Update on Preoperative Parathyroid Localization in Primary Hyperparathyroidism

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Parathyroidectomy is the treatment of choice for primary hyperparathyroidism when the clinical criteria are met. Although bilateral neck exploration is traditionally the standard method for surgery, minimally invasive parathyroidectomy (MIP), or focused parathyroidectomy, has been widely accepted with comparable curative outcomes. For successful MIP, accurate preoperative localization of parathyroid lesions is essential. However, no consensus exists on the optimal approach for localization. Currently, ultrasonography and technetium-99m-sestamibi–single photon emission computed tomography/computed tomography are widely accepted in most cases. However, exact localization cannot always be achieved, especially in cases with multiglandular disease, ectopic glands, recurrent disease, and normocalcemic primary hyperparathyroidism. Therefore, new modalities for preoperative localization have been developed and evaluated. Positron emission tomography/computed tomography and parathyroid venous sampling have demonstrated improvements in sensitivity and accuracy. Both anatomical and functional information can be obtained by combining these methods. As each approach has its advantages and disadvantages, the localization study should be deliberately chosen based on each patient's clinical profile, costs, radiation exposure, and the availability of experienced experts. In this review, we summarize various methods for the localization of hyperfunctioning parathyroid tissues in primary hyperparathyroidism.

Keywords: Hyperparathyroidism, primary; Ultrasonography; Radionuclide imaging; Four-dimensional computed tomography

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a status of normal or elevated parathyroid hormone (PTH) levels despite hypercalcemia [1]. The diagnosis is mostly confirmed by biochemical tests, and the clinical indications for surgery are relatively well established [1]. Surgical resection of the parathyroid lesion is indicated when serum calcium is >1 mg/dL above the upper limit of normal, skeletal or renal involvement is present, or the patient's age is under 50 years [1]. Imaging findings of the para-

thyroid glands are not required to diagnose PHPT or to decide on a treatment plan. Negative imaging does not indicate that there is no need for surgery. However, once a patient is selected as a surgical candidate, imaging is necessary for performing minimally invasive parathyroidectomy (MIP).

Detecting hyperfunctioning parathyroid tissues is not always easy, and there was a dictum that the only localizing study necessary is to locate an experienced parathyroid surgeon [2]. The conventional surgical exploration involves the surgeon exploring the bilateral neck area, finding the pathologic parathyroid

glands, and removing them [3]. However, MIP has been widely accepted as most patients with PHPT have a single parathyroid adenoma [4,5]. MIP has a lower risk of complications, shorter operation time, more rapid recovery, and more favorable cosmetic results than conventional bilateral neck exploration [3,5,6]. Preoperative localization is an integral part of performing MIP because surgeons need a direct approach to the pathologic parathyroid gland. Moreover, when the disease is persistent or recurrent and reoperation is planned, positive preoperative imaging is essential in planning reoperative parathyroidectomy, as the abnormal glands may be in ectopic locations [7,8].

Over the past few decades, advanced modalities for parathyroid localization have been developed. However, no consensus exists regarding the optimal localization procedure and imaging protocol, and the clinical approaches vary depending on local expertise and institutional factors [9]. In this review article, we summarize the modalities for parathyroid localization and clinical considerations for their employment.

ULTRASONOGRAPHY

Ultrasonography is widely used to detect pathologic parathyroid tissue [8,10,11]. Normal parathyroid glands are about 4 mm in size and are usually not visualized on ultrasonography [11]. However, parathyroid adenomas are larger than normal parathyroid glands and appear as round or oval well-defined hypoechogenic structures [10,11]. Larger parathyroid adenomas may show cystic changes, calcifications, and lobulations [10,11]. Ultrasonography is useful for detecting parathyroid adenomas located near the thyroid gland or the upper cervical portion of the thymus. However, ultrasonography often cannot detect parathyroid adenomas located behind the trachea or esophagus, or ectopic lesions [10]. Ectopic parathyroid regions, ranging from the carotid bifurcation to the sternal notch and the carotid artery, are strongly recommended to be included in the ultrasound field [12,13]. The sensitivity of ultrasonography varies depending on the location of the parathyroid lesion; its overall sensitivity was reported to be 55% to 87%, and it is especially low in cases with ectopic parathyroid tissues or normocalcemic PHPT [11,14,15]. The positive predictive value of ultrasonography ranges from 93% to 97%, and its specificity ranges from 40% to 98% [14].

