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Dual Tracer Tc99m-Sestamibi/Tc99m-Pertechnetate Double Image Subtraction Scintigraphy of Parathyroid Glands: A Monocentric Retrospective Study

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1. Abstract

1.1. Objective: Minimally invasive parathyroidectomy is the surgical trend to cure hyperparathyroidism based on reliable imaging techniques. Parathyroid scintigraphy is most commonly used for the preoperative localization of the hyperfunctioning parathyroid gland, which is often supported by an echography. Numerous scintigraphic protocols are practiced by the worldwide nuclear medicine community, without establishing a unified one. The choice of one or another of these protocols is tributary of the availability and the cost of the radiopharmaceuticals, the technical capabilities of the gamma camera, and the daily department load of isotopic explorations, especially that the majority of the usual protocols of parathyroid scintigraphy last 3 to 4 hours.

1.2. Methods: Our study evaluates retrospectively the performances of a dedicated in-house short execution time protocol of parathyroid scintigraphy that lasts up to 1 hour, expressed in terms of patient presence time in the nuclear medicine department and gamma camera occupation time. This protocol requires dual-tracers Tc-99m-sestamibi/Tc-99m-O4 successively intravenously injected and double image subtractions. The definitive histopathological examination of surgically excised lesions was gathered as a gold standard to analyze the performances of the protocol.

1.3. Materials: Between 2017 and 2020, 286 consecutive cases of parathyroid scintigraphy have been enrolled with clinically and biologically documented hyperparathyroidism. Primary hyperparathyroidism was present in 229 patients, and secondary hyperparathyroidism in 57 patients. None of the patients had undergone previous surgical exploration of the neck.

1.4. Results: In patients with primary and secondary hyperparathyroidism, the per-lesion sensitivity was 89% and 71% and the positive predictive value was 96% and 95% respectively. These results indicate promising performances.

1.5. Conclusion: The main particularities of our in-house protocol lie in its challenging results, short execution time, and relatively

low cost. Based on a review of the relevant literature data, we have discussed the strengths and the limitations of our dedicated technique and its potential role among others commonly used by the nuclear medicine community.

2. Introduction

Minimally Invasive Parathyroidectomy (MIP) is the surgical trend to cure Hyperparathyroidism (HPT). Most surgeons perform a targeted ablation of the Hyper-Functioning Parathyroid Glands (HFPG) based on reliable imaging techniques that allow the selection of eligible patients and identification of ectopic glands [1,2] In this objective, Parathyroid Scintigraphy (PTS) is the most commonly used as a first-line imaging modality, often supported by echography [3]. Dynamic Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are reserved as resolving methods in problematic cases [4]. Several recent studies have shown that 18F-Choline is a promising Positron Emission Tomography (PET) tracer for detecting HFPG, especially when they are multiple, or small in size. 18F-Choline PET CT is a potential "alternative" first-line method, even in patients with negative/equivocal standard imaging findings whenever available. However, the potential role of 18F-Choline requires confirmation by randomized works to demonstrate its cost-effectiveness [3].

Numerous PTS protocols have been practiced since the 1980s, which are divided into two main aspects, the single-tracer dual-phase Tc99m-sestamibi (MIBI) scintigraphy, and the dual-tracer Tl201/Tc99m-O4 (Tc), Tl201/I131, MIBI/I123 or MIBI/Tc subtraction scintigraphy [5, 6, 7]. The choice of one of these protocols depends on several factors: 1) the types of radiopharmaceuticals available and their costs; 2) the technical characteristics of the gamma camera, including its equipment with a pinhole collimator and capability to carry out single-photon emission computed tomography, in combination with computed tomography (SPECT CT); 3) the management of the Patient Presence time (PPt) in the nuclear medicine facility and the gamma camera occupation time (GCt), especially that majority of the usual scintigraphic protocols last 3 to 4 hours, a limiting factor, especially for departments with an overloaded daily schedule.

This study aims to describe the performance of a dedicated Dual-tracer Double Image Subtractions (DDS) protocol of parathyroid scintigraphy, with a short execution time, developed at HAMMOUD Hospital University Medical Center, Sidon Lebanon [5,8,9]. The Medical Ethics Committee of the hospital has agreed to implement this protocol and conduct a retrospective analysis of its results.

Based on a related literature review, the strengths and limitations of the DDS protocol are discussed, as well as its potential role among the most adopted ones by the nuclear medicine community.

