The role of radionuclide imaging in the surgical management of primary hyperparathyroidism

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Running title: Parathyroid imaging

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Total word count: 6716

Disclosure summary: The authors have nothing to disclose.

Abstract

Primary hyperparathyroidism is a frequent and potentially debilitating endocrine disorder for which surgery is the only curative treatment. The modalities of parathyroid surgery have changed over the last two decades, as conventional bilateral neck exploration is no longer the only surgical approach. Parathyroid scintigraphy plays a major role to define the surgical strategy, given its ability to orient a targeted (focused) parathyroidectomy and to recognize ectopic locations or multiglandular disease.

This review, which represents a collaborative effort between nuclear physicians, endocrinologists and endocrine surgeons, emphasizes the importance of performing imaging prior to any surgery for primary hyperparathyroidism, even in case of conventional bilateral neck exploration. We discuss the advantages and drawbacks of targeted parathyroidectomy and the performance of various scintigraphic protocols to guide limited surgery. We also discuss the optimal strategy to localize the offending gland before reoperation for persistent or recurrent hyperparathyroidism. Finally, we describe the potential applications of novel PET tracers with special emphasis on 18F-fluorocholine.

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Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder after diabetes and hyperthyroidism (*1*). The prevalence in women over 50 is about 2% (*2*). The diagnosis is often done in asymptomatic subjects during a routine serum calcium measurement (*1, 3*). PHPT classically associates elevated total serum calcium (after adjustment for albumin concentration) and elevated serum PTH level. However, in some patients PTH levels may be normal but inappropriate to hypercalcemia. Patients with vitamin D insufficiency may have higher PTH levels and thus 25(OH)D should be measured. One important differential diagnosis, because surgery is not warranted, is familial hypocalciuric hypercalcemia, which is due to heterozygous calcium-sensing receptor gene (*CaSR*) mutations and is associated with low urinary calcium.

The clinical signs and symptoms that are often associated with symptomatic PHPT involve the skeleton (osteoporotic fractures, pain, bone lesions, chondrocalcinosis), the kidneys (nephrolithiasis, nephrocalcinosis, impaired renal function) and, more rarely nowadays, the digestive tract (peptic ulcers, constipation, pancreatitis) and the cardiovascular system (hypertension) (*1-4*). PHPT may also cause neuropsychiatric symptoms, cognitive impairments and decreased quality of life. Hypercalcemic crisis is rare but is a life-threatening medical emergency.

Patients with asymptomatic PHPT may remain stable over many years or show progression. After 15 years of prospective follow-up, about one third of subjects develop additional signs of the disease (e.g., kidney stones, worsening hypercalcemia, reduced bone mineral density or fragility fractures) (*3*).

Surgery is the only curative treatment for PHPT. According to recent recommendations (*4*), surgery is indicated in any patient younger than 50, any symptomatic patient, and in asymptomatic patients with any of the following parameters at diagnosis or during follow-up: serum calcium >0.25 mmol/L (>1 mg/dL) above the upper limit of normal; a calculated creatinine clearance <60ml/min; a 24h-urine calcium >10 mmol (>400mg) and increased stone risk; nephrolithiasis or nephrocalcinosis on imaging (X-ray, ultrasound or CT); osteoporosis (T score of -2.5 or lower at lumbar spine, total hip, femoral neck, or distal 1/3 radius, measured by dual-energy X-ray absorptiometry), or vertebral fracture on imaging studies.

Although a single parathyroid adenoma is the most frequent occurrence, multiglandular disease (MGD) with two, sometimes three, adenomas or a multiglandular hyperplasia is present

in 15-20% of cases (*1, 5*). Parathyroid carcinoma is rare (<1% of cases of PHPT) and is associated with a ten-year recurrence-free and disease-specific survival of 69% and 91%, respectively (*6*).

MGD can be either sporadic or hereditary, such as in isolated familial PHPT or in MEN 1 (menin gene *MEN1* mutation), MEN 2A (*RET* oncogene mutation), MEN 4 (*CDKN1B* mutation) and hyperparathyroidism-jaw tumor (*HRPT2/CDC73* mutation; risk of parathyroid carcinoma) syndromes (*7*). MEN 2B (also called MEN-3) is rarely associated with PHPT. Parathyroid involvement is observed in 95% of MEN1 cases and is most often the initial manifestation. A correct diagnosis of MEN1 is important for performing adequate initial surgery and for early detection of other associated endocrinopathies (pancreaticoduodenal, pituitary, or thymic tumors and occasional bronchial carcinoids) (*7, 8*). It must be suspected in case of MGD or in case of PHPT in subjects younger than 30. Long-term treatment with lithium or a history of neck radiation is also associated with MGD.