The advantages of ultrasonography include a lack of radiation exposure, low cost, convenience, and the ability to screen for concomitant thyroid gland pathology. However, operator-dependent results and its low sensitivity for ectopic parathyroid tissue, small parathyroid adenomas, and intra-thyroidal masses

are limitations of this modality. False-positive results due to thyroid nodules and enlarged lymph nodes also should be taken into account [11].

Ultrasound-guided fine needle aspiration biopsy (FNAB) with intracystic PTH measurement might be considered in difficult cases. This is a highly specific method for parathyroid localization [16-18]. However, the risk of parathyromatosis, hematoma, abscess, and inflammation is a barrier to its widespread use [19]. In particular, parathyroid FNAB should not be performed when parathyroid cancer is suspected because of the risk of seeding or dissemination of parathyroid tissue [8]. In addition, parathyroid FNAB cannot reliably distinguish between benign and malignant parathyroid lesions [8]. Given the aforementioned risks, parathyroid FNAB should be limited to carefully selected patients [8,16].

RADIONUCLIDE IMAGING

Parathyroid scintigraphy has been employed to detect parathyroid lesions since ^{57}Co-cyanocobalamine and ^{75}Se-selenomethionine were first used [20,21]. However, due to their poor image quality, high radiation dose, and low sensitivity, the clinical use of those radiotracers was abandoned with suboptimal results [22]. Several new radioisotopes, such as technetium-99m (^{99m}Tc), were proposed and drew attention because radionuclide imaging has the advantage of being able to identify the functional status of parathyroid tissue [23,24]. When combined with single photon emission computed tomography/computed tomography (SPECT/CT), radionuclide imaging can provide information on both anatomical structures and functional activity [25].

Positron emission tomography/CT (PET/CT) is a molecular imaging technique that has high sensitivity and spatial resolution [26]. Several PET tracers have been utilized in parathyroid imaging, including ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{11}C-methionine, ^{11}C-choline, and ^{18}F-fluorocholine. In this section, we describe several radionuclide imaging methods that are currently used to localize parathyroid lesions.

^{99m}Tc-sestamibi scintigraphy

In 1989, ^{99m}Tc-sestamibi scintigraphy was first described as a radiopharmaceutical for detecting parathyroid lesions by Coakley et al. [24], and now it is a dominant isotope used for parathyroid scintigraphy [8]. ^{99m}Tc-sestamibi is a lipophilic cationic radiotracer, and its uptake depends on plasma and mitochondrial membrane potentials. Since adenomatous and hyperplastic parathyroid tissue has a large number of mitochondria in oxy-

phil cells, ^{99m}Tc-sestamibi uptake is avid and the washout is slow [25]. In contrast, uptake clears more rapidly in thyroid tissue than in parathyroid tissue [27]. Additionally, P-glycoprotein expression is associated with the transport of ^{99m}Tc-sestamibi across the cell membrane [28,29]. A transmembrane protein, P-glycoprotein is an energy-dependent influx and efflux pump [30]. Abnormal parathyroid tissues have lower levels of P-glycoprotein expression than normal parathyroid glands, leading to greater sestamibi retention [30].

Sestamibi scintigraphy is widely available and relatively inexpensive. Moreover, it has a wide imaging field which allows the detection of ectopic glands [22]. However, thyroid nodules, inflammatory thyroiditis, and lymphadenopathy might result in false-positive scans [31,32], and false-negative imaging results can occur for parathyroid adenomas weighing less than 600 to 800 mg [33]. The sensitivity of ^{99m}Tc-sestamibi scans was reported to range widely from 60% to 90% due to variations in study protocols and disease characteristics [34,35]. The sensitivity markedly decreased (30% to 45%) in patients with parathyroid hyperplasia or multiple adenomas [36].