3. Materials and Methods

This is a retrospective study reporting the results of our DDS protocol obtained between 2017 and 2020, in 286 consecutive patients, 74 males and 212 females, of 56 ± 13 years mean age, with clinically and biologically documented HPT and being candidates for surgical treatment. The pre-surgical diagnosis of pHPT was evoked in 229 patients, 39 males and 190 females, based on the serum levels of calcium (mean Ca+ =11.2 ±1.2 mg/dl) and parathyroid hormone (mean PTH =136 ± 61 ng/l). The remaining 57 patients, 35 males, and 22 females, experience sHPT, with mean serum levels of Ca+ of 10.5 ± 1.4 mg/dl and PTH of 785 ± 261 ng/L. None of the patients had undergone previous surgical exploration of the neck.

Since MIBI is taken up by both the HFPG and the normal thyroid parenchyma, it is used in conjunction with Tc, which is taken up only by the thyroid parenchyma. Then the corresponding two images are digitally subtracted, after normalization to the total count, allowing visualization of HFPG.

The gamma camera used is a single-head GE Brivo NM615, equipped with a pinhole and parallel holes low energy collimators. Through a three-way intravenous cannula, the patient receives the first injection of 8MBq/Kg of MIBI. Five minutes later a series of four MIBI images (Figure 1) are acquired, using a large field of view parallel holes collimator for the first image (a) of the neck and mediastinum (to exclude ectopic HFPG), and a pinhole collimator for the three following images of left lateral (b), right lateral (c) and anterior views (d) of the thyroid region. The patient is instructed not to move his head and neck, the second radiotracer with an activity of 3MBq/Kg of Tc is injected, and the latest 5th anterior view MIBI &Tc image of the thyroid region (image e) is acquired, the pinhole collimator still in place, after 10 min, in a time allowing regular distribution of the two radiotracers in the thyroid region.

Figures 2 and 3 represent the two steps of images subtraction of the DDS protocol. The first subtraction of image d (MIBI) from image e (MIBI & Tc) aims to generate a thyroid image Tc (Figure 2). The second subtraction after normalization of the generated thyroid image (Tc) from image d (MIBI) aims to obtain the HFPG image (Figure 3). A simplified single step of subtraction after normalization of image e (MIBI & Tc) from image d (MIBI) leads to the same result (Figure 4). The technical details of the DDS protocol illustrated by large iconographies of several clinical cases recorded in both primary and secondary HPT patients have been previously published. These iconographies include patients with mono and multi-glandular disease, ectopic HFPG, and pitfalls findings related to motion artifact or concomitant multi-nodular thyroid goiter [10].

We have also applied the DDS protocol to patients with multiglandular disease. Figure 5 represents the simplified subtraction procedure performed in a case of sHPT. The subtraction of the image (MIBI & Tc) from the normalized image (MIBI), reveals 3 foci of selective MIBI uptake, corresponding to HFPG as hyperplastic (red arrows). One focus is projected at the left lower lobe and two foci along the right upper and lower lobe.

When the anterior planar view of the neck/mediastinum highlights a focus of MIBI activity in an ectopic position, a supplement anatomical localization is carried out later through an enhanced MRI or CT scan. Figure 6 illustrates the scintigraphic MIBI and the enhanced CT images of an ectopic parathyroid adenoma disclosed in the upper anterior mediastinum in a patient with pHPT.

Experienced nuclear medicine physicians executed the different steps of image subtraction and interpreted the resulting data, with the contribution of experienced radiologists that read the complement radiological imaging. The negative or non-conclusive results of the PTS were considered non-positive, and pushed to carry out additional investigations by ECHO, enhanced CT, or enhanced MRI.

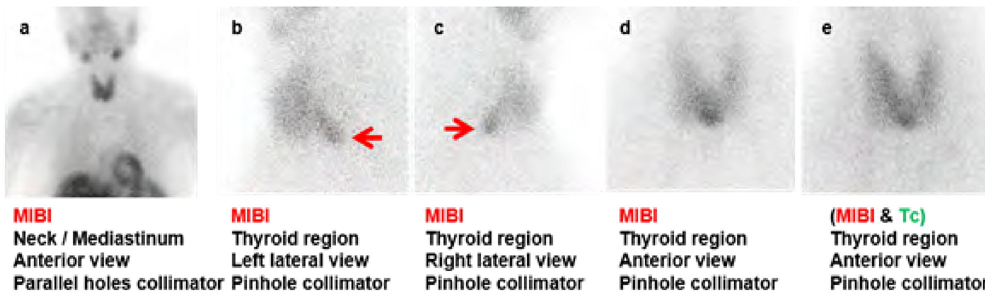

Figure 1: Represents the chronological order of 5 serial images; they were performed on the patient with pHPT; this case highlights the importance to acquire the left and right lateral views (images b and c) allowing the in-depth visualization of HFPG that is localized just behind the isthmus of the thyroid gland (red arrows).

