid tissue.[13,14] They are gen-erally 0.8 to 1.5 cm in length.[9] However, it should be kept in mind that different images, such as cystic degeneration, calcification, intralesional bleeding , and fibrosis may be observed.[13] Doppler imaging may help to distinguish suspected parathyroid lesions from the thyroid and lymph nodes. A parathyroid adenoma typically has peripheral rim vascularity and an asymmetric blood flow increase compared with the neighboring thyroid. The appearance of a polar feeding artery is important to differen-tiate the parathyroid gland from the lymph node. Lymph nodes usually have a hilar blood flow.[9, 13] The presence of a feeding artery seen with US increases the sensitivity by 10% and the accuracy by 54%.[9]

In a meta-analysis of 19 studies, the sensitivity of US was reported as 76.1% and the positive predictive value (PPV) was 93.2%.[15] It has also been said that the use of a contrast agent in US increased sensitivity; the sensitivity of contrastenhanced US has been described as 95.9%, and in patients with negative scintigraphy, it was reported to be 96.3%.[16] US demonstrates a high sensitivity in experienced hands. The main disadvantage of US is that it is operator-dependent. The effect on the evaluation of ectopic, and especially mediastinal, glands is limited.

However, axial rotation of the patient's head or breathing incidence of detection of ectopic adenomas.[9] US is not as sensitive in the detection of slightly enlarged glands or the evaluation of intrathyroidal glands.[13, 14]

Staged compression may increase the detection rate of small adenomas by up to 27%. Parathyroid adenomas are less exposed to compressive forces than the surrounding tissue.[9] The presence of a multinodular goiter decreases the sensitivity. The efficacy of US in obese patients is low.[13,14] Multiglandular disease also decreases the sensitivity. In a review that evaluated more than 20.000 cases, the sensitivity decreased from 78.5% to 34.9% in multiglandular disease, and to 16.2% in cases with double adenoma.[17]

Parathyroid Scintigraphy

Parathyroid scintigraphy is another of the initial preoperative imaging methods. Parathyroid scintigraphy was first performed in 1983 by Young et al.[18] and described as thallium 201-Tc99m substraction scintigraphy. In 1989, the use of Tc99m sestamibi scintigraphy, which used lipophilic sestamibi accumulating in the mitochondria-rich oxyphilic cells of the parathyroid gland was reported.[19] This agent greatly increased the sensitivity of scintigraphy and is still preferred in parathyroid scintigraphy. Several protocols are used in parathyroid scintigraphy; however, most frequently, single-agent 2-phase or 2-agent single-phase techniques are used.[13]

The introduction of the single-photon emission computed tomography (SPECT) application in sestamibi scintigraphy, and the combination of SPECT images with CT images (SPECT-CT fusion images) increased the sensitivity of the method and enabled more convenient localization of pathological glands with ectopic localizations. Both thyroid and parathyroid tissue have demonstrated uptake of Tc99m sestamibi. In 60% to 85% of parathyroid adenomas, sestamibi washout is slower when compared with normal thyroid and parathyroid tissue.[20] Due to this characteristic feature of sestamibi, single-isotope, dual-phase, planar scintigraphy performed within the first 10 to 30 minutes after sestamibi injection can reveal uptake in the thyroid and a pathological parathyroid, while in scintig-raphies taken within 90 to 180 minutes, secondary to wash-out from thyroid, uptake of the drug by the parathyroid is more conspicuously visualized.

However, it can be difficult to detect parathyroid adenomas occupying 15% to 40% of the gland due to rapid washout.[14] It has been reported that when the "pin hole" imaging was added to dual-phase scintigraphy, the sensitivity increased from 54% to 89%, but the specificity decreased from 89% to 77%. However, this technique now is little-used following the introduction of SPECT-CT.[21] Dualphase, single-isotope scintigraphy has advantages over US in that it is not as operator-dependent, and it can detect ectopic and deeply entrenched posterior lesions.[14] The sensitivity of sestamibi scintigraphy in single adenomas is 88.4%, while it decreases to 44.5% in multiglandular hyperplasia and 30% in double adenomas.[17]

Three-angle images can be obtained using the SPECT method in scintigraphy. Since SPECT increases sensitivity, use of SPECT with standard planar images has been recommended. The combined use may increase the detection rate of ectopic and deep-seated parathyroid ad-enomas, especially in the cervical region. SPECT images can reveal parathyroid lesions behind thyroid pathologies that cannot be seen in planar images. Hyperplasic lesions with a small diameter may cause false-negative SPECT images. Lesions greater than 1.5 cm in size may be more easily localized. In dualphase scintigraphy, the time of application of SPECT is controversial. However, many centers that obtain SPECT images in the early phase in order to view parathyroid adenomas have shorter wash-out times.[21]