About 10 to 15% of normal subjects harbor a "fifth parathyroid gland" (*9*). Supernumerary glands can cause recurrent disease (e.g., in MEN1).

Conventional surgery for PHPT relies on the inspection of the four parathyroid glands through bilateral cervical exploration (*5*). In recent years, there has been a significant shift towards targeted operations (*10*), which may be performed during open surgery (*7, 10*), or by endoscopic approaches (*11*). This shift has been driven by two technological developments: more sensitive imaging techniques, which enabled the preoperatory detection of the lesions, and intraoperative PTH monitoring, to verify the absence of other hyperactive glands (*12*).

Proposed by the team of O'Doherty and Coakley (*13*), ^{99m}Tc-MIBI scintigraphy rapidly gained widespread acceptance and rendered thallium-201 parathyroid scan obsolete. It was recognized as the most sensitive noninvasive imaging study in PHPT (*14-16*). Parathyroid ultrasound is often used as a complementary imaging technique, although its effectiveness depends on operator's skills (*10*). As stated in the EANM and SNMMI parathyroid guidelines, imaging is optional before bilateral surgery of PHPT, but is strongly recommended before targeted surgery or in case of re-intervention *(17, 18)*. Surgery of hyperparathyroidism secondary to renal failure is not discussed here. In these patients, preoperative scintigraphy can help select the least autonomous parathyroid tissue for preservation and identify ectopic or supernumerary parathyroid glands (*19-21*) which are the main cause of recurrent disease (*22*).

This review article addresses some key points related to imaging of PHPT. It is the product of collaboration between nuclear physicians, endocrinologist and endocrine surgeons and complies with ethical guidelines of the authors' institutions.

USEFULNESS OF PREOPERATIVE IMAGING PRIOR TO CONVENTIONAL BILATERAL SURGERY

Without imaging, bilateral cervical exploration is curative in 92-95% of patients operated for PHPT, as shown by older studies done before modern imaging was available (*5*). Indeed, an experienced surgeon can identify the majority of pathological glands (*9, 23-25*).

However, preoperative imaging allows selecting patients eligible for targeted surgery and identifying ectopic glands. The incidence of ectopic glands is estimated at 6 to 16% (*24*). The majority of ectopic glands present a minor ectopia (e.g. in thyrothymic ligaments, tracheo-esophageal groove or partially embedded in the thyroid) and are easily located by an experienced surgeon. However, some parathyroid glands present major ectopia, which might lead to surgery failure, even for experienced surgeons, and can be a source of medical litigation. For example, 1 to 2% of subjects have ectopic glands that require thoracic surgery instead of cervical surgery (*23, 24*).

In agreement with recent recommendation (*16*), we think that preoperative imaging should always be performed. Good imaging should be effective, provide morphological and functional information, be non-invasive and not too expensive. These conditions can be fulfilled by combining cervical ultrasound and scintigraphy.

Positive parathyroid scans

Even in case of classical bilateral cervicotomy, preoperative imaging allows: 1 - Reducing the extent of anatomical dissection or unnecessary thyroid resections and morbidity, especially with regards to recurrent laryngeal nerve palsy, hypoparathyroidism, hematomas. 2 - Reducing operation time; the surgeon starts by exploring the suspected site and the tumor can be sent for pathology examination meanwhile the surgeon proceeds with inspection of the remaining

parathyroid glands (*26*). 3 - Detecting ectopic cervical glands without the need of extensive dissections. 4 - Detecting thoracic glands which are not accessible through the neck (*26*).

In a retrospective series of 202 resected ectopic glands (major and minor ectopias), preoperative scintigraphy had a sensitivity of 89% and a positive predictive value of 90%. Among 59 patients who underwent both scintigraphy and ultrasound, scintigraphy was superior to ultrasound in 28 patients and inferior in 3 (*27*). Ultrasound detection is hampered in case of retrotracheal/retroesophageal or intrathoracic parathyroid gland.