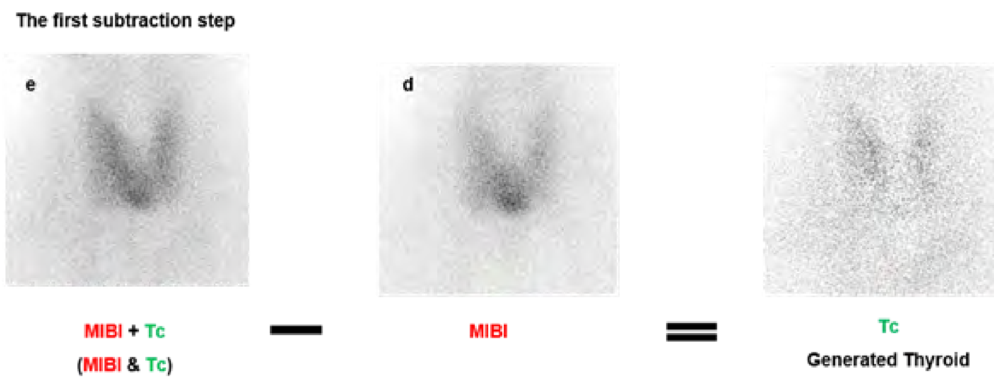

Figure 2: Represents the first step of subtraction of image d (MIBI) from image e (MIBI & Tc) aiming to generate the thyroid image Tc.

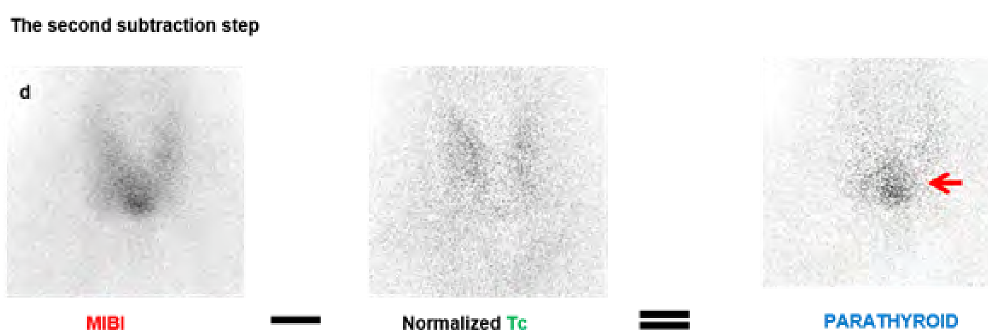

Figure 3: Represents the second step of subtraction after normalization of the generated thyroid Tc image from image d (MIBI) aiming to obtain the HFPG image (Figure 3), which is projected on the isthmic thyroid region.

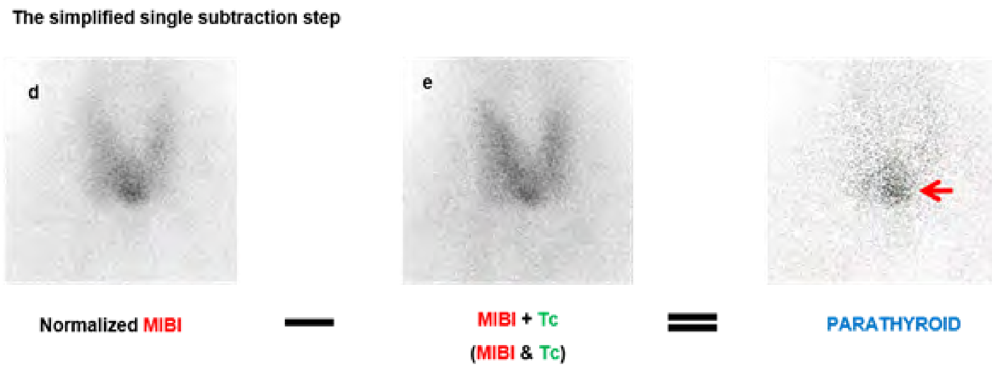

Figure 4: Represents the simplified subtraction procedure after normalization of image e (MIBI & Tc) from image (MIBI), resulting in the visualization of the HFPG, which is projected on the thyroid isthmus.