The recently introduced SPECT-CT method allows for the integration of SPECT images and conventional X-raybased CT images for both anatomical and functional evaluation in a single image. SPECT/CT increases the quality of anatomical localization and demonstrates the relationship of the pathological gland to adjacent structures.[14] In parathyroid adenomas localized in the mediastinum, in obese patients, or if there is a mild retention in the gland, CT increases the sensitivity of SPECT in the localization of the gland. In addition, it positively contributes to the identification of lesions in atypical ectopic localizations in the neck, such as retropha-ryngeal and retroesophageal regions.[21]

As with SPECT, there is no consensus about the timing of taking images using SPECT-CT. Early or delayed images, or both, can be obtained. SPECT-CT increases the exposure to the radiation when compared to conventional CT.[14] However the use of contrast medium for CT is still controversial, Mc Coy et al.[22] reported in their study of large series that the use of a contrast agent for CT did not increase sensitivity in detection of the parathyroid pathology.

In a meta-analysis of 18 studies, the sensitivity and PPV for planar scintigraphy were 63% and 90%, 66% and 82% for SPECT, and 84% and 95% for SPECT-CT, and SPECT-CT was found to be the superior method.[23] In a single-center, large-scale study of 1388 patients with pHPT who were evaluated before any intervention, 755 SPECT-CT and 633 SPECT examinations were compared. Sensitivity (96% vs 91%), PPV (90% vs 85%), and accuracy of SPECT-CT (83% vs 77%) were higher in a single-gland disease. Although the authors stated that negative imaging rates in multiglandu lar diseases were similar with both techniques, the accuracy of predicting multiglandular disease was better with SPECT-CT (36% vs 22%; p=0.04). In addition, SPECT-CT was found to have greater sensitivity (68% vs. 49%) and PPV (53% vs. 37%) than SPECT for multiglandular disease.

The researchers stated that when patients having singlegland disease and bilateral exploration due to a thyroid disease were excluded, there was much less need for BNE based on SPECT/CT images compared with SPECT examination. The researchers stated that SPECT/CT provided a more reli-able operative guideline for both single and multiglandular disease.[22] In another metaanalysis, 24 studies were evalu-ated and ectopic lesions were detected in between 4% and 20% of the patients, and SPECT/CT was found to be supe-rior to SPECT in the detection of ectopic lesions.[24]

The use of Ca channel blockers reduces the uptake of sestamibi by parathyroid cells and decreases the sensitivity of SPECT.[14] Iochemical values and severity of the disease can also affect the sensitivity. Scintig-raphy is more likely to yield positive results in the presence of high serum Ca levels, high PTH levels, and vitamin D de-ficiency. The presence of oxyphilic cells in parathyroid adenoma is thought to be necessary to obtain positive results with scintigraphy. Indeed, when the oxyphilic cell content is >20%, the likelihood of obtaining positive results with scintigraphy increases 4-fold. Radionuclide retention is regulated by the multidrug resistance system, and specifically by P-glycoprotein. There is a significant correlation between a high P-glycoprotein level and negative scintigraphy.[25]

Thyroid nodules, thyroiditis, and enlarged cervical lymph nodes may cause false positivity findings as a result of delayed washout.[13] Thyroid nodules are the most common cause of false positivity. Rapid washout is seen in some 15% to 40% of parathyroid adenoma cases, and it is very difficult to detect these glands with scintigraphy.[20] A dual isotope (dual radiotracer) technique has been recommended to reduce false positivity due to sestamibi retention in the thyroid nodule and to increase the sensitivity in multiglandular disease. This method includes applying both Tc99msestamibi and the isotopes I-123 or Tc99m-pertechnetate which demonstrate uptake only in the thyroid gland.

A digital subtraction technique is applied to images obtained with the 2 isotopes.[26] It has been reported that this method is faster and more sensitive than dual-phase scintigraphy. It increases the sensitivity from 79% to 94% and decreases the false positivity rate from 10% to 3%. Since the thyroid cannot be visualized in patients who have undergone thyroid surgery, patients with thyroiditis, pa-tients in whom iodinated contrast agent was used, or those treated with L-thyroxine treatment, this method can be ap-plied for other indications.[21] Use of the dual isotope tech-nique is recommended in the European Society of Nuclear Medicine guidelines because the method is more sensitive in multiglandular disease and because it can visualize thyroid nodules.[27]

Dual phase scintigraphy or SPECT-CT can be also used. İt has been reported that the sensitivity and PPV of SPECTCT increase up to 95% and 97%, respectively.[28, 29] Furthermore, in a prospective comparative study, the diagnostic accuracy of pinhole dual (sestamibi and iodine) phase parathyroid subtraction scintigraphy was found to be greater than that of single-agent, dual-phase scintigraphy, 4-dimensional (4D)-CT, and US.[30]