Ectopias can be acquired or congenital. Tumors from superior parathyroid glands (also named P4) might prolapse along the tracheo-esophageal groove into the lower neck or upper mediastinum, and can be found in para- or retro-esophageal position. By contrast, ectopias of the lower parathyroids (P3) are often congenital due to an abnormal migration of the glands. They may be located close to carotid and jugular vessels in the neck or inside the thymus in the anterior mediastinum. More rarely, pathological glands can be associated with the vagal nerve within the carotid sheath, or in the aorto-pulmonary window. Parathyroid glands completely buried in the thyroid parenchyma may be derived from P3, P4 or be supernumerary glands.

Suspecting a MGD on preoperative imaging may help the surgeon planning the surgical approach.

Finally, although thyroid nodules might be a cause of false positives on parathyroid scintigraphy, it should not be forgotten that a MIBI-positive, iodine-negative thyroid nodule is suspect of malignancy (*28*) and might justify fine-needle biopsy before parathyroid surgery.

Negative parathyroid scans

In principle, imaging results should not influence the surgical decision (*12, 29*). However, some recent studies (*30-32*), although not all (*33*), reported that surgical failure rate is higher when preoperative imaging studies are negative.

According to a multicentric study, patients with negative ultrasound and scintigraphy had smaller parathyroid lesions and a higher proportion of hyperplasia (22%). Moreover, cervicotomy involved a higher number of extended surgical procedures, such as thyroidectomy and thymectomy. Finally, PHPT was still present in 18% of subjects after surgery (*30*). Even in a center of great experience as the Mayo Clinic, the surgical failure rate in scintigraphy-negative patients can be as high as 10%, despite the use of intraoperative PTH assay (*31*).

Thus, a negative imaging is also informative and indicates that an experienced multidisciplinary team, including a surgeon, an endocrinologist, and imaging specialists should be entrusted with the case.

ADVANTAGES AND DRAWBACKS OF TARGETED SURGERY

Targeted parathyroidectomy entails several advantages: a lower rate of complications, such as hypoparathyroidism, nerve injury, or unaesthetic scars, a shorter operation time, and a higher possibility of outpatient surgery and local anesthesia.

The option of targeted surgery should however be entertained only if the rate of failure (e.g. unrecognized MGD) is acceptably low. A Swedish randomized study (*34*) showed an advantage for unilateral surgery, in terms of operative time and incidence of transient hypocalcemia, while the rate of failure (persistent or recurrent hyperparathyroidism) was not significantly higher (8.5% for unilateral surgery vs. 4.5% for bilateral surgery). However, a potential bias to these comparisons is that patients randomized for bilateral surgery did not undergo scintigraphy (*26*).

In order to reduce the risk of failure, several institutions associate targeted surgery with intraoperative PTH monitoring (*7*). PTH has a short half-life in plasma (2 to 4 minutes). According to the widely used Miami criterion (*35*), a 50% decrease in PTH levels 10 minutes after removal of the putative lesion suggests a curative surgery. However, the procedure might sometimes yield inaccurate results, as when PTH concentrations decrease even in presence of a second smaller lesion (*36, 37*). The prevalence of MGD, estimated on the basis of intraoperative PTH monitoring, is about 5% (*35*), much lower than the conventional rate of 15-20% (*5, 38*). Intraoperative PTH monitoring might also wrongly lead to bilateral surgery, due to delayed decay of PTH in case of excessive mobilization of the adenoma before its removal or slow elimination kinetics in some patients.

Although recommended when performing targeted parathyroidectomy (*7*), rapid PTH assays is not available to most surgeons worldwide (*7*). Moreover, PTH monitoring prolongs operation time and limits the feasibility of local anesthesia. As an alternative to intraoperative

PTH, some surgeons recommend inspection of the ipsilateral gland (*39*). In case of double-adenomas, however, bilateral distribution is expected, not only because of probability (two thirds of the cases), but also because they often originate from the two superior glands (*40*).

Another point to consider is that targeted surgery might require conversion to bilateral surgery in about 20% of cases (*41, 42*). Conversion is often due to imaging failure: wrong localization, multi-glandular disease missed by imaging and identified by inspection of the ipsilateral gland or intraoperative PTH monitoring (*41*).

In summary, as stated in the SNMMI and EANM guidelines, a good preoperative imaging study can play a major role in the selection of candidates for targeted surgery (17, 18).