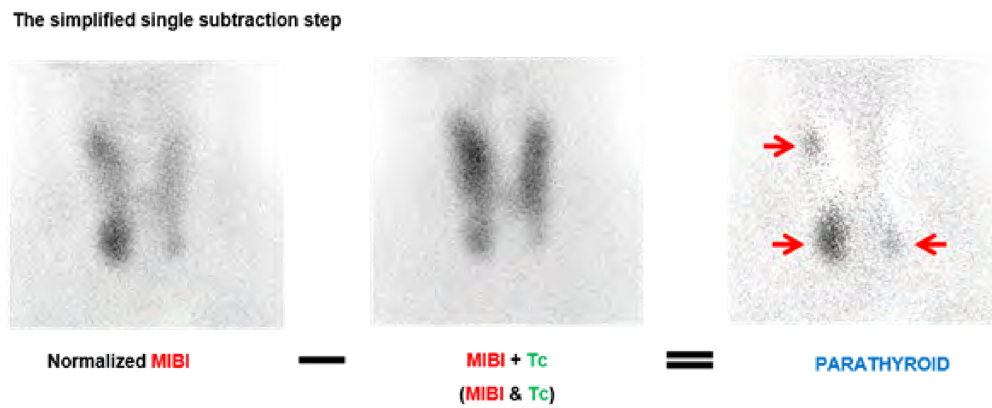

Figure 5: Represents the simplified subtraction procedure performed in a patient with sHPT; the image (MIBI & Tc) is subtracted from the normalized image (MIBI), resulting in the individualization of three HFPG, as hyperplastic projected on the left lower lobe, the right upper and the lower lobe.

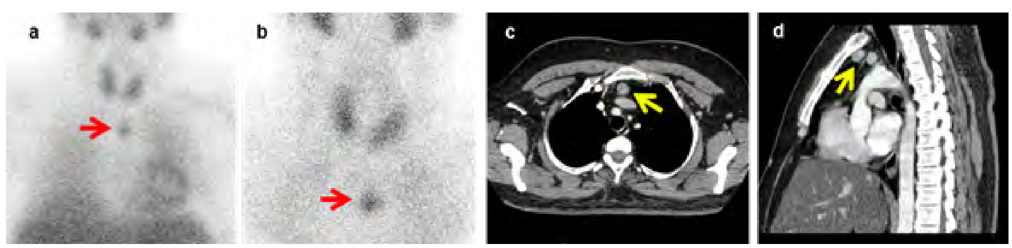

Figure 6: Dmonstrates the scintigraphic MIBI and the enhanced CT images of an ectopic parathyroid adenoma revealed in the upper anterior mediastinum in a pHPT patient. The MIBI image (a) of a large field anterior view of the neck/mediastinum, acquired with a parallel holes collimator, reveals a single abnormal focal activity projected in the upper anterior mediastinum (red arrow); the magnified MIBI pinhole image (b) shows no abnormal focus of tracer uptake along the thyroid region, and the single abnormal ectopic focus in the upper mediastinum (red arrow) is better identified as compared to the parallel holes collimator image. The confirmative transversal (c) and sagittal (d) cross-sectional images of the enhanced chest CT reveal a rounded tissue nodule in a retrosternal location (yellow arrows).

4. Results

4.1. Surgery and Pathology

Results of on-site open readings of DDS scintigraphy were used by surgeons to plan and perform surgical interventions. Surgeons also used data from the complement imaging modalities performed in the negative or non-conclusive cases of PTS, notably the ECHO, CT or MRI. Abnormal parathyroid glands were removed, commonly 1 in primary hyperparathyroidism, and 1 or more in secondary hyperparathyroidism. Histological analysis of frozen sections was used to confirm the presence of parathyroid tissue. The definitive histopathological examination was gathered as a gold standard to analyze the performance of our nuclear imaging protocol.