To improve the sensitivity and obtain additional anatomical information, a protocol that combined ^{99m}Tc-sestamibi and SPECT/CT was developed, and its diagnostic value was validated [37-39]. SPECT/CT is a combination of SPECT with CT, and the addition of SPECT/CT to a ^{99m}Tc-sestamibi scan improves sensitivity [38]. It not only provides anatomical information but also makes it possible to differentiate parathyroid lesions from other sources of ^{99m}Tc-sestamibi uptake, including thyroid nodules and cervical lymph nodes [40]. In a meta-analysis by Wong et al. [41], ^{99m}Tc-sestamibi-SPECT/CT showed an estimated pooled sensitivity of 86% (95% confidence interval [CI], 81% to 90%), which was superior to that of planar imaging (70%; 95% CI, 61% to 80%) and SPECT (74%; 95% CI, 66% to 82%). However, its sensitivity is unsatisfactory in specific situations such as multiglandular disease and ectopic adenoma [42,43]. According to the study by Tay et al. [44], the sensitivity of ^{99m}Tc-sestamibi SPECT/CT was 78% in patients with single-glandular disease, whereas it was only 31% in multiglandular disease. Moreover, the detection rate of ^{99m}Tc-sestamibi might be limited in cases with low PTH levels or normocalcemic PHPT [15,45]. However, it is currently used as a first-line imaging modality despite the several limitations mentioned above [46].

^{11}C-methionine PET/CT scans
^{11}C-methionine accumulates in abnormal tissue of the parathy-

roid gland, making it a promising radiopharmaceutical in parathyroid imaging [47]. Although the exact mechanism of ^{11}C-methionine uptake by parathyroid glands is not fully understood, ^{11}C-methionine might be involved in the synthesis of pre-pro-PTH [48]. The clinical use of ^{11}C-methionine-PET (MET-PET) for parathyroid disease was first described in 1994 [49], and the evolution from PET to PET-CT led to more accurate identification and localization of parathyroid lesions [47]. MET-PET/CT has been reported to show a comparable sensitivity to that of other traditional scintigraphy methods [50]. The per-patient sensitivity of MET-PET/CT and ^{99m}Tc-sestamibi-SPECT/CT was 65% and 61%, respectively [50]. The per-lesion sensitivity of MET-PET/CT and ^{99m}Tc-sestamibi-SPECT/CT was 91% and 73% for parathyroid adenomas, without a statistically significant difference [50]. However, Weber et al. [51] reported that the sensitivity of MET-PET/CT was markedly lower in multiglandular disease (67%) than in detecting a single parathyroid adenoma (83%). The lower sensitivity for multiglandular disease was probably because the hyperplastic glands had less PTH synthesis and lower uptake of ^{11}C-methionine than parathyroid adenomas [52]. Another limitation is the short half-life of ^{11}C, leading to limited availability of the ^{11}C-methionine tracer, its high cost, and a substantial workload for preparation [47,53,54].

Choline PET/CT scans
Radiolabeled choline (^{11}C-choline or ^{18}F-choline) has recently been explored and used as a promising PET tracer for detecting hyperfunctioning parathyroid tissue. Choline uptake is increased by choline kinase upregulation, and phospholipid-dependent choline kinase is upregulated where PTH is oversecreted. Based on this, radiolabeled choline PET can be used to detect parathyroid lesions [55,56]. ^{18}F-choline PET has wider availability than ^{11}C-choline PET because it has a long half-life; thus, it does not need an on-site cyclotron [55].

Compared to MET-PET/CT, ^{18}F-choline PET/CT was reported to be more sensitive for parathyroid localization in patients with PHPT who had negative or inconclusive ^{99m}Tc-sestamibi-SPECT [57]. The per-patient sensitivity of ^{18}F-choline PET/CT and MET-PET/CT was 96% and 60%, respectively [57]. Moreover, ^{18}F-choline PET/CT showed comparable or superior sensitivity compared to ^{99m}Tc-sestamibi-SPECT/CT [42,58]. In a study by Araz et al. [58], the sensitivity of ^{18}F-choline PET/CT and ^{99m}Tc-sestamibi SPECT/CT was 96% and 78%, respectively.