PERFORMANCE OF DIFFERENT SCINTIGRAPHIC PROTOCOLS TO GUIDE TARGETED SURGERY

A valuable pre-surgical imaging technique should be able to 1) identify MGD, 2) limit the rate of false positives (e.g. thyroid nodules) and 3) detect small lesions. Small lesions are more and more frequent, because of earlier detection of PHPT. In the study of Almquist, the median weight of adenomas decreased from 750 mg for women operated between 1990 and 1995 to 520 mg for those operated between 2000 and 2007 (*43*).

Ultrasound is not accurate enough to be used alone for targeted surgery. It has low sensitivity for MGD or ectopic lesions. In the study by Haber and colleagues (*44*), ultrasound recognized only 17% of MGD cases (1/6) and 25% of ectopic glands (2/8).

Although a meta-analysis showed that scintigraphy is superior to ultrasound, its sensitivity decreases in case of MGD (88.44% for single adenoma, 44.46% for hyperplasia; 29.95% for dual adenoma). Moreover, sensitivity varies greatly among different studies (*15*). Description of the single-tracer "dual-phase" and dual-tracer "subtraction" parathyroid scintigraphy protocols can be found in the SNMMI and EANM guidelines (17, 18). A summary of the techniques is also provided in Table-1 (supplementary data).

Dual-phase ^{99m}Tc-MIBI scintigraphy, generally using a parallel collimator and images at 15 min and 2-3h, cannot detect MGD most of the times (*45, 46*). Indeed, many hyperplastic parathyroid lesions do not significantly retain the tracer at a late time. Among the eleven MGD patients of the study by Martin et al, double-phase scintigraphy wrongly suggested a single

adenoma in nine cases and was negative in the remaining two (*46*). In addition, this technique has a high rate of false positives, due to the absence of a thyroid-specific tracer. The sensitivity of ^{99m}Tc-MIBI single-tracer scintigraphy can be improved by adding pinhole acquisitions and SPECT/CT (*47*). The percentage of detected MGD cases remains, however, limited. Therefore, we think that single-tracer dual-phase scintigraphy cannot reliably guide targeted parathyroid surgery.

For the same reason, the use of intraoperatory gamma probes to opt for targeted surgery has severe limits. Murphy and Norman argued that any excised tissue containing more than 20% of background activity, in a patient with positive ^{99m}Tc-MIBI scan, is likely to be a solitary adenoma (*48*). However, because MGD is rarely seen on late scintigraphic images (*17, 46*), this approach has been recently abandoned by the very team who first proposed it (*49*).

Importance of Simultaneous Dual-Tracer Imaging

Hindié and colleagues proposed a ^{99m}Tc-MIBI/^{123}I subtraction protocol based on the simultaneous acquisition of the two tracers (instead of a sequential acquisition) (*26*). Dual-isotope acquisition is possible by using two narrow and non-overlapping energy windows. This approach minimizes motion artifacts, allows a better sensitivity and reduces acquisition time (*50*). In addition to the cervico-mediastinal image, a magnified view of the thyroid bed area with a pinhole collimator increases spatial resolution and thus the sensitivity to detect hyperfunctioning parathyroid glands (*50*) (Fig-1). The advantages of dual-isotope subtraction scintigraphy have been highlighted by several recent studies (*51-54*). In a comparative analysis on 37 patients (41 lesions), Caveny and colleagues confirmed the superiority of the simultaneous dual-tracer technique over the single-tracer "double-phase" protocol both in terms of sensitivity (94% vs. 66%, p <0.01) and number of false positive foci (0 *vs.* 2). The authors also suggested that, in light of the information obtained with subtraction images, the late ^{99m}Tc-MIBI image did not provide any additional information (on the contrary, it reduced the sensitivity and confidence in the interpretation of the data) (*51*). The same team also underscored the importance of adding a pinhole acquisition; the use of a parallel collimator alone would result in a loss of about 20 points of sensitivity (*53*).

Simultaneous dual-isotope acquisition has high sensitivity for the identification of MGD (*55*) (Fig-2). Careful image analysis is nevertheless required because MGD is commonly

characterized by the presence of glands of unequal size and unequal intensity of tracer uptake (*55*). Thus, a pinhole view is necessary for optimal sensitivity (*17, 53, 54*). Moreover, image subtraction should be carefully monitored. A subtraction by gradual steps is preferable to avoid that smaller glands disappear with the background (*17*).