A total of 477 HFPGs were surgically excised, 256 in the primary HPT patients and 221 in the secondary HPT patients. In the pHPT setting, a single adenoma was found in 207 patients (including 3 ectopics, being 2 mediastinal and 1 retro-tracheal), 2 adenomas in 12 patients, 3 adenomas in 3 patients, 2 hyperplastic glands in 5 patients, and 3 hyperplastic glands in 2 patients. Whereas, in the sHPT setting, 5 hyperplastic glands were found in 1 patient, 4 in 49 patients, 3 in 6 patients, and 2 in 1 patient.

4.2. DDS Scintigraphy

The Sensitivity (SS) and positive Predictive Value (PPV) of our dedicated imaging test are calculated separately in the pHPT and sHPT patients. Corresponding values are expressed per-lesion and per-patient basis.

- In the pHPT settings, the per-lesion SS was 92% in the single adenoma patients, 79% in the multiple adenoma patients, and 69% in the multiple hyperplastic glands patients; the pooled SS per-lesion was 89% and per-patient was 91%; the PPV is 96 %; 10 foci of activity in 10 patients (4%) were falsely interpreted as positive, and corresponding, 5 to thyroid nodules and 5 to motion artifacts.

- In the sHPT settings the SS was 71% per lesion and 89% per patient; the PPV was 95%; 8 foci of activity in 8 patients (14%) were interpreted falsely positive corresponding5 to thyroid nodules and 3 to motion artifacts.

- Overall, for our primary and secondary HPT patients, the SS was 81% per-lesion and 91% per patient; the PPV was 95%.

5. Discussion

The different radiotracers used in PTS are non-specific and were originally introduced for radio-isotopic imaging of myocardium, as the Thallium 201-citrate (Tl201), the Tc99m-sestamibi (MIBI), and the Tc99m-tetrofosmin (TFSM). They are taken up by both the HFPG and the thyroid parenchyma. The radiotracers used in conjunction for the delineation of thyroid parenchyma, to perform a dual-tracer pair images visual comparison or images subtraction are the Tc, the I123, and the I131 [11, 7].

The dual-tracers Tl201/Tc subtraction PTS is the oldest subtraction protocol practiced in the 1980s [12]. The long half-life of 3.045 days of the Tl201 exposes the patients to an effective dose 3 times higher than that of the Tc99m labeling pharmaceuticals [13]. After describing the accidental accumulation of MIBI in HFPG in 1989 [14], this radiopharmaceutical has become nowadays the reference in the imaging diagnosis of HPT. It is a lipophilic molecule that crosses the cell membranes and intracellularly accumulates in the mitochondria [15, 16, 17]. Since the 1990s, the MIBI replaced the Tl201 because of more favorable dosimetry, superior image quality, and improved detection sensitivity [18].

Several variants of PTS based on MIBI radiopharmaceutical, 18 at least, have been used by the nuclear medicine community in planar mode, or by Single-Photon Emission Computed Tomography (SPECT) often combined with CT scan (SPECT CT) [19]. They could be inscribed under 2 main methodologies: the single-tracer dual-phase imaging, and the dual-tracer Tc/MIBI, I123/MIBI, and I131/MIBI subtraction imaging [5, 7, 11]. At close performances, these protocols can be restrictive due to their high cost and/or plenty of long execution time, especially in departments with a heavy daily schedule. Until today there is no established uniform protocol for PTS.

The single MIBI tracer dual-phase (early and delayed phase) PTS was suggested by Taillefer et al based on the observation that MIBI washes out more rapidly from the thyroid gland than from HFPG [18].The "Differential Washout" phenomenon improves target-to-background activity revealing a selective tracer uptake by HFPG that should become more visible during the delayed phase (2 to 3 hrs. after injection). This dual-phase technique requires a prolonged patient stay in the nuclear medicine facility for at least 3 hrs., is moderately sensitive, and most of the time cannot identify cases with multiple HFPG [5, 7, 20, 21]. This methodology can lead to False-Negative (FN) detection of HFPG characterized by rapid leaching of MIBI [22]. Moreover, coexistent nodular goiter and autoimmune diseases of the thyroid are responsible for False Positive (FP) results by enhancement and prolonged retention of MIBI [23]. Therefore, imaging subtraction techniques are helpful because not all parathyroid lesions retain for long the MIBI, and not all thyroid lesions wash it out quickly.