Combination of Ultrasonography and Scintigraphy

US and scintigraphic methods are the most commonly used techniques for initial imaging. In many centers, these 2 imaging methods are routinely combined before primary intervention.[31] The combination of US and scintigraphic methods increases the sensitivity.[32]

The combination of SPECT or SPECT-CT and US performed by an experienced ultrasonographist is considered to be an optimal com-bined option.[33]

Four-Dimensional Computed Tomography

Conventional CT has a lower sensitivity in the imaging of a pathological parathyroid gland than other imaging modalities. According to the American Society of Endocrine Surgeons, although the sensitivity of the 4D-CT protocol is lower in multiglandular disease, its use is increasing.[10] Use of 4D-CT in parathyroid imaging was first reported in the literature in 2006.[34]

Four-dimensional CT is a dynamic phase CT method. The 3 dimensions used are axial, coronal, and sagittal multiplanar imaging. The fourth dimension is based on the evaluation of the contrast enhancement of the parathyroid perfusion characteristics; i.e., from the noncontrast phase to the arterial and late venous phase.[13, 21]

The image characteristics of the adenoma or hyperplastic gland increase and peak with the use contrast in the arterial phase, and it is reduced or completely cleared in the venous phase.

In an analysis of 2 studies in which 4D-CT was performed in patients who were undergoing a parathyroidectomy, the sensitivity, and PPV of 4D-CT was 89.4% and 93.5%, respectively.[14] Although 4D-CT is used as the first imaging modality in some centers, it is also oftentimes used to solve problems in challenging cases where previous images yielded negative or inconsistent results.[35] In cases where US and scintigraphy did not localize the lesion, or the results were contradictory, the sensitivity, and PPV of 4D-CT have been reported to be 67% to 89% and 65% to 97%, respectively.[36–38]

The sensitivity has been reported to range between 43% and 67% in multiglandular disease.[38, 39]

The sensitivity and PPV of 4D-CT have been reported to be 50% to 88% and 69% to 100%, respectively, in patients undergoing unsuccessful exploration.[38, 40, 41] The performance of 4D-CT has been found to be superior to scintigraphy and US.[14]

The main disadvantages of this method are the relatively high radiation exposure of the patient and the inexperience of some radiologists with this technique.[14]

Mahajan et al.[42] found that the estimated annual level of background radiation exposure for an individual was about 3 mSV. The radiation dose in 4D-CT and SPECT scintigraphy in their study was 10.4, and 7.8 mSV, respectively. The thyroid was exposed to a 57-times greater dose of radiation with 4D-CT when compared with SPECT scintigraphy. (92.0 vs. 1.6 mGy).

The risk of 4D-CT-related thyroid cancer developing in a 20-year-old woman exposed to this radiation dose was estimated as nearly 0.1%. Nonetheless, reservations about the radiation dose still remain, and in many centers 4D-CT is used as a secondary or confirmative study in problematic primary cases or as an imaging modality in reoperative cases, rather than as the first-stage imaging method.[13]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is used less frequently because its accuracy is similar to US and scintigraphic methods. Similar to 4D-CT, it is used as a secondary imaging method to solve problems.[13] It has been reported that MRI detected abnormal parathyroid glands in 74% of 44 cases with persistent pHPT.[43] Although MRI does not contain radiation and provides comprehensive anatomical information, including ectopic areas, motion artifacts that may occur due to the length of time required for shooting limit the contribution of MRI, especially in secondary interventions.[9] Recent advances in technology and technique have led to promising results assessing the hypervascular structure of a parathyroid adenoma with dynamic images. Although MRI imaging performed using a 3 Tesla (3T) MRI device with high-resolution has a lower sensitivity and PPV when compared with Tc99m sestamibi scintigraphy, MRI was found to have detected parathyroid adenoma in 57% of patients with negative scintigraphy results in 1 study.[44] In other research, the sensitivity and PPV of 3T MRI (97.8% vs 93.7%) were greater than those of US (89.1% vs 93.1%) and scintigraphy (83.6% vs 95%), but similar to those of US and scintigraphy combination (93.4% vs 95%). MRI scans could visualize 6 of 8 adenomas missed with scintigraphy, and 2 of 7 adenomas overlooked using US. Combined use of US and MRI detected all of the enlarged parathyroid glands in multiglandular disease. MRI was also able to visualize 7 of 7 ectopic adenomas. The authors stated that preoperative localization of parathyroid adenoma had high diagnostic power and MRI could be preferred to select appropriate patients for MIP.[45]

Recently, it has been reported that dynamic multiphase 4D-MRI based on the evaluation of parathyroid perfusion properties such as 4D-CT has a 96% accuracy in distinguishing parathyroid lesions from thyroid and lymph nodes.[46] The sensitivity and PPV value of 4D-MRI was reported to be 90% to 93% and 90%, respectively, in cases of reoperation.[47, 48]

Although these new MRI studies have yielded promising results, additional studies are needed for routine use of MRI instead of US, scintigraphy, or 4D-CT. It may be considered instead of 4D-CT particularly in difficult cases where exposure to radiation is contraindicated.