If not available, ^{123}I can be replaced by ^{99m}Tc-pertechnetate; the sensitivity for MGD detection is about 60% (*56, 57*). In fact, the use of ^{99m}Tc-pertechnetate precludes the acquisition of a simultaneous image and the subtraction image may thus suffer from motion artifacts. Moreover, dual isotope SPECT/CT acquisition would not be possible.

Dual-tracer imaging should be performed at least three weeks after radiologic examinations involving iodine contrast media administration. Also, thyroid hormone replacement therapy should be withheld for two weeks before imaging. This is necessary even in case of previous thyroidectomy as ^{123}I would allow the correct identification of residual thyroid tissue, which can be mistaken for an enlarged parathyroid on ^{99m}Tc-MIBI single-tracer scintigraphy or at neck ultrasound (Fig-3).

The Role of Dual Isotope SPECT/CT

Tomographic imaging of parathyroids (SPECT or SPECT/CT) is less sensitive than, and therefore cannot replace, pinhole imaging, especially because the shoulders stand in the field of view (*58*). In a prospective study by Neumann and colleagues, subtraction SPECT/CT had an overall sensitivity of 70% (*59*). The subtraction of dual-isotope tomographic images is more complex than with pinhole planar images. In our clinical practice, we prefer to compare visually the three tomographic projections of ^{99m}Tc-MIBI and ^{123}I images, without subtraction. We perform subtraction only on the pinhole images (Fig-2).

However, complementary SPECT/CT provides useful information (59, *60*), such as the correct anatomical localization of a lesion on the anteroposterior axis. For instance, posterior adenomas are preferably resected through a lateral approach. When SPECT/CT machines were not available, this information was less accurately obtained through anterior oblique or lateral pinhole views. Lateral views, and now SPECT/CT, can also help differentiate thyroid from parathyroid foci, or identify a parathyroid lesion situated behind a thyroid nodule or behind another parathyroid lesion (*51, 55, 58*).

Finally, SPECT/CT is very useful for ectopic parathyroid lesions and to differentiate pathological from physiological foci of uptake (e.g., brown fat, muscle, bone marrow).

Multiphase "4D-CT" Scanner

Some reports suggest superiority of 4D-CT compared to scintigraphy and recommend it as an initial localization study in PHPT (*61*). Despite its sophisticated images, it is still controversial whether 4D-CT scanner can reliably identify MGD or differentiate thyroid nodules from parathyroid lesions. Especially since, in the existing studies, 4D-CT was not compared to subtraction scintigraphy. Sensitivity of 4D-CT in diagnosing MGD was only 32% in the study by Kukar (*61*) and 14% in the study by Madorin (*62*). Because 4D-CT scanner uses a 3- or a 4-phase CT protocol, it delivers a high dose to the thyroid, which is problematic in younger patients (*62*), and needs the injection of contrast medium in a population where renal impairment is not uncommon.

IMAGING STRATEGY BEFORE REOPERATION FOR PERSISTENT OR RECURRENT HYPERPARATHYROIDISM

Reoperation should be decided carefully, as the complication rate is higher than for a first surgery, even for experienced teams (*63*). Accurate preoperative localization is therefore essential.

First-line imaging should include both scintigraphy and neck ultrasound. Concordant localization by two modalities is required. In case of a cervical image of uncertain origin, ultrasound-guided fine needle aspiration for PTH assay may be performed (*16*). Contrast-enhanced CT scan (or MRI) is used to confirm a thoracic gland found by scintigraphy or if neck ultrasound and scintigraphy are negative or inconclusive. 4D-CT scanner seems to offer good sensitivity, at the price of a high number of false positives (e.g., exophytic thyroid nodules or lymph nodes) (*64*). When available, PET/CT with ^{11}C-methionine, ^{11}C-choline or ^{18}F-fluorocholine can also be proposed (see next section). Finally, when imaging tests are inconclusive, invasive procedures such as selective venous sampling with PTH measurements may be warranted (*16*) but the yield is highly dependent upon operator's expertise (*65, 66*). If the

pathological gland(s) cannot be identified beforehand, the rationale of reoperation is questionable and medical treatment (e.g. with calcimimetics) should be discussed.