Some nuclear medicine teams adopting the single-tracer MIBI dual-phase protocol follow the planar acquisition by a SPECT mode to increase the sensitivity of detection of HFPG. Other teams using hybrid machines recommend a simultaneous combination of functional SPECT and high-resolution anatomical CT scan images, which is highly valuable data before minimally invasive parathyroidectomy. A large meta-analysis was made on prospective and retrospective studies concerning these methodologies using a single MIBI tracer in pHPT [19]. It has been concluded that the combination of SPECT and CT data was by far more sensitive and accurate in the detection and localization of specific lesions than the planar mode or the SPECT mode alone. The SPECT and the planar modes had low diagnostic efficacy given the limited degree of anatomical details provided [4, 5, 19, 20, 24].

The pinhole collimator acquisition applied in our DDS protocol magnifies the images, enhances both spatial resolution and lesion/background contrast, and improves the detectability of the HFPG [25]. The left and right lateral views of the cervical region acquired in addition to the anterior view allow the in-depth visualization of the HFPG, which are often located behind the upper and lower poles of the thyroid lobes (Figure 1). The lateral views can also help to detect some superior ectopic HFPG which could be in retro-tracheal or retro-esophageal locations and are not visualized on the anterior view [26]. Even though pin-hole and SPECT/CT acquisitions improve the sensitivity of the single tracer MIBI PTS, the percentage of detected cases of multi-HFPG remains limited [3] and cannot reliably guide targeted parathyroid surgery [6] (Table 1). The subtraction protocol of PTS using dual radioisotopes of MIBI and I123 has demonstrated high performance even in multiglandular disease patients. It is based on the pinhole simultaneous acquisition of the dual gamma peak energies of the two radiotracers [5, 21, 27, 28]. The I123 is administered for 2 to 3 hrs. before the commencement of the gamma camera imaging [22, 29, 30, 31, 32, 33], a fact making quite long the PPt, and subsequently the execution time of the protocol that lasts 3 to 4 hours.

Similar to any scintigraphic protocol, the SS of the DDS protocol was superior in pHPT patients (89%) than in sHPT (71%), while the PPV was excellent in both clinical settings with 96% and 95% respectively [20]. For comparative purposes, and based on literature review data, Table 2 summarizes the performance of the principal scintigraphic techniques that are practiced in pHPT on a worldwide scale [20, 21]. This table includes our DDS protocol, which is the shortest, expressed in terms of GCt and ppT in the nuclear medicine department, not exceeding 1 hr, comparatively to the others lasting 2 to 4 hrs. According to this data, our protocol provides challenging results in pHPT. The use of the two radiotracers, the pinhole collimator, and the subtraction process allow the DDS protocol to reach good values of SS and PPV, in both single and multiple glandular disease patients. The SS and PPV values of the DDS protocol are superior to those performing single-MIBI tracer dual-phase or dual tracer MIBI/Tc protocols, using parallel holes collimator with either planar or SPECT acquisition. The combination of the CT scan with the MIBI SPECT provides precise 3D anatomical details and improves the methodology's performance, equivalent to our subtraction technique. The dual-isotopes MIBI/I123 simultaneous acquisition using a pinhole collimator and performing complement SPECT CT images has the highest SS and PPV.

The same is true for sHPT patients, where the per-lesion SS (70%) of the DDS protocol is superior to those reported in the literature of the single MIBI tracer dual-phase protocols using the pinhole collimator (63.2%). The SS of these protocols is reduced when using a parallel holes collimator (56.2%). In this clinical setting, the dual-isotopes I123/MIBI simultaneous planar mode acquisitions that use a pinhole collimator and the SPECT mode imaging have the highest SS of 75.4% [30, 31]. Once more, the scintigraphic techniques allow sHPT patients to discriminate the major and the minor HFPG, which are in our representative sHPT case projected on the right and the left lower poles respectively (Figure 5). These valuable qualitative data should allow the surgeon to preserve the minor gland to avoid morbid hypocalcemia [32].

Our DDS parathyroid scintigraphy is one of the cheapest protocols using Tc99m-labelled vectors, which are radiotracers of low costs as compared to the I123 and Tl201. This factor is valuable for public health systems with a modest economy [33]. In non-industrial countries, the availability of I123 lucks is often for commercial or economic logistic reasons. In these situations, our DDS protocol turns out to be a good alternative at the expense of mild loss of SS (compared to the dual isotopes techniques), notably in patients with multi-HFPG.