PET-CT

In recent years, PET-CT studies with 18F-fluorocholine and 11C-methionine have been shown to be particularly promising for visualization in difficult parathyroid cases.[13, 14]

Methionine is precursor amino acid for PTH and choline is the precursor for cell membrane synthesis.[13] In a recent meta-analysis, the sensitivity and PPV of methionine in the localization of parathyroidism was reported to be 69% and 98%, respectively.[49] In recent years, the sensitivity and PPV of PET-CT studies with fluoroquinolone to detect parathyroid lesions was reported as 93% to 100% and 90% to 100%, respectively.[50–52]

In a recent study involving 29 patients who had undergone neck surgery, the lesion detection rates of 4DCT and fluorocholine PET-CT were evaluated. The sensitivity of fluorocholine PET-CT was found to be greater than that of 4D-CT regarding the number of lesions (96% vs 75%) and patients (85% vs 63%), respectively. The authors suggested that in patients with neck surgery; fluorocholine PET-CT is a promising method, while 4D-CT is a confirmatory imaging modality.[53]

In a meta-analysis of 11 studies on fluorocholine PET-CT, the rate of detection of lesions was determined to be 97% in patient-based analysis and 94% in lesionbased analysis. The investigators identified this study as the most promising examination for imaging pHPT and stated that it could replace sestamibi scintigraphy in parathyroid imaging.[54]

In patients with persistent or recurrent disease with negative imaging results who are scheduled for reoperation, fluorocholine PET-CT has begun to take its proper place as one of the imaging methods that may be considered for visualization of the parathyroid gland before invasive procedures.

Invasive Localization Studies

Measurement of Parathormon with Fine-Needle

Aspiration Biopsy

In some cases, it may be necessary to confirm whether the suspect parathyroid nodule is definitively the parathyroid. Parathyroid and thyroid nodules may be confused in imaging methods; however, a precise distinction of parathyroid tissue from thyroid follicle cells can be difficult even in cytological examination.[10] US or CT-guided FNAB was performed for suspected lesions based on US and CT results, and the aspirate obtained was washed with 1 cc saline. PTH in the irrigation fluid was measured to diagnose the lesion (PTH washout test).[55]

In the literature, the sensitivity, and specificity of a PTH washout test has been reported as 75% to 100% and 75% to 100%, respectively, and the diagnostic value is greater than that of cytology. A high PTH value is specific for parathyroid tissue, but it does not contribute to the differentiation of parathyroid adenoma from cancer.[10] It is a method that can increase the likelihood of detecting a pathological parathyroid gland, especially before secondary surgical intervention. It can confirm suspected lesions observed on US in scintigraphynegative reoperated cases, and thus it may allow for more focused surgery.[56]

Measurement of Parathormone in Blood Samples Obtained via Bilateral Jugular Vein Sampling

In this method, with the aid of preoperative US or intraoperatively, the PTH level of a blood sample obtained from both jugular veins at the lowest level of the neck possible is measured to lateralize the pathological gland. If the PTH value is 10% higher on 1 side of the neck than in the contralateral side, the test is considered positive.[57] This method is generally recommended to lateralize the lesion in scintigraphy-negative patients undergoing primary surgery and with the intention to perform MIP, if possible. Ito et al.[58] reported that it would provide an additional contribution to localization in most cases and could be used particularly in scintigraphy-negative cases.[58] Carneiro- Pla asserted that in suspect lesions detected with US performed by a surgeon, if US-guided bilateral venous sampling yields a positive result then sestamibi scintigraphy may eliminate and shorten the preoperative evaluation process.[59] Barczynski et al.[60] sampling was the most appropriate method to detect a solitary adenoma suitable for MIP.[61] In a prospective, casecontrolled study, Alvarado et al.[62] found a 56% positive lateralization in a study with both positive and negative pHPT patients, and a positive lateralization of 76% in the group with total thyroidectomy in patients without parathyroid disease. Among 30 scintigraphy-negative patients, 17 had positive lateralization: in 11, the side of the adenoma was accurately lateralized and in 5 patients, bilateral disease was detected despite lateralization findings. In the remaining patient, the lesion was detected on the contralateral side. Of 13 patients who could not undergo lateralization, 3 had bilateral disease and 10 had a solitary parathyroid adenoma. Seventeen of 30 scintigraphy-positive patients also had a positive lateralization: in 15, the parathyroid adenoma was lateralized accurately, while in 2 cases the parathyroid adenoma was detected on the contralateral side. The authors suggested that bilateral venous sampling should not be used as an additional test for focused parathyroidectomy, and that standard BNE should be performed in scintigraphy-negative patients.[61] It has been reported that this method alone or together with intraoperative US had a sensitivity of 77% to 80% and specificity of 65% to 71% and increased the rate of accurate localization from 33% to 65%. The major disadvantage of this method is that the pathological lesion may be below the area of venous sampling or located in the mediastinum. The contribution of this method in primary cases may be questioned. However, it may be considered as an additional method in persistent or recurrent cases, before or in the absence of more complicated techniques, such as selective venous sampling. These interventions should be performed in patients with persistent or recurrent HPT or when noninvasive methods yielded negative results in patients who have undergone severe neck surgery that previously deformed the anatomy.