Other advantages of ^{18}F-choline PET/CT include a shorter imaging time [42], higher spatial resolution [59], and a lower

radiation dose (2.8 mSv) than ^{99m}Tc-sestamibi SPECT/CT (6.8 mSv) [60-62]. Despite its superior diagnostic performance compared to conventional imaging in detecting parathyroid lesions, its use is still limited due to its high cost and low availability [61].

Other radionuclide imaging in special situations

^{18}F-FDG is the most widely available PET tracer. It reflects metabolic activity by measuring the accumulation of FDG, which is an analog of glucose [63]. ^{18}F-FDG PET is used to detect malignancy, monitor treatment response, and predict the disease prognosis [63]. As with other tumors, ^{18}F-FDG PET can be employed for parathyroid cancer [64,65]. A case report by Neumann et al. [65] showed that ^{18}F-FDG PET could localize recurrent postoperative parathyroid cancer cases that ^{99m}Tc-sestamibi scintigraphy and magnetic resonance imaging failed to detect. Several studies have investigated the role of ^{18}F-FDG PET in parathyroid adenoma based on the hypothesis that FDG would accumulate in parathyroid adenoma in a sufficient amount to be visualized on PET images [66-68]. In the 1990s, the Neumann et al. [66] reported that ^{18}F-FDG PET showed superior sensitivity compared to ^{99m}Tc-sestamibi-SPECT, and suggested ^{18}F-FDG PET as a promising tool for preoperative localization in patients with PHPT [67]. In contrast, Melon et al. [68] concluded that the sensitivity of ^{18}F-FDG-PET is too low for preoperative parathyroid detection in PHPT. At present, ^{18}F-FDG-PET is not widely utilized in parathyroid adenoma patients. The possible false-positive results due to inflammation should be considered [69,70].

With the advent of radiolabeled peptides, somatostatin receptor PET imaging, such as gallium^{68} (^{68}Ga)- 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-D-Phe1-Tyr3–octreotide (TOC) PET, ^{68}Ga-DOTA-1-Nal3-octreotide PET, and ^{68}Ga-DOTA-D-Phe1-Tyr3-octreotate PET has emerged for detecting neuroendocrine tumors [71]. In neuroendocrine tumors, the lesion identification rate of ^{68}Ga-DOTA-TOC PET was higher than that of somatostatin receptor scintigraphy [72-74]. It was hypothesized that somatostatin receptor PET imaging might be utilized in parathyroid adenomas that express surface somatostatin receptors [75]. However, in a study by Froeling et al. [76], MEN-associated parathyroid adenomas were not detected by ^{68}Ga-DOTA-TOC PET and were identified by only CT. To date, somatostatin receptor PET imaging is not generally recommended as an ideal imaging modality for parathyroid adenomas [75,76].

FOUR-DIMENSIONAL COMPUTED TOMOGRAPHY

Conventional CT is usually not used for parathyroid localization due to its inferiority to other modalities [22]. Parathyroid four-dimensional-CT (4D-CT) was first recognized as a tool for localization in 2006 by Rodgers et al. [77]. The name of 4D-CT is derived from the fact that a dimension from the changes in contrast perfusion over time is added to three-dimensional CT [77]. A 4D-CT examination consists of pre-contrast, post-contrast, and delayed phases. In the pre-contrast image, parathyroid adenomas have similar attenuation as the surrounding muscles and are distinguished from the iodine-rich dense thyroid gland [11]. In early and delayed post-contrast images, parathyroid adenomas are seen as hypervascular tissue with variable enhancement and rapid washout.

