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Chapter

Parathyroid Scintigraphy

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Abstract

The visualization of abnormal parathyroid glands is difficult due to their variations in number and localization. Noninvasive parathyroid imaging studies include ^{99m}Tc-sestamibi scintigraphy, ultrasonography, computed tomography scanning, magnetic resonance imaging, and positron emission tomography. There is a general consensus that the most sensitive and specific imaging modality, especially when it is combined with single-photon emission CT is the scintigraphy with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin. ^{99m}Tc-sestamibi scintigraphy significantly increases the role of preoperative scintigraphy in patients with hyperparathyroidism and allows unilateral surgical approach with minimally invasive parathyroidectomy to be used. Generally, three protocols with the use of two radiopharmaceuticals, ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin, are most widely applied: single-phase dual-isotope subtraction, dual-phase single-isotope and combination of both. Each one of them has specific advantages and disadvantages. While single parathyroid adenomas are localized with greater precision, hyperfunctioning parathyroid hyperplastic cells represent a real challenge to the imaging modalities. Several factors can influence the radionuclide uptake in pathologically changed parathyroid cells, like the size, the level of their functional activity, the quantity of oxyphilic cells, mitochondria, P glycoprotein and other MDR gene products.

Keywords: parthyroid scintigraphy, SPECT, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, ^{99m}Tc pertechnetate

1. Introduction

Noninvasive parathyroid imaging studies include technetium (^{99m}Tc) sestamibi scintigraphy, ultrasonography (US), computed tomography (CT) scanning, magnetic resonance imaging (MRI) and positron emission tomography (PET). Parathyroid glands need to be examined in case of a diagnosed hyperparathyroidism as a part of preoperative localization of the abnormal glands. Hyperparathyroidism is characterized by elevated parathyroid hormone (PTH) levels in the blood. Due to the underlying cause, it can be divided into primary and secondary. The primary hyperparathyroidism (PHPT) is due to excessive production of PTH from one or more abnormal parathyroid glands. Secondary hyperparathyroidism (SHPT) is a result of hypocalcemia caused by other concomitant diseases (end stage kidney renal disease, etc.). In SHPT usually more than one parathyroid glands are affected. Considered rare disease in the past, the incidence of PHPT has changed dramatically during the last 30 years with the introduction of routine calcium measurements in clinical practice, and is now considered to be approximately 42 per 100,000 persons. Women are affected more frequently than

men, in a ratio of approximately 3:1. PHPT occurs predominantly in individuals in their middle years with a peak incidence between ages 50 and 60 years and can reach 4 cases per 1000 persons in women after their 60s. At the time of diagnosis, most patients with PHPT do not have classic symptoms like osteitis fibrosa cystica, nephrocalcinosis, nephrolithiasis or other signs associated with the disease. Symptomatic PHPT is now exception rather than the rule, with more than three-fourths of patients having no symptoms making detected changes of the blood values of calcium, phosphorus and parathyroid hormone (PTH) to be the only reason for diagnosis [1, 2]. By far, the most common lesion found in patients with PHPT is the solitary parathyroid adenoma, occurring in 85–90% of patients, while in the rest 10–15% primary hyperplasia of the parathyroid glands is present [3]. In the past the standard surgical approach for PHPT was the bilateral four-gland parathyroid exploration with the removal of each gland which showed changes macroscopically. While in most of the patients with PHPT only one parathyroid gland is being affected, the above mentioned surgical approach is inappropriate in all cases. Unilateral approaches are appealing in a disease in which only a single gland is involved. So nowadays, the currently most widely used surgical approach is the minimally invasive parathyroidectomy which is connected with less post-surgical complications and shortens the time of operation [4]. To be successful this procedure needs to rely on a precise preoperative localization of the abnormal parathyroid glands. That is, why preoperative parathyroid imaging gained so large importance. The rationale for locating abnormal parathyroid glands prior to surgery is that they can be notoriously unpredictable in their location.

2. Anatomy of the parathyroid glands

Parathyroid glands differ in shape and size. Typically four glands are present and are located adjacent to the dorsal surface of the thyroid lobes-two upper and two lower pairs. Normal glands tend to be flat and oval and normal measurements are 3 × 5 × 7 mm [5]. The combined weight of all parathyroid glans is 90–130 mg and the superior glands are smaller than the inferior [6, 7]. Autopsy series demonstrate that four glands are found in 91% in subjects, five glands in 4%, and three glands in 5% [8]. Approximately 5% of humans have supernumerary (more than four) parathyroid glands [9]. Supernumerary glands are most commonly found within the thymus. Although gland distribution may deviate widely, the superior parathyroid glands, originating from the fourth pharyngeal pouch, are commonly found along the posterior surface of the upper two-thirds of the thyroid gland (92%). The inferior parathyroid glands have a more variable distribution than the superior ones. They originate from the third pharyngeal pouch together with the thymus. They migrate caudally until they reach the lower pole of the thyroid gland and 17% of them touch the inferior border of the thyroid gland, 26% are within the superior horn of the thymus, and 2% are in the mediastinal thymus [10]. The variable anatomic distribution makes the inferior glands more difficult to locate than the superior ones. Histologically parathyroid glands are made of chief, oxyphillic and transient oxyphillic cells mixed with fat tissue. Chief cells produce PTH. The oxyphillic cells which are rich of mitochondria are with poorly defined function [11].

3. Noninvasive parathyroid imaging

The normal parathyroid glands cannot be visualized. The lack of the perfect imaging method for precise localization of parathyroid adenomas had led to search

for an alternative imaging techniques. Ultrasonography (US) is one of the most widely used procedures. Because of the great anatomic variations of the parathyroid glands, their small sizes, the presence of more than one abnormal gland and the higher frequency of concomitant morphological changes of the thyroid gland, US proved to be specific but with low sensitivity. The success of US is highly operator dependent [12]. Rapid spiral thin-slice CT scanning of the neck and mediastinum with evaluation of axial, coronal and sagittal views can add much to the search for elusive parathyroid tissue [13]. MRI can also identify abnormal parathyroid tissue, but it is time consuming and expensive. It is also less sensitive than other modalities. It can nonetheless be useful when the search with the other noninvasive approaches has been unsuccessful. PET/CT can be used, but like MRI, it is expensive and does not have the kind of experiential basis that make it attractive. There are limiting data for using PET/CT in parathyroid imaging. PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) was used with varying success. One study showed that ^{18}F-FDG PET was more sensitive but less specific than ^{99m}Tc-sestamibi SPECT [14]. Others reported very low sensitivity for detecting abnormal parathyroid glands [15]. Using PET with ^{11}C-methionine in parathyroid examination has been studied in some patients but because of the very short half-life of ^{11}C-methionine, only 20 min its use is limited only to nuclear medicine centers located near to a cyclotron. There is a general consensus that the most sensitive and specific imaging modality, especially when it is combined with single-photon emission CT (SPECT) is the scintigraphy with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin.

4. Parathyrod scintigraphy

Historically, the success of scintigraphy had been compromised by the failure of finding a pharmaceutical agent with specific topic accumulation in parathyroid glands and their close proximity to the thyroid gland. That is why to find a reliable method to differentiate both glands on scintigraphy was crucial. This was first achieved by a combined use of two radionuclides with different uptake in the thyroid and parathyroid cells. The latter allowed to perform a subtraction of the obtained images of both glands and to visualize only the abnormal parathyroid gland, but this proved to be time consuming and with greate radiation exposure to the patients. The first widely used radionuclide for detecting hyperfunctioning parathyroid glands during the 80s was ^{201}Thallium chloride (^{201}Tl). ^{201}Tl chloride accumulates equally in thyroid and parathyroid cells. To make differentiation possible, its application was followed by an injection of ^{99m}Tc pertechnetate, with predominant thyroid uptake. Then ^{99m}Tc pertechnetate thyroid images were digitally subtracted from the images obtained with ^{201}Tl chloride to allow visualization only of the parathyroid glands [16].