Selective Venous Sampling

Selective venous sampling (SVS) is an invasive procedure which is almost always applied to the persistent or recurrent HPT patients having discordant or negative noninvasive imaging modalities.

In SVS, a venous angiography is performed and blood samples are drawn from the brachiocephalic vein, internal jugular vein, and the points where thyroid veins drain into the jugular vein. Blood samples collected through a thin catheter inserted into thyroid veins or more proximal parts of the venous anastomoses closer to the thyroid gland is called superselective venous sampling. A 2-fold increase in PTH value relative to the PTH level in a peripheral vein is considered a positive result in SVS. This value is much higher in superselective venous sampling.[63] In a recent meta-analysis of 12 studies of selective venous sampling performed in patients with recurrent or persistent HPT, the sensitivity, specificity, and positive likelihood ratio were found to be 74%, 41%, and 1.55%, respectively. The sensitivity, positive likelihood ratio, and positive posttest probability of SVS were significantly higher than those of noninvasive methods. Among SVS methods, superselective venous sampling has the highest sensitivity, accuracy, and positive posttest probability.[64] In a study that included 28 patients who had previously undergone surgical exploration and in whom pathological glands could not be localized using other imaging modalities, the sensitivity of SVS for lateralization was 93.3%, the PPV was 66.7%, and accuracy rate was 63.6%. When combined with 4D-CT, SVS has been reported to increase sensitivity from 50% to 95% and accuracy from 55% to 91% compared to 4D-DT alone.[65]

Parathyroid Arteriography

In parathyroid arteriography, both the common carotid artery and inferior thyroid arteries are catheterized from the femoral artery, and the results are evaluated based on the appearance of hypervascular blush in the parathyroid lesion with the delivery of a contrast agent. The true and false positivity rate has been reported as 59% and 9%, respectively.[66] It has more of a historical importance today, since 4D-CT and 4D-MRI have begun to be used.

Conclusion

Preoperative localization studies should be performed for all patients with pHPT with an indication for surgery. Today, pathological parathyroid glands can be localized in 80% to 90% of patients with pHPT using preoperative imaging methods. MIP has become the standard treatment for pHPT in selected patients with positive imaging. Surgical treatment with a BNE is still the gold standard.

The first choice of imaging is the combination of US and scintigraphy for patients who will undergo their first intervention. In cases where these imaging modalities yield negative results or in noncompliant patients, innovative methods such as 4D-CT or fluorocholine PET-CT are recommended for an additional contribution in some centers, but usually a BNE is performed. Invasive procedures have no place in primary cases. In patients with persistent or recurrent pHPT, scintigraphy and 4D-CT, fluorocholine PET-CT, or MRI may be applied after US. Invasive localization studies can be performed in cases with negative results.