Thus, ^{99m}Tc-MIBI scintigraphy plays a major role before surgical decision. Unfortunately, several studies have reported low sensitivity. In a series of 19 patients reoperated (18 glands resected in 17 patients and 2 patients with negative surgery), the sensitivity of ^{99m}Tc-MIBI scintigraphy (double-phase planar imaging + SPECT) was 33% (6/18) and the positive predictive value 67% (6/9). This translated into a low cure rate (11/19 patients) (*67*). Again, the sensitivity of dual-tracer scintigraphy in patients with persistent hyperparathyroidism seems to be quite higher than that of single-tracer scintigraphy, as shown in a prospective study by Schalin-Jantti and colleagues comparing different techniques for the localization of parathyroid glands (*68*). Reoperation, after taking into account the results of the various techniques, cured 18/21 patients (86%) and led to the resection of 19 pathological glands. The sensitivity of subtraction scintigraphy (planar imaging with a parallel-hole collimator only) was 59% and that of single-tracer ^{99m}Tc-MIBI (double-phase + SPECT/CT) was 19% (p <0.01). There were no false positives with both techniques. Selective venous sampling with PTH assay yielded a sensitivity of only 40% with 9 false positives, including the three patients in whom reoperation was unfruitful (*68*).

PARATHYROID IMAGING WITH NOVEL PET TRACERS

[11]C-methionine seems to be a sensitive tracer to image patients before re-operation (*65, 68, 69*). In the study by Schalin-Jantti, the sensitivity of ^{11}C-methionine PET was comparable to that of subtraction scintigraphy (65% *vs*. 59%) but with one false positive (*68*). In another series that investigated patients with previous neck surgery and negative single-tracer ^{99m}Tc-MIBI SPECT/CT, ^{11}C-methionine PET/CT was positive in 6 out of 15 (40%) cases (*69*). However, because of restricted availability and cost, there probably is little role for routine use of ^{11}C-methionine in PHPT patients undergoing the first operation. Moreover, preliminary data suggest that sensitivity of ^{11}C-methionine in MGD patients is limited (*70*).

^{18}F-FDG PET has poor sensitivity in unselected PHPT patients. However, it can offer complementary information to ^{99m}Tc-MIBI in patients with parathyroid carcinoma.

Recently, several short series of patients imaged with choline tracers have been published. Orevi and colleagues compared ^{11}C-choline to ^{99m}Tc-MIBI / ^{99m}Tc-pertechnetate scintigraphy in 40 patients with hyperparathyroidism, 27 of whom received surgery. In 23 patients, both techniques correctly identified parathyroid lesions. Of the four discordant cases, one was a ^{99m}Tc-MIBI false-positive and a ^{11}C-choline true-positive and two cases were negative on MIBI with false-positive findings on ^{11}C-choline (*71*).

In view of its wider availability, recent findings with ^{18}F-fluorocholine are of particular interest. Lezaic and colleagues compared ^{18}F-fluorocholine (with imaging at 5min and 60min) to ^{99m}Tc-MIBI (double-phase imaging + early SPECT/CT and perthechnetate thyroid scan). In 24 patients operated for PHPT, surgery identified 39 lesions (17 patients had solitary adenoma and 7 had MGD). ^{18}F-fluorocholine images were better defined at 60min than at 5min (better lesion-to-background and lesion-to-thyroid contrast). ^{18}F-fluorocholine showed higher sensitivity than ^{99m}Tc-MIBI scintigraphy (92% *vs.* 64%), notably in patients with MGD (*72*). While the findings from this study are appealing, sensitivity of ^{99m}Tc-MIBI was lower than what would be expected in previously unoperated PHPT patients (*51*). In another series, ^{18}F-fluorocholine with both dynamic and static acquisitions was used in patients with discordant findings at ultrasonography and subtraction scintigraphy. In the 8 patients with PHPT who received surgery, ^{18}F-fluorocholine offered good sensitivity, although its results mostly confirmed the findings of ^{99m}Tc-MIBI/^{123}I subtraction imaging (Table-2 in (*73*)). Parathyroid lesions were more clearly seen on ^{18}F-fluorocholine in two patients and on ^{99m}Tc-MIBI/^{123}I subtraction in one patient. In one patient, ^{18}F-fluorocholine identified a contralateral lesion not seen on ^{99m}Tc-MIBI/^{123}I subtraction, which turned out however to be a false-positive.