Introduced in clinical practice by Coakley et al. [17], the ^{99m}Tc-sestamibi scintigraphy significantly increased the role of preoperative scintigraphy in patients with hyperparathyroidism. Firstly used as a cardiotropic agent this radionuclide showed increased accumulation in a variety of benign and malignant tumors. ^{99m}Tc-sestamibi consists of lipophilic cationic molecules. After being intravenously injected these molecules distribute throughout the body accordingly to the local blood supply and by passive diffusion through cell's membrane accumulate intracellularly into the mitochondria [18, 19]. Normally ^{99m}Tc-sestamibi distributes in parotid and submandibular salivary glands, thyroid gland, the heart and the liver, but not in normal parathyroid glands. Visualization of parathyroid adenomas and hyperplastic parathyroid glands depends on the presence of oxyphillic cells, which are rich of mitochondria. The cells of parathyroid adenomas have plenty of

mitochondria [20], while the normal parathyroid cells do not [21]. The highest rates of uptake of ^{99m}Tc-sestamibi are seen in the solitary adenomas of the parathyroid glands [22]. Not only the amount of intracellular mitochondria is important but also the quantity of oxyphillic cells in the tumors. If the percentage of oxyphillic cells exceeded 25%, accumulation of ^{99m}Tc-sestamibi was observed in 78% of parathyroid adenomas. Also false negative results are possible if the oxyphillic cells do not content sufficient amount of mitochondria [23]. Accumulation of ^{99m}Tc-sestamibi into the cells also can be influenced by their metabolic activity, the weight and the size of the tumor. This new radionuclide rapidly replaced ^{201}Tl chloride because it showed better quality of the images and higher sensitivity for detecting abnormal parathyroid glands, with less radiation exposure [24].

^{99m}Tc-tetrofosmin another myocardial perfusion agent was also used for visualizing parathyroid glands in scintigraphy, but the data for its use so far are limited. ^{99m}Tc-tetrofosmin shows some similarities with ^{99m}Tc-sestamibi although the way of accumulation is different and it is retained mainly in the cytosol rather than in the mitochondria of the target cells. When used for parathyroid scintigraphy ^{99m}Tc-tetrofosmin shows slower washout from the thyroid gland, which makes it unsuitable for single-isotope dual-phase scintigraphy [25]. Nevertheless its sensitivity increases when used in combination with SPECT. Several studies [26, 27] of the diagnostic value of ^{99m}Tc-tetrofosmin scintigraphy for topic localization of the hyperfunctioning parathyroid glands in patients with PHPT, showed that this method was useful for the clinical practice and that the accumulation of ^{99m}Tc-tetrofosmin depends on the weight of the tumor and the level of PTH.

4.1 Protocols for nuclear medicine examination of parathyroid glands

Generally three protocols are most widely used: single-phase dual-isotope subtraction, dual-phase single-isotope and combination of both [28].

In single-phase dual-isotope modality two types of radiopharmaceuticals with different organ uptake are used. One isotope (^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin) with equal thyroid and parathyroid glands accumulation and another (^{123}I or ^{99m}Tc-pertechnetate) with predominant uptake in the thyroid gland are applied consecutively. The obtained images are digitally subtracted and if there is a residual radionuclide accumulation on the subtracted images a hyperfunctioning parathyroid gland can be suspected [28]. Disadvantages of this method are the use of two radionuclides, the necessity of full collaboration from the patient's side to stay calm and motionless during the examination and the need of very precise positioning of the patient. In addition there is an increase possibility for the presence of artifacts on the subtracted images [29, 30].

The rationale of the single-isotope protocol is based upon the different washout periods of the radionuclide from the thyroid and parathyroid glands. In this method, after an injection of a single radionuclide, early (at 10–15 min) and late (at 1.5–3 h) images are obtained [28].

There are a very few studies directly comparing the results from single-isotope dual-phase modality with single-phase dual-isotope subtractional scintigraphy and the results are inconclusive [31, 32]. So far there is no clear confirmed advantages of one type over another.

4.1.1 Preparation of the patient

No preliminary preparation of the patients before performing single isotope dual-phase scintigraphy is necessary. In subtractional modality some preliminary conditions should be followed such as: discontinuation of Levothyroxine or Iodine

containing drugs minimum 20 days before the examination. A case history of every patient about the duration of the disease, any concomitant diseases and medications, especially drugs that could possibly interfere with the calcium-phosphate homeostasis, and family history should be taken.

4.1.2 Radiopharmaceuticals

^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin: they are applied intravenously from 740 to 1110 MBq (20–30 mCi).

^{99m}Tc-pertechnetate has a half-life of 6 h and possesses energy of 140 keV. It is used for visualization of the thyroid gland because it accumulates in a functioning thyroid cells. Intravenously ^{99m}Tc-pertechnetate is applied form 74–350 MBq (2–10 mCi).

4.2 Single-isotope dual-phase scintigraphy with ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin

4.2.1 Single-isotope dual-phase scintigraphy with ^{99m}Tc-sestamibi

^{99m}Tc-sestamibi accumulates in the thyroid and parathyroid glands, but the washout time from both glands differs, showing faster disappearing from the thyroid and retention in parathyroid cells. This allows successful visualization of pathologically changed parathyroid glands on the obtained later images—1.5–2 h after the injection of the radionuclide. This different retention time in both glands may be related to some down-regulation of the P-glycoprotein system in parathyroid adenomas, which delays washout of the nuclide [33]. Just the opposite, in parathyroid hyperplasia these so-called multidrug-related resistance molecules can be upregulated and can cause faster washout of ^{99m}Tc-sestamibi and lead to false negative results [34, 35].

To avoid this disadvantage and to improve sensitivity and specificity, the use of single-isotope dual phase (early and late) scintigraphy, based upon the suggestion that ^{99m}Tc-sestamibi is washed out faster from the thyroid gland than from the hyperfunctioning parathyroid cells, is recommended [36]. This single-isotope dual phase scintigraphy gained popularity due to its convenience. The fact that ^{99m}Tc-sestamibi can also be accumulated in solitary thyroid nodules diminishes the specificity of this procedure, especially in areas with higher incidence of nodular goiter [37, 38]. Some parathyroid adenomas also show rapid washout of ^{99m}Tc-sestamibi and make their visualization difficult by this procedure [39]. This led to an introduction of a modified protocol for subtractional scintigraphy by adding a second radionuclide with a preferential accumulation in the thyroid tissue.

^{99m}Tc-sestamibi scintigraphy is generally regarded to be the most sensitive and specific imaging modality especially when it is combined with other imaging procedures. The combination of US examination with dual-isotope ^{99m}Tc pertechnetate/^{99m}Tc-sestamibi scintigraphy for preoperative localization of parathyroid adenomas leads to visualizing of the parathyroid adenomas in 95.2% of the cases (20 patients out of 21). Reaching such high diagnostic precision allows to minimize the extent of the surgical procedure and gives way to apply routinely and successfully minimally invasive parathyroidectomy only of the pathologically changed glands [40, 41].

Comparing different imaging methods,^{99m}Tc-sestamibi scintigraphy has higher sensitivity and specificity than US and CT in discovering adenomas of the parathyroid glands. With regards to the hyperplasia of the parathyroid glands ^{99m}Tc-sestamibi scintigraphy shows to be of less value [42, 43]. Hyperplastic parathyroid glands

are visualized in 10–62.5% of the cases [44, 45]. In multiple endocrine neoplasia syndrome (MEN), where hyperplasia of the parathyroid glands is common, only 55% of the abnormal glands are seen on ^{99m}Tc-sestamibi scintigraphy [42, 46, 47]. ^{99m}Tc-sestamibi scintigraphy shows to be highly effective in discovering ectopic hyperfunctioning parathyroid glands, which in some studies, are observed in approximately 20% of the cases with PHPT and represent a diagnostic and therapeutic challenge [48]. Visualizing small parathyroid adenomas represents a specific problem. One study showed, that in surgically removed adenomas weighted less than 0.5 g, preoperative US was negative, but ^{99m}Tc-sestamibi scintigraphy discovered adenomas in 87% of cases and the combination with SPECT increased sensitivity to 95% [21].