Disclosures

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References

1. Walker MD, Bilezikian JP. Primary hyperparathyroidism: recent advances. Curr Opin Rheumatol 2018;30:427–39.
2. Uludag M, Aygun N. Primary Hyperparathyroidism: Current Situation in the Clinical and Biochemical Presentation. Med Bull Sisli Etfal Hosp 2016;50:171–80.
3. Mallick R, Chen H. Diagnosis and Management of Hyperparathyroidism. Adv Surg 2018;52:137–53.
4. Felger EA, Kandil E. Primary hyperparathyroidism. Otolaryngol Clin North Am 2010;43:417–32.
5. Callender GG, Udelsman R. Surgery for primary hyperparathyroidism. Cancer 2014;120:3602–16.
6. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014;99:3561–9.
7. Wu JX, Yeh MW. Asymptomatic Primary Hyperparathyroidism: Diagnostic Pitfalls and Surgical Intervention. Surg Oncol Clin N Am 2016;25:77–90.
8. Egan RJ, Scott-Coombes DM. The surgical management of sporadic primary hyperparathyroidism. Best Pract Res Clin Endocrinol Metab 2018;32:847–59.
9. Kunstman JW, Kirsch JD, Mahajan A, Udelsman R. Clinical review: Parathyroid localization and implications for clinical management. J Clin Endocrinol Metab 2013;98:902–12.
10. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg 2016;151:959–68.
11. Gallagher SF, Denham DW, Murr MM, Norman JG. The impact of minimally invasive parathyroidectomy on the way endocrinologists treat primary hyperparathyroidism. Surgery 2003;134:910–7.
12. Arima M, Yokoi H, Sonoda T. Preoperative identification of tumor of the parathyroid by ultrasonotomography. Surg Gynecol Obstet 1975;141:242–4.
13. Liddy S, Worsley D, Torreggiani W, Feeney J. Preoperative Imaging in Primary Hyperparathyroidism: Literature Review and Recommendations. Can Assoc Radiol J 2017;68:47–55.
14. Bunch PM, Kelly HR. Preoperative Imaging Techniques in Primary Hyperparathyroidism: A Review. JAMA Otolaryngol Head Neck Surg 2018;144:929–37.
15. Cheung K, Wang TS, Farrokhyar F, Roman SA, Sosa JA. A meta-analysis of preoperative localization techniques for patients with primary hyperparathyroidism. Ann Surg Oncol 2012;19:577–83.
16. Agha A, Hornung M, Schlitt HJ, Stroszczynski C, Jung EM. The role of contrast-enhancend ultrasonography (CEUS) in comparison with 99mTechnetium-sestamibi scintigraphy for localization diagnostic of primary hyperparathyroidism. Clin Hemorheol Microcirc 2014;58:515–20.

17. 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.
18. Young AE, Gaunt JI, Croft DN, Collins RE, Wells CP, Coakley AJ. Location of parathyroid adenomas by thallium-201 and technetium-99m subtraction scanning. Br Med J (Clin Res Ed) 1983;286:1384–6.
19. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins RE. 99Tcm sestamibi--a new agent for parathyroid imaging. Nucl Med Commun 1989;10:791–4.
20. Greenspan BS, Dillehay G, Intenzo C, Lavely WC, O'Doherty M, Palestro CJ, et al. SNM practice guideline for parathyroid scintigraphy 4.0. J Nucl Med Technol 2012;40:111–8.
21. García-Talavera San Miguel P, Gómez-Caminero López F, Villanueva Curto JG, Tamayo Alonso MP, Martín Gómez ME. Update of the role of Nuclear Medicine techniques in the pre-surgical localization of primary hyperparathyroidism. Rev Esp Med Nucl Imagen Mol 2019 Feb 6 [Epub ahead of print], doi: 10.1016/j.remn.2018.12.007.
22. McCoy KL, Ghodadra AG, Hiremath TG, Albarano A, Joyce JM, Yip L, et al. Sestamibi SPECT/CT versus SPECT only for preoperative localization in primaryhyperparathyroidism: a single institution 8-year analysis. Surgery 2018;163:643–7.
23. Wei WJ, Shen CT, Song HJ, Qiu ZL, Luo QY. Comparison of SPET/CT, SPET and planar imaging using 99mTc-MIBI as independent techniques to support minimally invasive parathyroidectomy in primary hyperparathyroidism: A meta-analysis. Hell J Nucl Med 2015;18:127–35.
24. 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.
25. Mihai R, Simon D, Hellman P. Imaging for primary hyperparathyroidism- an evidence-based analysis. Langenbecks Arch Surg 2009;394:765–84.