Larger prospective studies are needed to compare ^{18}F-fluorocholine PET/CT to state of the art conventional scintigraphy in order to clarify the role of choline imaging in specific settings (reoperative PHPT, patients undergoing their first operation with unconclusive imaging, etc.).

A potential advantage of ^{18}F-fluorocholine imaging is the higher resolution associated with PET technology (Fig-4) and the shorter imaging time. Potential drawbacks are the higher cost and the absence of a specific thyroid tracer, with risk of false-positive from thyroid nodules but also from inflammatory lymph-nodes. Intravenous contrast medium administration during choline PET/CT imaging might further improve results, especially in case of recurrent disease.

CONCLUSION

The long-term cure rate of parathyroid surgery depends on the ability to resect hyperfunctioning parathyroid tumors and to identify MGD and ectopic glands. Preoperatory detection of pathological glands would avoid inappropriate surgery and reduce the rate of surgical conversions or failure. A subtraction scintigraphy after simultaneous acquisition of ^{99m}Tc-MIBI and ^{123}I images provides better sensitivity than a double-phase ^{99m}Tc-MIBI scan. Imaging with the pinhole collimator offers optimal resolution. Complementary SPECT/CT images are of great value for anatomic localization and should be obtained routinely before reoperation to identify ectopic glands.

Choline PET tracers may open new venues for radionuclide imaging of parathyroid glands.

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Figure Legends

Figure-1: Simultaneous dual-tracer ^{99m}Tc-MIBI and ^{123}I scan in a 55-year-old patient with primary hyperparathyroidism. Upper row: Parallel-hole collimator images with ^{99m}Tc-MIBI (A), ^{123}I (B) and subtraction (C). Lower row: Pinhole images of the neck with ^{99m}Tc-MIBI (left), ^{123}I (middle) and subtraction (right).

Subtraction on parallel-hole collimator images (C) shows a residual focus on the right side (arrow) which is difficult to interpret. Pinhole images offer better resolution. After subtraction (F), two foci are clearly seen on the right side, one corresponding to a ^{123}I-cold thyroid nodule (arrowhead) and the other at the inferior pole corresponding to a parathyroid lesion (arrow).
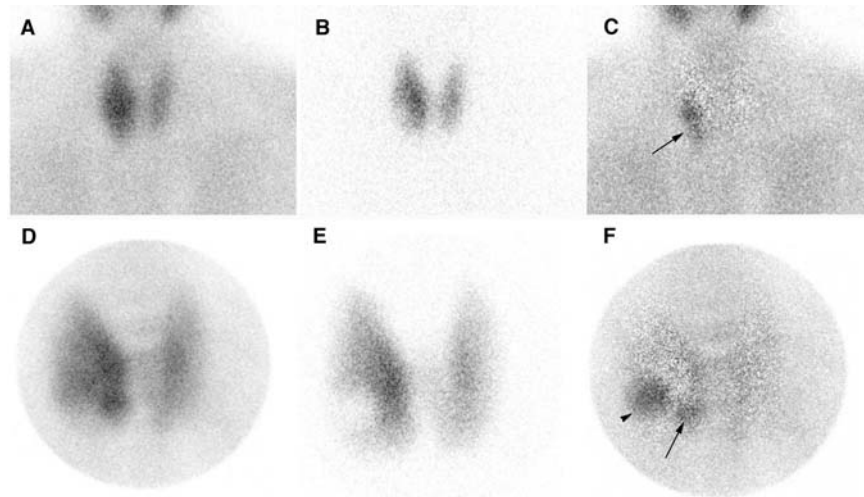
Figure-2: 42-year-old patient with primary hyperparathyroidism. Simultaneous dual-tracer ^{99m}Tc-MIBI and ^{123}I scan.

A to C: Planar pinhole images with ^{99m}Tc-MIBI (A), ^{123}I (B), and subtraction (C). The subtraction image shows two residual foci in both inferior poles of the thyroid (arrows).