In patients with SHPT, seems to have a direct correlation between ^{99m}Tc-sestamibi uptake with the blood level of parathyroid hormone and the phase of the cells' cycles [49]. The lowest level of accumulation corresponds to G(0) phase and the highest to phase G(2) + S. No such correlation with the weight of the glands is found [49]. The fixation of the radionuclide depends on the functional status of the tissues, i.e., increased accumulation accompanies the cells' active growing phase or is directly connected to the state of autonomy of the parathyroid cells [46].

The reason why not all pathologically changed parathyroid glands accumulate radionuclide remains unclear. This may be due to the different degree of activity and proliferation of the cells of the parathyroid adenomas. It was suggested that there is a relationship between nuclide accumulation and the degree of autonomy of the cells of the adenoma, i.e., the loss of the suppressive effect of calcium upon the secretion of the parathyroid hormone. The cells of the parathyroid adenomas and these of the hyperplastic glands show higher threshold for calcium suppression or have no threshold at all in comparison with the normal parathyroid cells. Due to this fact, these cells secrete more PTH for any given blood calcium level, show higher metabolic rate and capability to accumulate more ^{99m}Tc-sestamibi. Hyperplastic parathyroid glands are to some extent with preserved functional regulation, respond to the normal suppressive stimuluses, have lower metabolic rate and accumulate less of the radionuclide.

Due to its higher affinity to the parathyroid adenomas, ^{99m}Tc-sestamibi scintigraphy was used in cases of relapse of the hyperparathyroidism after parathyroidectomy or after autotransplantation of parathyroid glands.

Nowadays, there are several imaging methods for discovering hyperplastic parathyroid glands. The results so far are inconclusive. The dual-phase ^{99m}Tc-sestamibi scintigraphy in preoperative localization of the hyperplastic parathyroid glands in patients with profound secondary hyperparathyroidism do not show high sensitivity, but is of help to discriminate between patients with nodular and diffuse hyperplasia [50].

The role of ^{99m}Tc-sestamibi scintigraphy in patients with end-stage renal disease and secondary hyperparathyroidism is still unclear. The uptake of ^{99m}Tc-sestamibi can be suppressed by the use of calcitriol in these patients. In one study [51] ^{99m}Tc-sestamibi scintigraphy managed to visualize 1 or more (maximum 3) parathyroid glands in most, but not in all patients on hemodialysis with PHT levels above 600 pg/ml. Performing suppressive test with calcitriol (2 mg of calcitriol applied i.v. after each hemodialysis for two consecutive weeks) showed suppression of ^{99m}Tc-sestamibi uptake at least in one parathyroid gland in 57% of the cases and full suppression in all glands in 36%. The basal level of PHT or its lowering after this test showed to be of no predictive value for the suppression of ^{99m}Tc-sestamibi uptake in the parathyroid glands. Because of its lower sensitivity, the ^{99m}Tc-sestamibi scintigraphy was found to be of limited value in preoperative evaluation in uremic patients with secondary hyperparathyroidism, but its significance grew up in localizing hyperfunctioning glands left after the first operation [51].

Single-isotope dual phase ^{99m}Tc-sestamibi scintigraphy is easily performed, and needs only application of ^{99m}Tc-sestamibi. After injection of the radiopharmaceutical, early (10–15 min), and late planar (1,5–3 h) images are obtained (**Figures 1** and **2**).

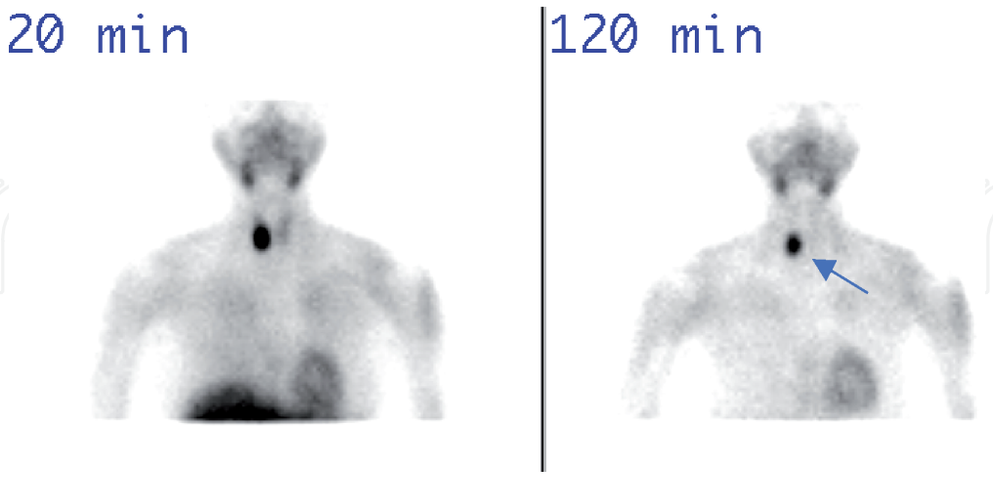


Figure 1.
Single-isotope dual-phase scintigraphy with ^{99m}Tc-sestamibi. The late image (120 min) shows a focus of a residual activity (arrow), caudally of the right thyroid lobe consistent with adenoma of the right lower parathyroid gland.

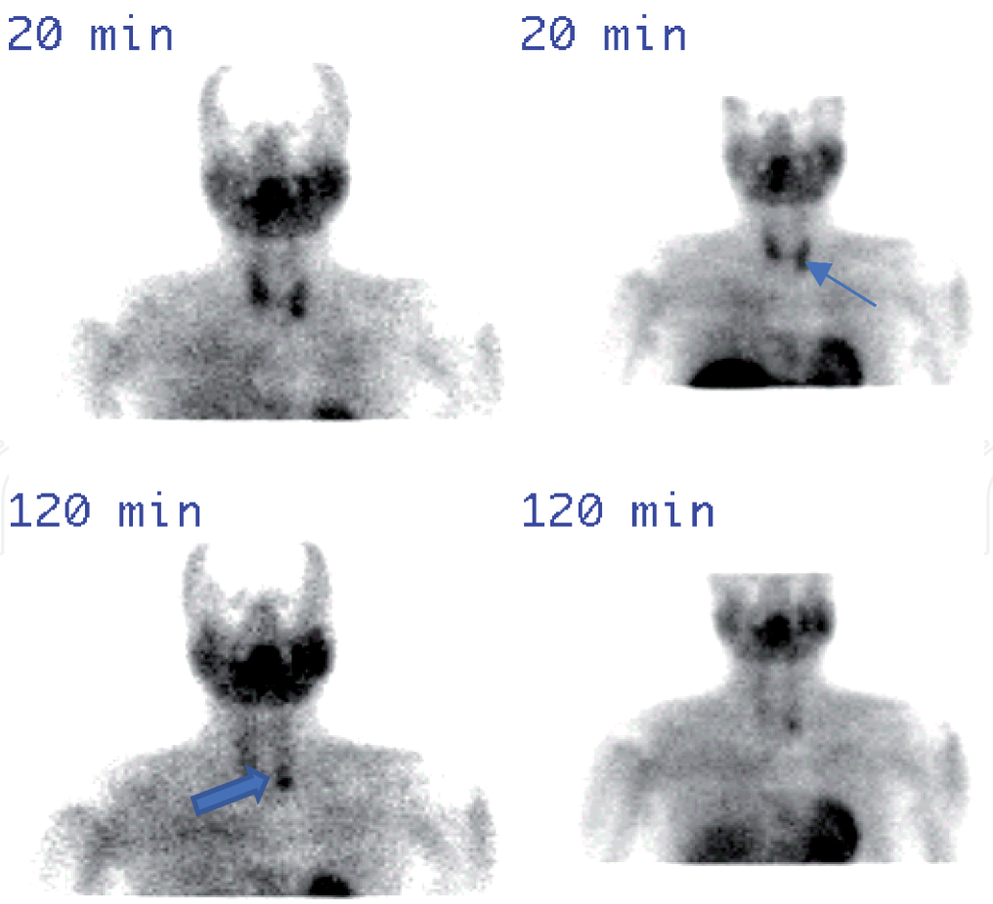


Figure 2.
Single-isotope dual-phase scintigraphy with ^{99m}Tc-sestamibi. On the early images (20 min) relatively diffuse uptake in the area of the thyroid gland and a focus of increased accumulation of the radionuclide (thin arrow), caudally of the left thyroid lobe are seen. On the late phase images (120 min) only a focus of a residual activity (thick arrow), caudally of the left thyroid lobe is visualized-suggesting adenoma of the lower left parathyroid gland.