26. Hindié E, Ugur O, Fuster D, O'Doherty M, Grassetto G, Ureña P, et al. 2009 EANM parathyroid guidelines. Eur J Nucl Med Mol Imaging 2009;36:1201–16.
27. Hindié E, Ugur O, Fuster D, O'Doherty M, Grassetto G, Ureña P, et al. 2009 EANM parathyroid guidelines. Eur J Nucl Med Mol Imaging 2009;36:1201–16.
28. Caveny SA, Klingensmith WC 3rd, Martin WE, Sage-El A, McIntyre RC Jr, Raeburn C, et al. Parathyroid imaging: the importance of dual-radiopharmaceutical simultaneous acquisition with 99mTc-sestamibi and 123I. J Nucl Med Technol 2012;40:104–10.
29. Woods AM, Bolster AA, Han S, Poon FW, Colville D, Shand J, et al. Dual-isotope subtraction SPECT-CT in parathyroid localization. Nucl Med Commun 2017;38:1047–54.
30. Krakauer M, Wieslander B, Myschetzky PS, Lundstrøm A, Bacher T, Sørensen CH, et al. A Prospective Comparative Study of Parathyroid Dual-Phase Scintigraphy, Dual-Isotope Subtraction Scintigraphy, 4D-CT, and Ultrasonography in Primary Hyperparathyroidism. Clin Nucl Med 2016;41:93–100.
31. Varadharajan K, Choudhury N. Current practice in the surgical management of parathyroid disorders: a United Kingdom survey. Eur Arch Otorhinolaryngol 2018;275:2549–53.
32. Tunca F, Akici M, Işcan Y, Cem Sormaz I, Giles Senyurek Y, Terzioğlu T. The impact of combined interpretation of localization studies on image-guided surgicalapproaches for primary hyperparathyroidism. Minerva Endocrinol 2017;42:213–22.
33. Siegmund T, Kolassa R, Thomas A. Clinical update on insulin pump therapy in combination with continuous glucose monitoring. Minerva Endocrinol 2013;38:133–43.
34. Rodgers SE, Hunter GJ, Hamberg LM, Schellingerhout D, Doherty DB, Ayers GD, et al. Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. Surgery 2006;140:932–40.
35. Hoang JK, Williams K, Gaillard F, Dixon A, Sosa JA. Parathyroid 4D-CT: Multi-institutional International Survey of Use and Trends. Otolaryngol Head Neck Surg 2016;155:956–60.
36. Lubitz CC, Hunter GJ, Hamberg LM, Parangi S, Ruan D, Gawande A, et al. Accuracy of 4-dimensional computed tomography in poorly localized patients with primary hyperparathyroidism. Surgery 2010;148:1129–37.
37. Day KM, Elsayed M, Beland MD, Monchik JM. The utility of 4-dimensional computed tomography for preoperative localization of primary hyperparathyroidism in patients not localized by sestamibi or ultrasonography. Surgery 2015;157:534–9.
38. Tian Y, Tanny ST, Einsiedel P, Lichtenstein M, Stella DL, Phal PM, et al. Four-Dimensional Computed Tomography: Clinical Impact for Patients with Primary Hyperparathyroidism. Ann Surg Oncol 2018;25:117–21.
39. Chazen JL, Gupta A, Dunning A, Phillips CD. Diagnostic accuracy of 4D-CT for parathyroid adenomas and hyperplasia. AJNR Am J Neuroradiol 2012;33:429–33.
40. Ginsburg M, Christoforidis GA, Zivin SP, Obara P, Wroblewski K, Angelos P, et al. Adenoma localization for recurrent or persistent primary hyperparathyroidism using dynamic four-dimensional CT and venous sampling. J Vasc Interv Radiol 2015;26:79–86.
41. Muscari F, Suc B, Msika S, Hay JM, Flamant Y, Fourtanier G, et al. Surgeon-dependent predictive factors for mortality after elective colorectal resection and immediate anastomosis for cancer or nonacute diverticular disease: multivariable analysis of 2,605 patients. J Am Coll Surg 2008;207:888–95.
42. Mahajan A, Starker LF, Ghita M, Udelsman R, Brink JA, Carling T. Parathyroid four-dimensional computed tomography: evaluation of radiation dose exposure during preoperative localization of parathyroid tumors in primary hyperparathyroidism. World J Surg 2012;36:1335–9.
43. Stevens SK, Chang JM, Clark OH, Chang PJ, Higgins CB. Detection of abnormal parathyroid glands in postoperative patients with recurrenthyperparathyroidism: sensitivity of MR imaging. AJR Am J Roentgenol 1993;160:607–12.
44. Grayev AM, Gentry LR, Hartman MJ, Chen H, Perlman SB,