^{99m}Tc-MIBI SPECT/CT fusion images with axial (D) and sagittal (F) views reveal that the parathyroid lesion on the left side corresponds to an orthotopic inferior (P3) parathyroid gland (arrow), while the lesion on the right side (cross-marked) is located posteriorly, behind the thyroid and trachea. This is a typical feature of a prolapsed superior (P4) parathyroid gland which can be difficult to detect on ultrasound. The corresponding ^{123}I SPECT/CT fusion images (E, G) confirm the absence of iodine uptake in both parathyroid lesions.
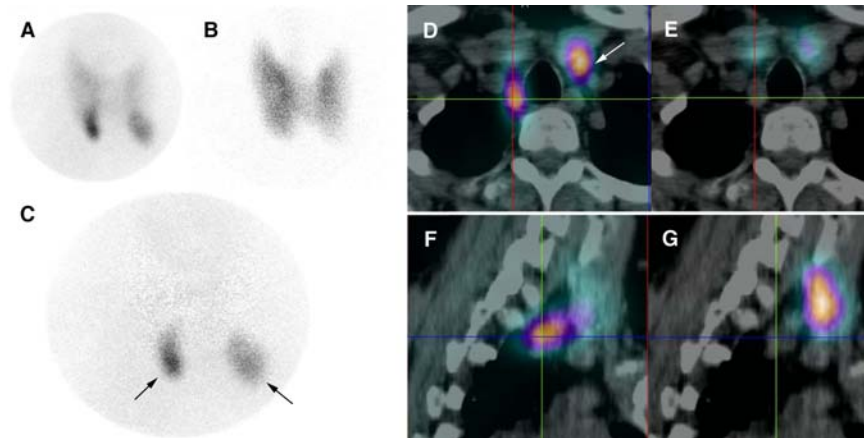
Figure-3: Patient with PHPT and previous history of subtotal thyroidectomy for Graves' disease. Neck ultrasound examination suggested a parathyroid lesion on the lower right side. Simultaneous dual-tracer acquisition of ^{99m}Tc-MIBI and ^{123}I was performed after thyroid hormone replacement therapy was withheld for two weeks.

Upper row: large-field of view parallel-hole collimator images of ^{99m}Tc-MIBI (A), ^{123}I (B) and subtraction (C). The suspicious lesion on ultrasound would seem to correspond to a thyroid remnant with no visible neck foci on the subtraction image (also confirmed on pinhole view). There is an intense focus of ^{99m}Tc-MIBI uptake in the thorax.

Axial ^{99m}Tc-MIBI SPECT/CT fusion image (D) and corresponding CT view (E) identify a $9 \times 9 \times 15$mm mediastinal lesion in front of the ascending aorta. At surgery, it corresponded to a 537 mg parathyroid adenoma.
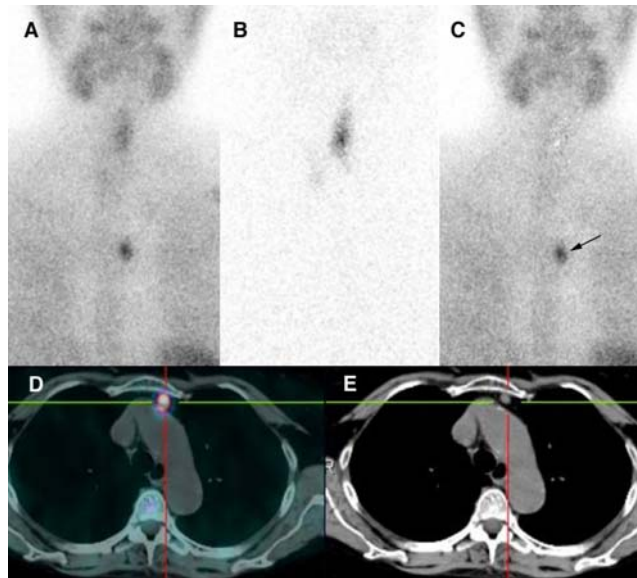
Figure-4: ^{18}F-fluorocholine PET/CT (contrast-enhanced CT) performed 20min after I.V. injection of ^{18}F-fluorocholine (3MBq/kg) in a patient with primary hyperparathyroidism and doubtful ^{99m}Tc-MIBI scintigraphy performed in another institution (not repeated).

PET, CT and PET/CT fusion images are displayed as axial (A, B, G), coronal (C, D, E) and sagittal (H, I, J) views, as well as PET maximum intensity projection (F). There is a choline-avid hyperfunctioning parathyroid gland located at the upper pole of the left thyroid lobe (arrow). Neck ultrasound confirmed the presence of a hypoechoic $10 \times 5 \times 12$ mm nodule behind the left upper pole of the thyroid.