In some cases, the obtained early and late images show no signs of abnormal accumulation of radionuclide, but when combined with SPECT, than adenomas located at the back of the thyroid gland become visible (**Figure 3a** and **b**).

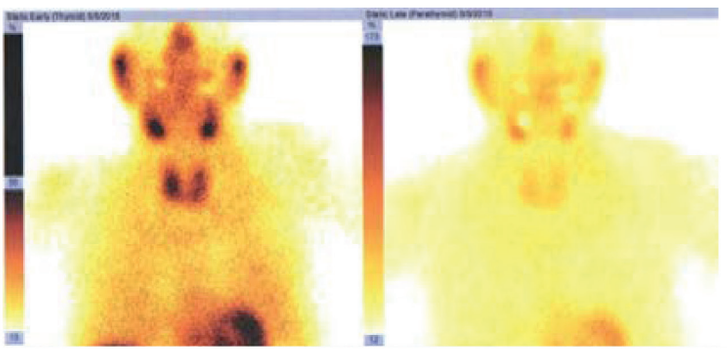
So, the combination of a single-isotope dual-phase scintigraphy with ^{99m}Tc-sestamibi with SPECT can be of great help.

During many years in the past, two-dimensional images have been obtained, mainly AP-images, and rarely this was combined with lateral and oblique images [52, 53].

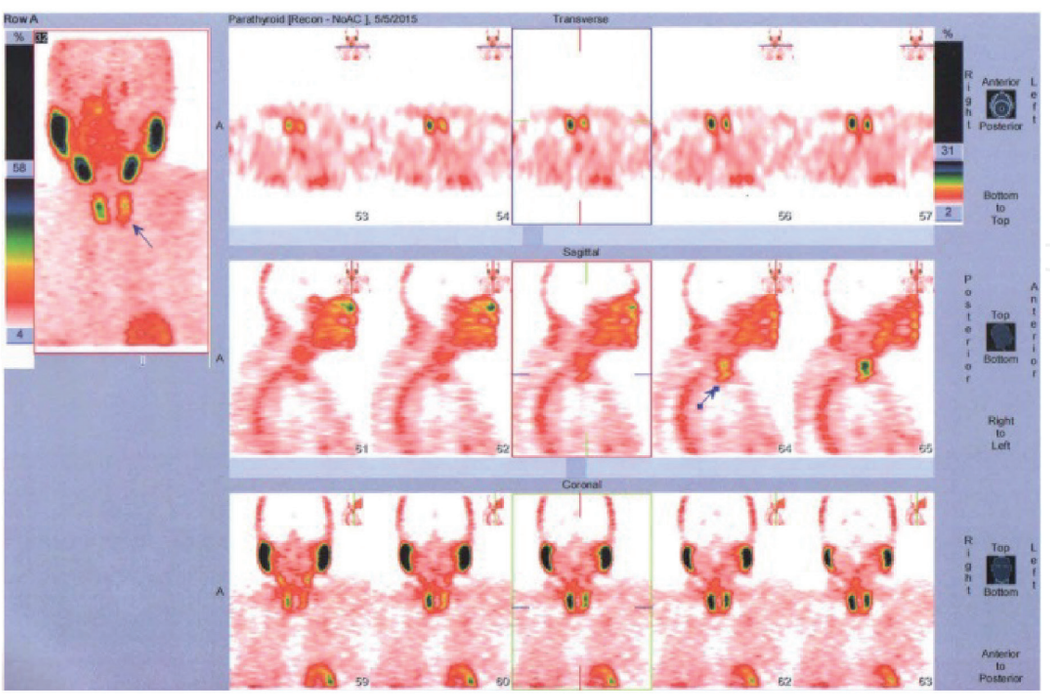
SPECT has gained more importance, because it gives three-dimensional images. There are accumulating data from the literature, that it improves sensitivity for discovering and localizing the hyperfunctioning parathyroid glands [54, 55]. The main reason for this is the improved contrast resolution of SPECT (**Figure 4**).

4.2.2 Single-isotope dual-phase scintigraphy with ^{99m}Tc-tetrofosmin

^{99m}Tc-tetrofosmin, another myocardial perfusion agent, is also used for parathyroid scintigraphy, but there are limited data in the literature for its use. Several



(a)



(b)

Figure 3.
(a) Single-isotope dual-phase scintigraphy with ^{99m}Tc-sestamibi. Early planar images show diffuse uptake in the thyroid gland. Late planar images show no sign of a focus of residual activity in the neck area or mediastinum. (b) (The same patient) ^{99m}Tc-sestamibi SPECT images show an area of a residual activity, located dorsally and caudally of the left thyroid lobe (arrows) suspicious for a parathyroid adenoma.

studies [26, 27] assess the diagnostic value of ^{99m}Tc-tetrofosmin scintigraphy for topic localization of the hyperfunctioning parathyroid glands in patients with PHPT. They show that this method was useful for the clinical practice and that the accumulation of ^{99m}Tc-tetrofosmin depended on the weight of the tumor and the level of PTH. The early images (15th min) prove to be better than the late ones (120th min). ^{99m}Tc-tetrofosmin is washed out more slowly from the thyroid gland than ^{99m}Tc-sestamibi but both radionuclides give better results in comparison with ^{99m}Tc-pertechnetate/^{201}Tl-substractional technique [56]. ^{99m}Tc-tetrofosmin looks promising alternative of ^{99m}Tc-sestamibi with similar properties and capabilities of localizing parathyroid adenomas.

Dual-isotope substractional scintigraphy with ^{99m}Tc-tetrofosmin/^{99m}Tc-pertechnetate and SPECT represent highly sensitive method for localization of parathyroid adenomas and their combination can further improve the diagnostic precision [57]. ^{99m}Tc-tetrofosmin, like ^{99m}Tc-sestamibi is not perfect for localization of hyperplastic parathyroid glands in patients with SHPT, because of its lower sensitivity [56]. ^{99m}Tc-tetrofosmin has some similarities with ^{99m}Tc-sestamibi, but its mechanism of accumulation in the cells is different. In contrast with ^{99m}Tc-sestamibi, which accumulation depends on mitochondria's membrane potential, retention of ^{99m}Tc-tetrofosmin depends mainly on cell's membrane potential [25]. ^{99m}Tc-tetrofosmin, shows slower wash out from the thyroid on the late planar images (120 min). This leads to the necessity to obtain additional later planar images—between 150 and 160 min. This slower wash out makes ^{99m}Tc-tetrofosmin to be unsuitable for performing single-isotope, dual-phase scintigraphy [25]. To avoid misleading, because of prolonged retention of the radiopharmaceutical in the thyroid adenomas, an US examination should be performed, especially in iodine deficient areas [56].

Figure 5 is presented a single-isotope dual-phase scintigraphy with ^{99m}Tc-tetrofosmin, combined with SPECT in a patient with PHPT.

In ^{99m}Tc-tetrofosmin scintigraphy early images at 20th min show better quality than the later ones at 120th min (**Figure 6a–c**).

Late planar images (120 min)—negative scan.