Reeder SB. Presurgical localization of parathyroid adenomas with magnetic resonance imaging at 3.0 T: an adjunct method to supplement traditional imaging. Ann Surg Oncol 2012;19:981–9.

45. Argirò R, Diacinti D, Sacconi B, Iannarelli A, Diacinti D, Cipriani C, et al. Diagnostic accuracy of 3T magnetic resonance imaging in the preoperative localisation of parathyroid adenomas: comparison with ultrasound and 99mTc-sestamibi scans. Eur Radiol 2018 May 7 [Epub ahead of print], doi: 10.1007/s00330-018- 5437-8.
46. Nael K, Hur J, Bauer A, Khan R, Sepahdari A, Inampudi R, et al. Dynamic 4D MRI for Characterization of Parathyroid Adenomas: Multiparametric Analysis. AJNR Am J Neuroradiol 2015;36:2147–52.
47. Aschenbach R, Tuda S, Lamster E, Meyer A, Roediger H, Stier A, et al. Dynamic magnetic resonance angiography for localization of hyperfunctioning parathyroid glands in the reoperative neck. Eur J Radiol 2012;81:3371–7.
48. Kluijfhout WP, Venkatesh S, Beninato T, Vriens MR, Duh QY, Wilson DM, et al. Performance of magnetic resonance imaging in the evaluation of first-time and reoperative primary hyperparathyroidism. Surgery 2016;160:747–54.
49. Kluijfhout WP, Pasternak JD, Drake FT, Beninato T, Gosnell JE, Shen WT, et al. Use of PET tracers for parathyroid localization: a systematic review and meta-analysis. Langenbecks Arch Surg 2016;401:925–35.
50. Thanseer N, Bhadada SK, Sood A, Mittal BR, Behera A, Gorla AKR, et al. Comparative Effectiveness of Ultrasonography, 99mTc-Sestamibi, and 18F-Fluorocholine PET/CT in Detecting Parathyroid Adenomas in Patients With Primary Hyperparathyroidism. Clin Nucl Med 2017;42:e491–7.
51. Beheshti M, Hehenwarter L, Paymani Z, Rendl G, Imamovic L, Rettenbacher R, et al. 18F-Fluorocholine PET/CT in the assessment of primary hyperparathyroidism compared with 99mTc-MIBI or 99mTc-tetrofosmin SPECT/CT: a prospective dual-centre study in 100 patients. Eur J Nucl Med Mol Imaging 2018;45:1762–71.
52. Araz M, Soydal Ç, Özkan E, Kir MK, İbiş E, Güllü S, et al. The efficacy of fluorine-18-choline PET/CT in comparison with 99mTc-MIBI SPECT/CTin the localization of a hyperfunctioning parathyroid gland in primaryhyperparathyroidism. Nucl Med Commun 2018;39:989–94.
53. Amadou C, Bera G, Ezziane M, Chami L, Delbot T, Rouxel A, et al. 18F-Fluorocholine PET/CT and Parathyroid 4D Computed Tomography for Primary Hyperparathyroidism: The Challenge of Reoperative Patients. World J Surg 2019 Jan 18, [Epub ahead of print] doi: 10.1007/s00268-019-04910-6.
54. Broos WAM, van der Zant FM, Knol RJJ, Wondergem M. Choline PET/CT in parathyroid imaging: a systematic review. Nucl Med Commun 2019;40:96–105.
55. Winters R, Friedlander P, Noureldine S, Ekaidi I, Moroz K, Kandil E. Preoperative parathyroid needle localization: a minimally invasive novel technique in reoperative settings. Minim Invasive Surg. 2011;2011:487076.
56. Gökçay Canpolat A, Şahin M, Ediboğlu E, Erdoğan MF, Güllü S, Demir Ö, et al. Diagnostic accuracy of parathyroid hormone levels in washout samples of suspiciousparathyroid adenomas: A single-centre retrospective cohort study. Clin Endocrinol (Oxf) 2018;89:489–95.
57. Solorzano CC, Carneiro-Pla D. Minimizing cost and maximizing success in the preoperative localization strategy for primary hyperparathyroidism. Surg Clin North Am 2014;94:587–605.
58. Ito F, Sippel R, Lederman J, Chen H. The utility of intraoperative bilateral internal jugular venous sampling with rapid parathyroid hormone testing. Ann Surg 2007;245:959–63.
59. Carneiro-Pla D. Effectiveness of "office"-based, ultrasound-guided differential jugular venoussampling (DJVS) of parathormone in patients with primary hyperparathyroidism. Surgery 2009;146:1014–20.
60. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, Cichon S, Nowak W. Utility of intraoperative bilateral internal jugular venous sampling with rapid parathyroid hormone testing in guiding patients with a negative sestamibi scan for minimally invasive parathyroidectomy-a randomized controlled trial. Langenbecks Arch Surg 2009;394:827–35.
61. Alvarado R, Meyer-Rochow G, Sywak M, Delbridge L, Sidhu S. Bilateral internal jugular venous sampling for parathyroid hormone determination in patients with nonlocalizing primary hyperparathyroidism. World J Surg 2010;34:1299–303.
62. Mazeh H, Chen H. Intraoperative adjuncts for parathyroid surgery. Expert Rev Endocrinol Metab 2011;6:245–53.
63. Yamada T, Ikuno M, Shinjo Y, Hiroishi A, Matsushita S, Morimoto T, et al. Selective venous sampling for primary hyperparathyroidism: how to perform an examination and interpret the results with reference to thyroid vein anatomy. Jpn J Radiol 2017;35:409–16.
64. Ibraheem K, Toraih EA, Haddad AB, Farag M, Randolph GW, Kandil E. Selective parathyroid venous sampling in primary hyperparathyroidism: A systematic review and meta-analysis. Laryngoscope 2018;128:2662–7.
65. Ginsburg M, Christoforidis GA, Zivin SP, Obara P, Wroblewski K, Angelos P, et al. Adenoma localization for recurrent or persistent primary hyperparathyroidism using dynamicfour-dimensional CT and venous sampling. J Vasc Interv Radiol 2015;26:79-86.
66. Jaskowiak N, Norton JA, Alexander HR, Doppman JL, Shawker T, Skarulis M, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroidadenoma. Ann Surg 1996;224:308-20.