In previous studies, 4D-CT demonstrated better sensitivity than ^{99m}Tc-sestamibi scans and ultrasonography [78,79]. In a study by Starker et al. [78], 4D-CT showed higher sensitivity (85.7%) than ^{99m}Tc-sestamibi-SPECT (40.4%) and ultrasonography (48%). It also showed superior sensitivity in reoperative cases [79]. In patients who had previous neck surgery, 4D-CT had a sensitivity of 88%, which was superior to ^{99m}Tc-sestamibi (54%) or ultrasonography (21%) [79]. Moreover, 4D-CT can be useful in patients with multiglandular disease or ectopic glands, although multiglandular disease remains a challenging clinical entity even with 4D-CT [79-81]. The main drawback of 4D-CT is the high radiation dose to the patient despite the use of dose reduction techniques [82,83]. A high false-positive rate, difficult interpretation, and low availability are also limitations of this modality [22]. Still, when ultrasonography and ^{99m}Tc-sestamibi scans are negative and SPECT/CT is not available, 4D-CT might be a beneficial method both in primary and reoperative cases.

PARATHYROID VENOUS SAMPLING IN DIFFICULT CASES

Selective parathyroid venous sampling (PVS) can be a useful technique when localization is inconclusive with the noninvasive tests described above or when the disease recurs after the first operation [22,84]. Venous access is usually acquired via the femoral vein, and blood samples are obtained from the superior vena cava, bilateral brachiocephalic, internal jugular, vertebral, thymic, and superior, middle, and inferior thyroid veins [22]. Although a 2-fold higher PTH level than the peripheral level

was conventionally used as a cutoff value [85,86], the optimal cutoff has not been fully validated. In a recent study, a 1.5-fold elevation of PTH was suggested as an optimal cutoff that improved discriminative performance [87]. The sensitivity of PVS has been reported to range from 71% to 90% due to the significant heterogeneity of enrolled patients and methodology [84,88-90]. In cases of persistent or recurrent PHPT, PVS showed significantly higher sensitivity than 99mTc-sestamibi-SPECT, which were 75% versus 30%, respectively [91]. PVS also demonstrated a high concordance rate (94.1%) with the pathological examination in cases with negative or inconsistent imaging tests [92].

One of the main concerns regarding PVS is its invasiveness. Bleeding, infection, arteriovenous fistulae, and pseudoaneurysms are possible complications of PVS, although they rarely occur [92]. Radiation exposure during PVS ranges from 1.26 to 5.3 mSv, which is approximately half the dose of 4D-CT (10.4 mSv) [93,94]. Other drawbacks of PVS include its relatively high cost and the need for experienced radiologists [10].

Due to these limitations, the use of PVS is considered only in cases of reoperation or difficult localization [8,10]. However, considering that an accurate localization by PVS enables the use of MIP, PVS can be a promising tool for localization in difficult cases.

FUTURE DIRECTIONS: INTRAOPERATIVE LOCALIZATION

Parathyroid glands are small and their location varies widely. Therefore, distinguishing parathyroid glands from the surrounding tissue is often difficult during neck surgery. This task is particularly difficult when the pathogenic glands are smaller and multiglandular, as is often observed in normocalcemic PHPT [95,96]. Frozen section analysis and intraoperative PTH assays are traditional methods of parathyroid tissue confirmation [8]. However, the confirmation cannot be made before the gland is surgically resected. Moreover, these methods are invasive or require a longer operative time [97].

A gamma probe is a handheld gamma detector that can be utilized intraoperatively after radionuclide injection [98]. It was once speculated that using a gamma probe after preoperative 99mTc-sestamibi injection would not be beneficial in cases with a negative 99mTc-sestamibi scan [99]. However, Buicko et al. [99] reported that a gamma probe showed high sensitivity (90.5%) in identifying parathyroid adenoma in patients with negative preoperative 99mTc-sestamibi scans. Moreover, the gamma probe was effective in cases with multiple or ectopic parathyroid adenomas [99-101]. Jaskowiak et al. [102] reported two reoperative cases with dense scars and obscured anatomy in which a gamma probe provided crucial aid in localization. However, the utility of gamma probes remains limited to an adjunctive role, and it cannot replace preoperative imaging or localization modalities [103].

As another intraoperative localization technique, fluorescence imaging has been proposed, as it is a real-time, accurate and rapid technique that can be used to identify parathyroid glands before they are resected [97,104]. It can be employed both in parathyroidectomy and thyroidectomy, so that postsurgical hypoparathyroidism can be avoided [97]. The parathyroid gland shows a unique pattern of autofluorescence and is displayed in the blue color channel when exposed to near-infrared light [104]. The intensity of fluorescence appears greater in parathyroid tissue than in other surrounding tissues such as the thyroid, lymph nodes, and adipose tissue [104]. Methylene blue and aminolevulinic acid have been studied as exogenous contrast materials in near-infrared autofluorescence (NIRAF) imaging [105,106].