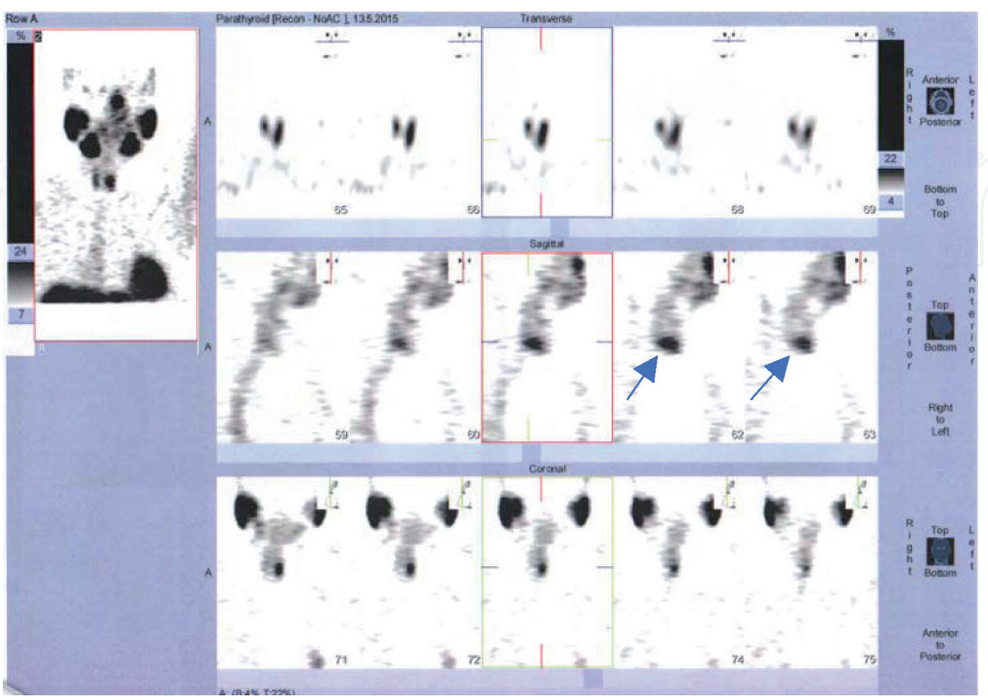
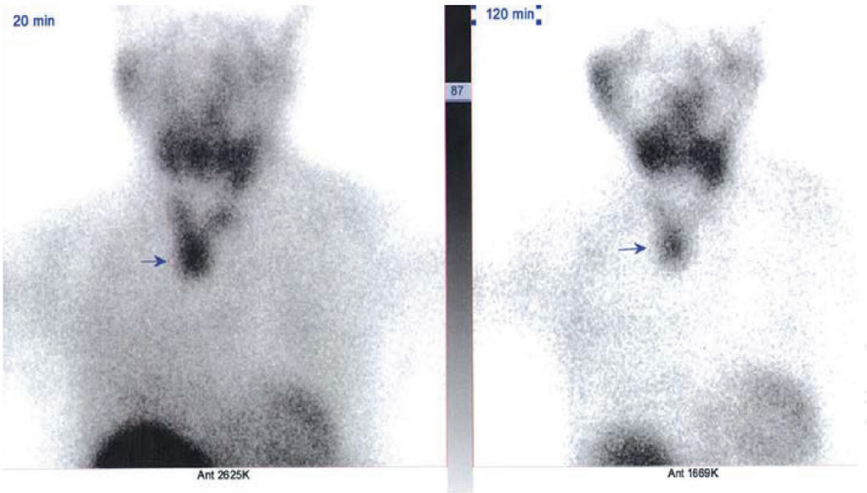
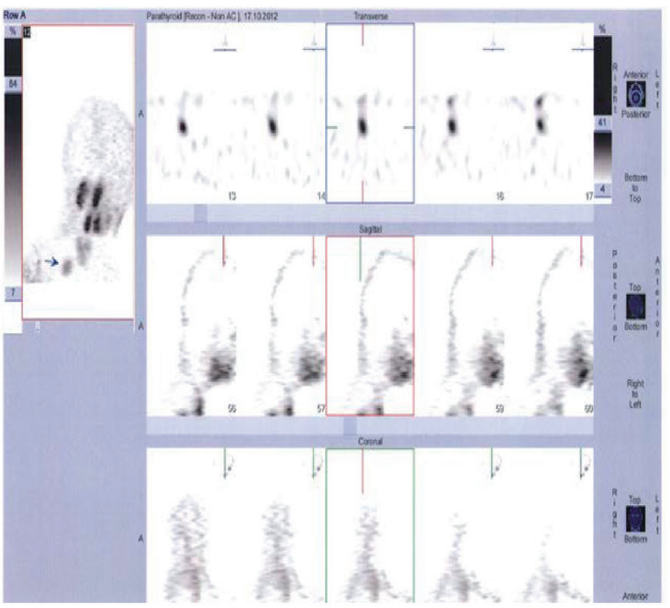


Figure 4.
Early ^{99m}Tc-sestamibi SPECT images showing an area of radionuclide accumulation (arrows), located dorsally and caudally of the left thyroid lobe.



(a)



(b)

Figure 5.
(a) Early phase image (20 min) shows an intense uptake of the radionuclide at the lower part of the right thyroid lobe, which activity is still present on the late image (120 min) (arrows) and (b) (same patient) SPECT images showing an intense uptake dorsally and caudally of the right thyroid lob (arrow), suggestive for adenoma of the right lower parathyroid gland.

In this case, early SPECT gives opportunity to visualize adenomas, which were not seen on the late planar images, which is probably due to the rapid wash out of the radiopharmaceutical from some adenomas, as well as to the small sizes of the adenomas. When combined with SPECT, dual-phase scintigraphy with ^{99m}Tc-tetrofosmin can detect adenomas with rapid wash out of the radiopharmaceuticals.

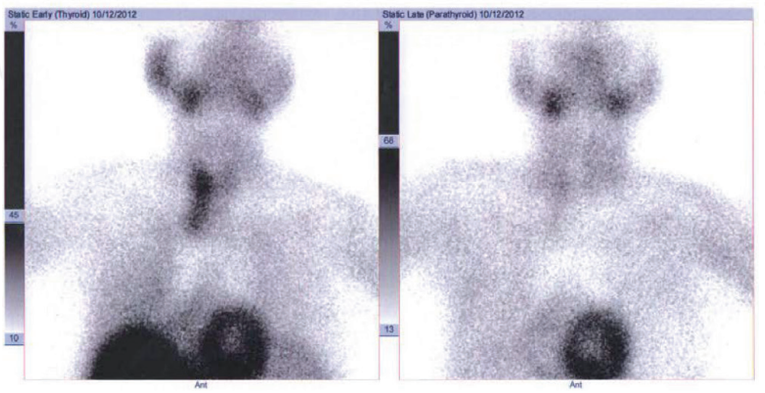
Pearls/pitfalls:

a. The single isotope dual-phase scintigraphy with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin could miss parathyroid adenomas with rapid washout of the radionuclide. The combination with early SPECT improves sensitivity.

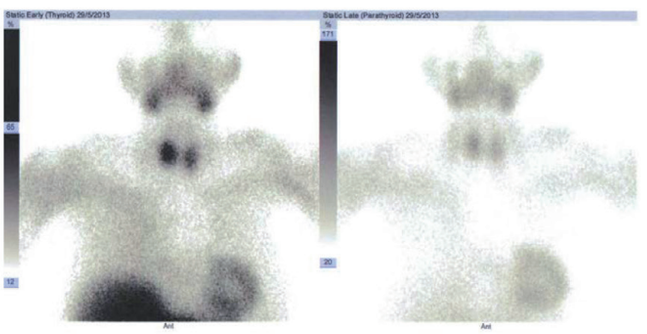
b. The single isotope dual-phase scintigraphy with ^{99m}Tc-tetrofosmin in patients with PHPT and SHPT is with less sensitivity and specificity, because of the

poor quality of the obtained images and slower washout of the radionuclide from the thyroid gland.