Table 1: summarizes the data on patient demography, blood tests, surgery, and DDS scintigraphy

<table>
<tr><th colspan="3">Disease</th><th>Total HPT</th><th colspan="2">pHPT</th><th>sHPT</th></tr>
<tr><td colspan="3">Patients number</td><td>286</td><td colspan="2">229</td><td>57</td></tr>
<tr><td colspan="3">Males</td><td>74</td><td colspan="2">39</td><td>35</td></tr>
<tr><td colspan="3">Females</td><td>212</td><td colspan="2">190</td><td>22</td></tr>
<tr><td colspan="3">Ca^{+} mg/dl</td><td></td><td colspan="2">11.2 ± 1.2</td><td>10.5 ± 1.4</td></tr>
<tr><td colspan="3">PTH ng/L</td><td></td><td colspan="2">136 ± 61</td><td>785 ± 261</td></tr>
<tr><td colspan="3" rowspan="4">Surgical pieces histopathology</td><td rowspan="4">477 HFPG</td><td colspan="2">256 HFPG</td><td rowspan="4">221 HFPG hyperplasia</td></tr>
<tr><td colspan="2">207 patients with single adenoma (3 ectopics)</td></tr>
<tr><td colspan="2">15 patients with multiple adenomas</td></tr>
<tr><td colspan="2">7 patients with hyperplasia</td></tr>
<tr><td rowspan="6">DDS Protocol</td><td rowspan="5">SS</td><td rowspan="4">Per-Lesion</td><td rowspan="4">81%</td><td>Single adenoma</td><td>92%</td><td rowspan="4">71%</td></tr>
<tr><td>Multiple adenomas</td><td>79%</td></tr>
<tr><td>Multiple Hyperplasia</td><td>69%</td></tr>
<tr><td>Pooled</td><td>89%</td></tr>
<tr><td>Per-Patient</td><td>89%</td><td colspan="2">91%</td><td>81%</td></tr>
<tr><td>PPV</td><td>Per-Lesion</td><td>95%</td><td colspan="2">96%</td><td>95%</td></tr>
</table>

PTH= parathyroid hormone; Ca+ = calcium; HPT = hyperparathyroidism; pHPT = primary hyperparathyroidism; sHPT = secondary hyperparathyroidism; HFPG = hyperfunctioning parathyroid glands; SS = sensitivity; SP = specificity; PPV = positive predictive value.

Table 2: Summarizes the performance of the principal scintigraphic PTS protocols practiced on a worldwide scale in the pHPT, it includes our DDS short execution time technique not exceeding 1 hr.

PROTOCOLS	TRACERS	COLLIMATORS	ACQUISITION	PPt h	GCt min	SS %	PPV %
Dual-phase	Single MIBI	Parallel holes	Planar	2 to 3	20	63	90
Dual-phase	Single MIBI	Pinhole	Planar	2 to 3	30	66	83
Dual-phase	Single MIBI	Parallel holes	Planar SPECT	2 to 3	60	66	82
Dual-phase	Single MIBI	Parallel holes	Planar SPECT/CT	2 to 3	60	84	95
Single-phase DDS	Dual MIBI/Tc	Pinhole Parallel holes	Planar	1	50	89	95
Single-phase Subtraction	Dual Isotopes I123/MIBI	Pinhole Parallel holes	Planar SPECT CT	3 to 4	40	94	97

PPt = patient presence time in the nuclear medicine facility; GCt = gamma camera occupation time; SS = sensitivity; PPV = positive predictive value.

6. Conclusion

Among the numerous scintigraphic protocols described in the literature, the dual-isotope MIBI/I123 subtraction scintigraphy with the 2 mandatory pin-hole and SPECT/CT simultaneous acquisitions has the highest performance in patients with either single or multi HFPG.

Our in-house DDS protocol is a challenging methodology encompassing several strong points that encourage its adoption in HPT. It is easy to execute serial steps of 2 radiotracers injections and 5 images acquisitions with simple processing steps of images subtraction that privilege the detection of both orthotopic and ectopic lesions. The results of our study enrolled a non-negligible number of 286 cases showing good performance to detect and localize HFPG expressed in terms of SS and PPV. These results are based on a retrospective monocentric sample that must be confirmed in a larger multi-centric study. This short execution time technique expressed in terms of PPt and GCt should interest the nuclear medicine facilities with overloaded daily schedules and equip them with a basic gamma camera. The two radiopharmaceuticals required in the DDS scintigraphy are traceable by the Tc, a radioisotope daily available in any nuclear medicine department. The DDS methodology is much cheaper than others, requiring expensive radioisotopes of iodine or SPECT CT machinery.

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