The use of NIRAF imaging in the localization of hyperfunctioning parathyroid tissue is still limited because the accuracy of NIRAF in distinguishing pathologic from normal parathyroid glands has not been fully validated, with inconsistent reports reported in the literature [107-110]. Some studies reported that adenomas had higher NIRAF intensity than normal parathyroid glands [108], but others reported contradictory findings [107, 109,110]. Pathologic parathyroid glands showed lower NIRAF intensity in other situations [107], or similar intensity compared to normal parathyroid tissue [109,110]. The first report on the NIRAF pattern of parathyroid carcinoma was recently published as a case series, and autofluorescence was absent in three patients with parathyroid cancer [111]. Further studies are warranted to determine whether NIRAF can be used to detect hyperfunctioning parathyroid tissue in patients with PHPT.

In cases when all glands should be exposed, such as multiglandular disease, recurrent PHPT, multiple endocrine neoplasia, and secondary hyperparathyroidism, these intraoperative localization techniques may offer a benefit for detecting the parathyroid glands [104,112]. The routine use of NIRAF or gamma probes is not currently widely accepted.

CONCLUSIONS

Although several parathyroid imaging modalities have been developed, no consensus exists regarding their indications and ap-

Table 1. Advantages and Disadvantages of Localization Modalities

	Advantages	Disadvantages
Ultrasonography	Inexpensive Lack of radiation exposure Convenient Widely available	Operator-dependent Limited ability to assess ectopic glands
Technetium-99m-sestamibi scan-SPECT/CT	Assessment of ectopic glands Acquisition of both functional and anatomical information	False-positive results Low sensitivity in detecting multiglandular disease
[11]C-methionine-positron emission tomography	Assessment of ectopic glands	Low availability Short half-life (20 minutes) Low sensitivity in detecting multiglandular disease
Choline-positron emission tomography	High sensitivity Assessment of ectopic glands	High costs Low availability
Four-dimensional computed tomography	Anatomical detail Assessment of multiglandular disease and ectopic glands	High radiation dose Difficult interpretation Low availability
Parathyroid venous sampling	Assessment of ectopic glands, recurrent disease, and discordant or unlocalized lesions by various imaging studies	Invasive High cost An experienced radiologist is required
Near-infrared autofluorescence	Real-time, rapid technique	Not well validated in detecting hyperfunctioning parathyroid tissue