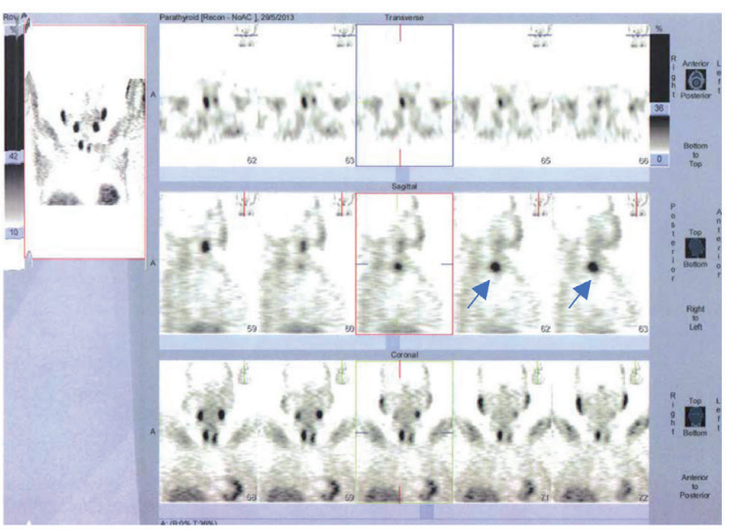
c. SPECT combined with single-isotope scintigraphy and subtractional methods for visualization of hyperfunctioning parathyroid adenomas in patients with PHPT and SHPT is a reliable additional modality. It does not cause additional and unnecessary exposure of the patients to the gamma-rays and can increase sensitivity.



(a)



(b)



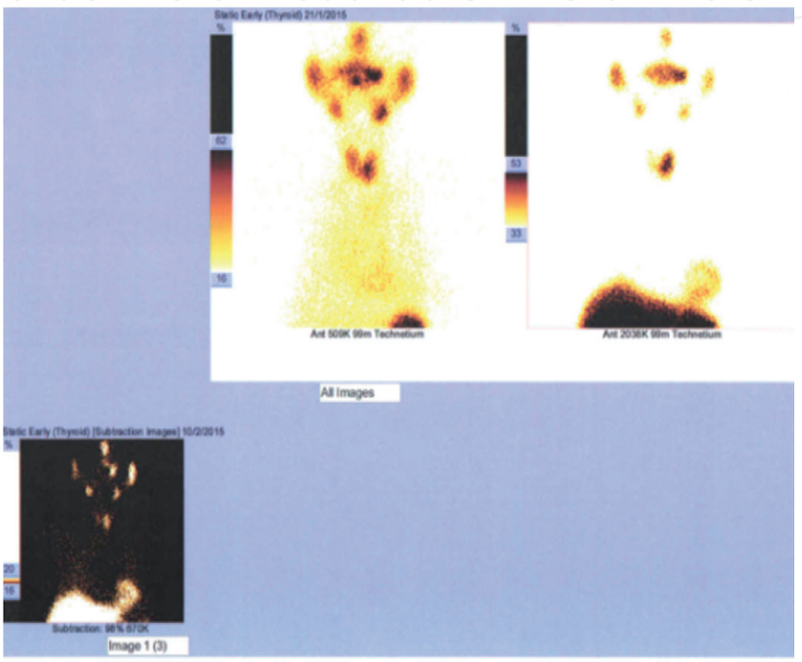
(c)

Figure 6.
(a) Single-isotope dual-phase scintigraphy with ^{99m}Tc-tetrofosmin. Early planar images (20 min) are with better quality, (b) (same patient) single-isotope dual-phase scintigraphy with ^{99m}Tc-tetrofosmin and (c) ^{99m}Tc-tetrofosmin SPECT images—an area (arroes) with high uptake located dorsally of the lower right lobe is seen, consistent with adenoma of the right lower parathyroid gland.

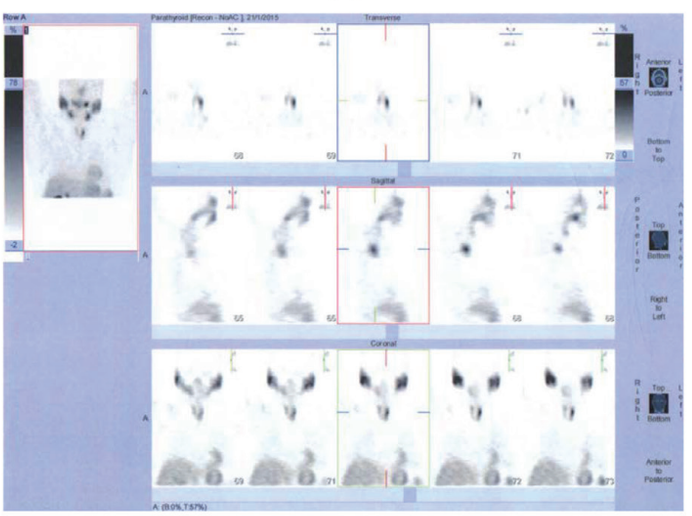
4.3 Dual-isotope subtractional scintigraphy with: ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi or ^{99m}Tc-pertehnetat/^{99m}Tc-tetrofosmin

4.3.1 Dual-isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi

The rationale that stands behind dual-isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi, is that ^{99m}Tc-sestamibi accumulates in both, thyroid gland and hyperfunctioning parathyroid glands, while ^{99m}Tc-pertechnetate uptakes only in the thyroid. First thyroid specific radionuclide ^{99m}Tc-pertechnetate



(a)



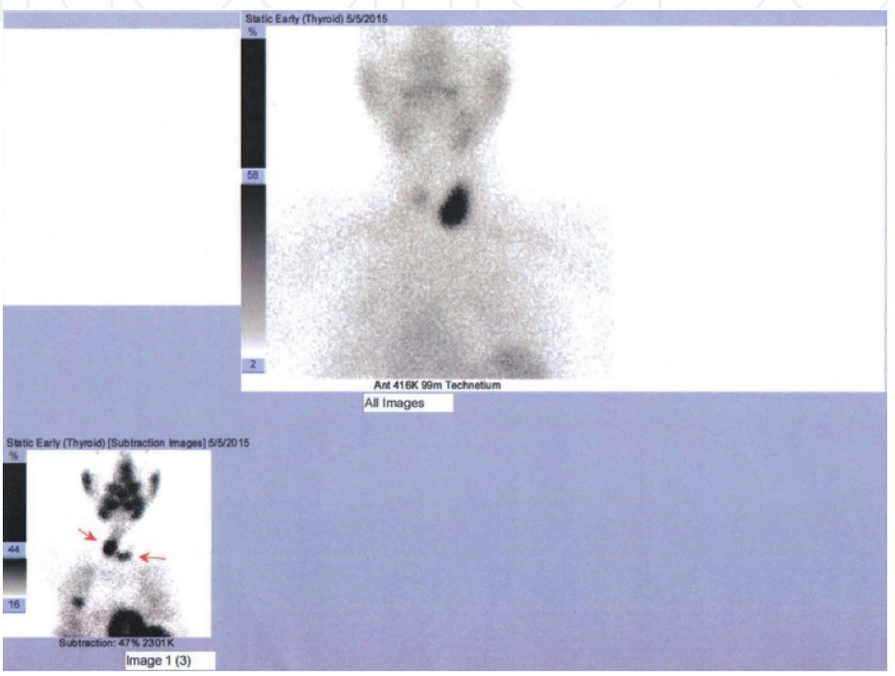
(b)

Figure 7.
(a) Dual-isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi. Upper image on the left-image of thyroid gland obtained with ^{99m}Tc-pertehnetat. Upper image on the right an image obtained with ^{99m}Tc sestamibi (arrow). Lower image. Subtractional image showing a focus of a residual activity (arrow) in upper back part of the left thyroid lobe consistent with left parathyroid adenoma and (b) (same patient) dual-isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi. Early SPECT images showing an area of intense uptake located dorsally and cranially of the left thyroid lobe.