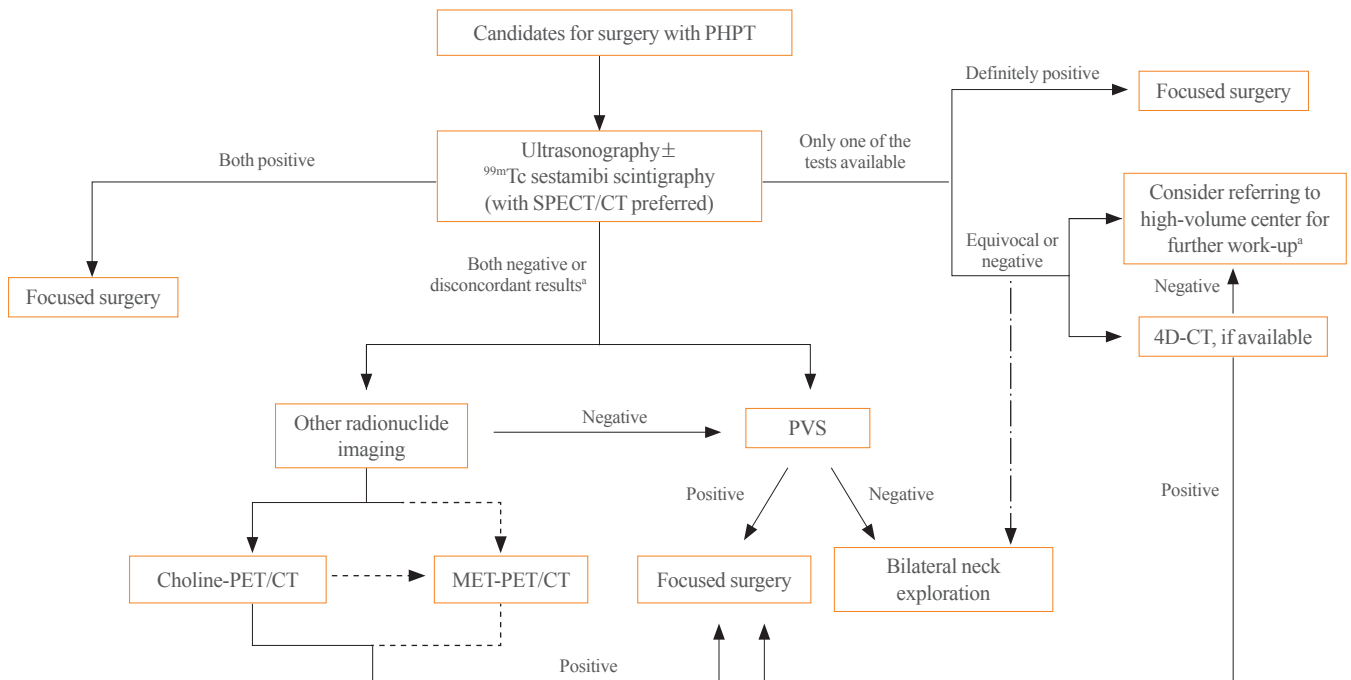SPECT/CT, single photon emission computed tomography/computed tomography.

Fig. 1. Possible preoperative localization process for primary hyperparathyroidism. Dashed lines (---): Choline-positron emission tomography (PET) could be preferred to ^{11}C-methionine (MET)-PET. Dot-dashed lines (—·—·): This process could be chosen with an experienced parathyroid surgeon. PHPT, primary hyperparathyroidism; SPECT/CT, single photon emission computed tomography/computed tomography; PVS, parathyroid venous sampling; 4D-CT, four-dimensional computed tomography; PET/CT, positron emission tomography/computed tomography. [a]When a patient is referred to a high-volume center, this process might be followed.

plications, leading to their less efficient usage or underutilization in clinical practice. Thus, we reviewed the current preoperative localization of parathyroid glands in patients with PHPT in this article. Table 1 summarizes the advantages and disadvantages of each preoperative modality, and Fig. 1 depicts the possible preoperative localization process for surgical candidates with PHPT.

A combination of ultrasonography and ^{99m}Tc-sestamibi SPECT/CT is currently a favored approach to localize pathologic parathyroid tissue at most institutions. These modalities have fair sensitivity when the etiology is a single adenoma containing an ample amount of mitochondria. However, PHPT may arise from multifocal lesions with various histology, including smaller adenoma, hyperplasia, or cancer. The sensitivity of conventional imaging modalities is low for pathologic parathyroid lesions that are multiglandular or ectopic [113,114]. Parathyroid localization is challenging in patients with previous neck surgery; recurrent, persistent, or normocalcemic hyperparathyroidism; ectopic parathyroid glands; multiglandular disease; or parathyroid hyperplasia [45,114,115].

Choline PET and 4D-CT are imaging tests that might provide superior localization in certain situations. Because previous studies have reported superior sensitivity of choline PET compared to MET-PET [57,116], choline PET could be preferred to MET-PET. PVS is an invasive technique, but it plays an important role in difficult cases such as remedial cases or those with negative imaging tests. However, modalities such as choline PET, MET-PET, 4D-CT, and PVS are not widely available. Therefore, it might be helpful to repeat ^{99m}Tc-sestamibi SPECT/CT at a high-volume center when the first scan is negative [117]. Unfortunately, appropriate localization is still clinically challenging in cases with multiglandular disease and parathyroid hyperplasia. New methods, including NIRAF, are being studied and are expected to enable better preoperative localization in the future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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