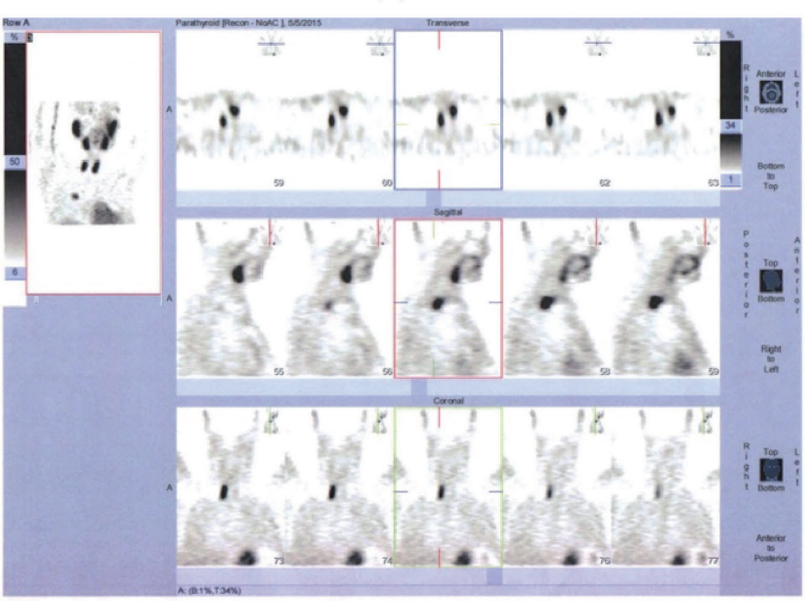
is injected and at 30th min images are obtained. Afterwards, while the patient is still under the detector, second radionuclide ^{99m}Tc sestamibi with dual accumulation is applied and a second set of images on the 20th min are obtained. Later images are subtracted digitally from the first set of images and if a focus of residual activity on the subtractional images is detected, a hyperfunctioning parathyroid gland is supposed. The combination with early SPECT can improve sensitivity (**Figure 7a** and **b**).

The subtraction could be of help, when the patients had undergone surgery of the thyroid, but some thyroid parenchyma is still present. This method is important in the presence of more than one abnormal parathyroid gland.

Dual-isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi combined with SPECT in a 51 years old man with MEN-type 1



(a)



(b)

Figure 8.
(a) Dual-isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi. Subtractional image showing two areas of intense uptake consistent with two parathyroid adenomas and (b) SPECT images showing an area of intense uptake located dorsally and caudally of the right thyroid lobe.

syndrome—pheochromocytoma, parathyroid adenoma and prolactinoma, who had previously undergone thyroid (subtotal thyroidectomy) and parathyroid (left upper parathyroid gland) surgery. Subtractional images (**Figure 8a**) and early SPECT images (**Figure 8b**) show two areas of intense uptake located below the remnants of the both thyroid lobes. SPECT images show that the lesion below the right thyroid lobe was located also adjacent to the back part of the right thyroid lobe.

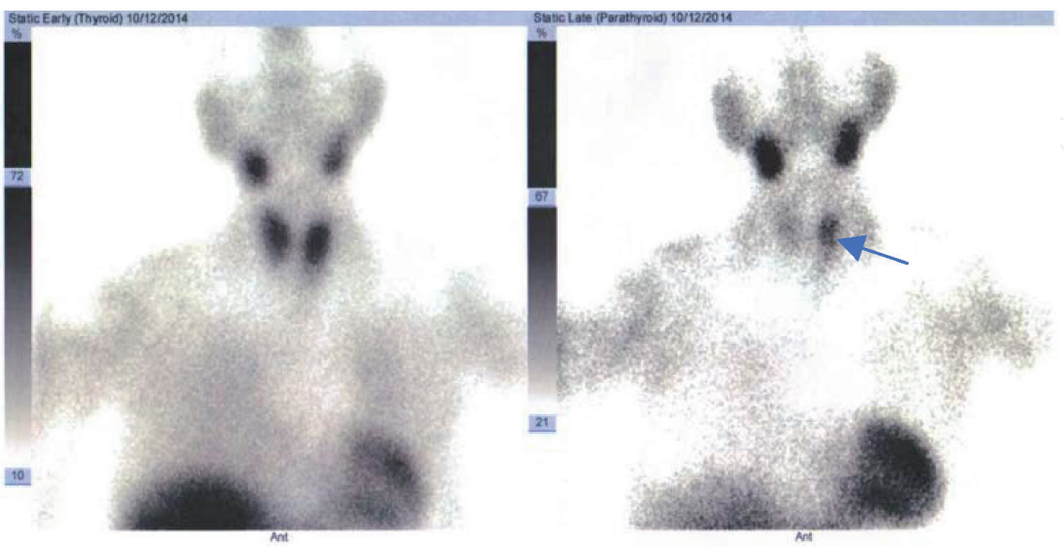
In some cases, obtaining late images could also be of help. Combining dual-isotope, ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi, subtractional scintigraphy with SPECT, and also recording late planar images on the 120th min (late phase) would improve sensitivity (**Figures 9** and **10**).

Pearls/pitfalls

a. Dual isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi or ^{99m}Tc-pertehnetat/^{99m}Tc-tetrofosmin allows visualization of abnormal parathyroid glands after subtraction is performed, even on the early obtained images.



(a)

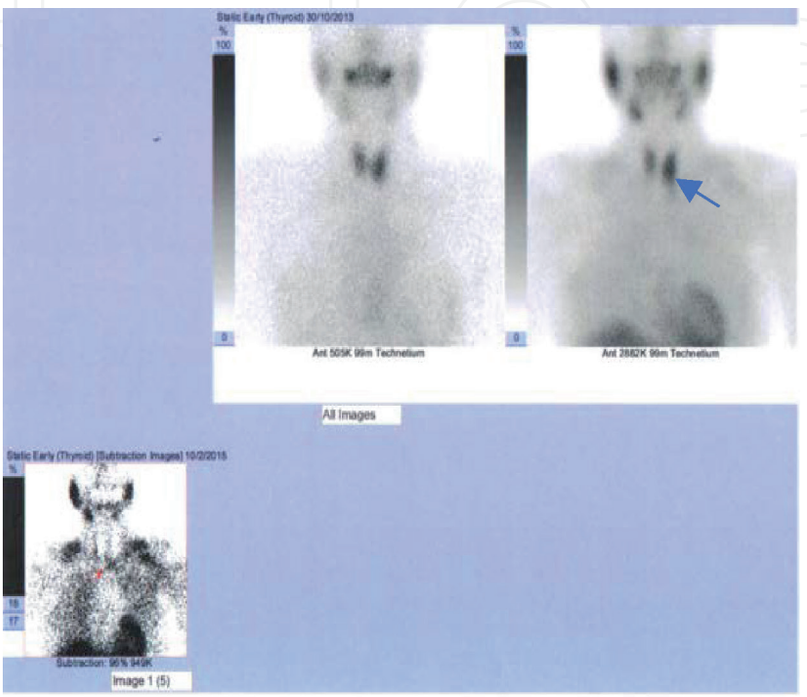


(b)

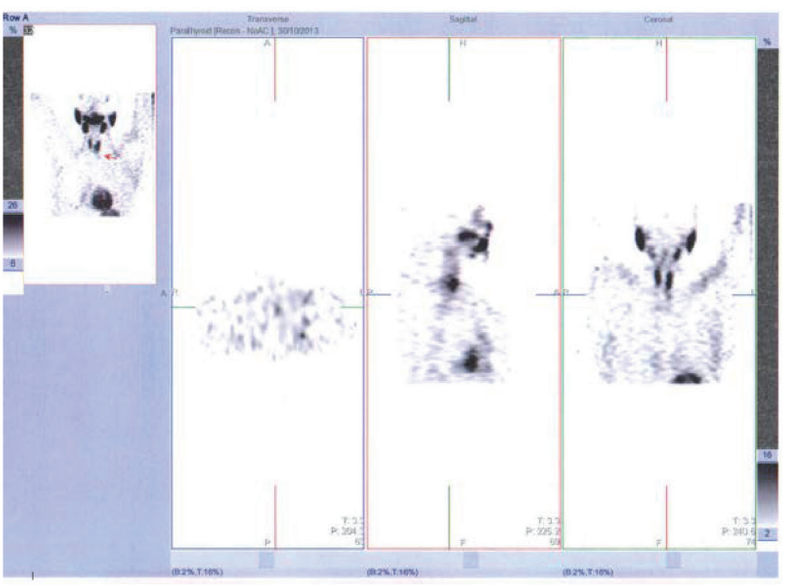
Figure 9.
(a) Dual-isotope subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi. Subtractional image showing no residual activity in the areas of the neck and chest and (b) late planar images showing a residual activity (arrow) in the middle of the left thyroid lobe, consistent with left parathyroid adenoma.

This helps to shorten the time of examination to 80–90 min and is of great use in the postsurgical follow up and when more than one abnormal gland is present.

b. Disadvantages of the subtractional scintigraphy with ^{99m}Tc-pertehnetat/^{99m}Tc sestamibi or ^{99m}Tc-pertehnetat/^{99m}Tc-tetrofosmin are: necessity of applying of two radionuclides, the need of very precise positioning of the patients in this dual phase method requiring full collaboration from patient's side and the probability of the presence of artifacts in the obtained images.



(a)



(b)

Figure 10.
(a) Dual-isotope subtractional method with ^{99m}Tc-pertehnetat/^{99m}Tc-tetrofosmin. The upper row: on the left image of the thyroid gland with ^{99m}Tc-pertehnetat and on the right image of the parathyroid gland with ^{99m}Tc-tetrofosmin (arrow). The lower row shows subtractional image representing adenoma of left parathyroid gland and (b) dual-isotope subtractional method with ^{99m}Tc-pertehnetat/^{99m}Tc-tetrofosmin early SPECT images showing an area of hyper fixation, located caudally of the left thyroid lobe.

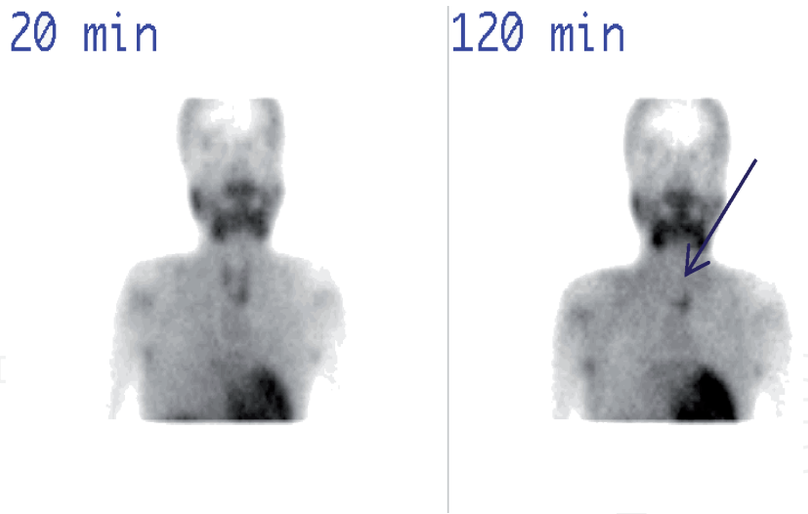
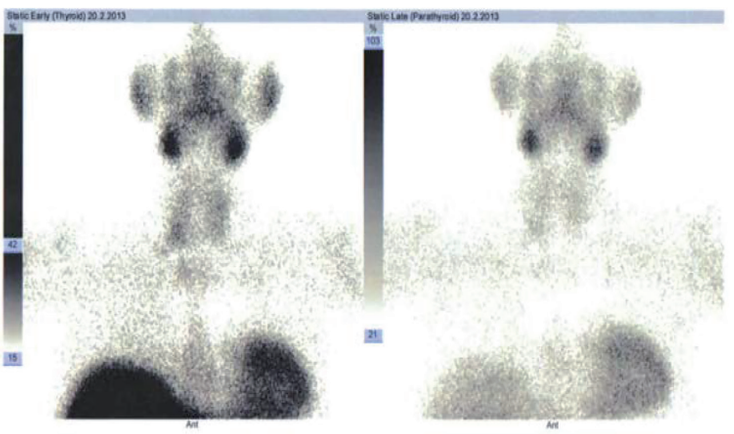
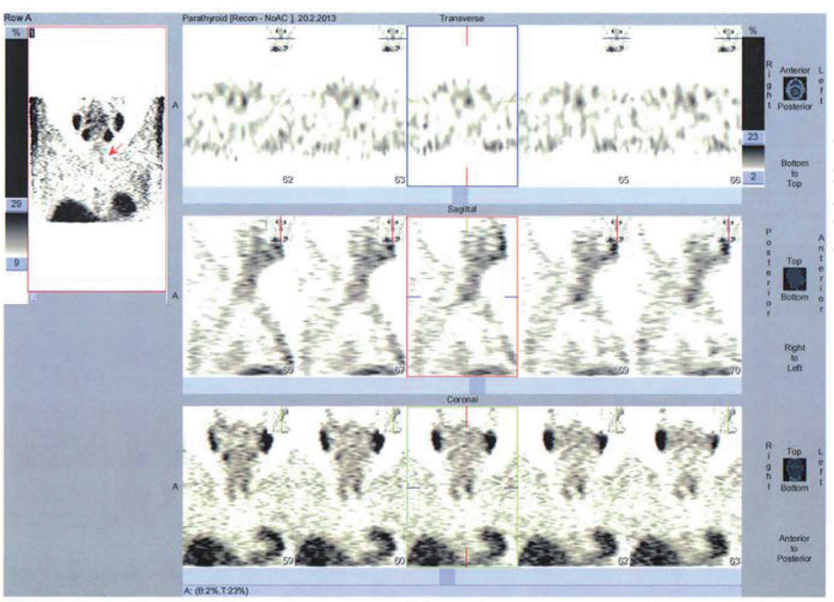


Figure 11.
Single-isotope, dual-phase scintigraphy with ^{99m}Tc-sestamibi in a patient with secondary hyperparathyroidism. The late phase (120 min) show a focus of residual activity (arrow)—consistent with parathyroid adenoma (probably tertiary hyperparathyroidism).



(a)



(b)

Figure 12.
(a) Single-isotope, dual-phase scintigraphy with ^{99m}Tc-tetrofosmin in a patient with secondary hyperparathyroidism. Early (20 min) and late (120 min) images show no focus of a residual activity in the area of neck and mediastinum and (b) (same patient) early SPECT images showing an area of nuclide accumulation caudally of the left thyroid lobe, suspicious for parathyroid adenoma.

4.4 Secondary hyperparathyroidism

Secondary hyperparathyroidism is characterized with hyperplasia of parathyroid glands, because it is caused by longstanding uncontrolled hypocalcemia, which leads to a profound overstimulation of a previously normal parathyroid glands. Over time this overstimulation causes hyperplasia and eventually adenomatous changes (tertiary hyperparathyroidism) of the parathyroid glands with PTH levels far more exceeding those observed in PHPT (**Figure 11**). Nevertheless, hyperplastic parathyroid glands usually show faster wash out of the radionuclides in comparison to solitary adenomas, which makes them more difficult to be visualized with scintigraphy (**Figure 12**). Negative scans, may be associated with the possible suppression of the accumulation of radiopharmaceuticals in the parathyroid cells as a result of the concomitant calcitriol intake. The use of calcium channel blockers may affect the uptake of ^{99m}Tc-sestamibi by parathyroid cells and reduce the sensitivity of the method. A study found that negative scans are twice as likely in patients taking calcium antagonists than those who do not take these medications (OR2, 88.95% CI, 1.03–8.10, p 0.045) [58]. So, adding the poor general condition of the patients, pathologically changed parathyroid glands are more difficult to be localized in SHPT than in PHPT.

5. Conclusions

The visualization of abnormal parathyroid glands is difficult due to their variations in number and localization. Noninvasive parathyroid imaging studies include ^{99m}Tc-sestamibi scintigraphy, ultrasonography, computed tomography scanning, magnetic resonance imaging, and positron emission tomography. There is a general consensus that the most sensitive and specific imaging modality is the scintigraphy with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin. ^{99m}Tc-sestamibi scintigraphy significantly increases the role of preoperative scintigraphy in patients with hyperparathyroidism and allows unilateral surgical approach with minimally invasive parathyroidectomy to be used. Generally three protocols with the use of two radiopharmaceuticals, ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin, are most widely applied: single-phase dual-isotope subtraction, dual-phase single-isotope and combination of both. Each one of them has specific advantages and disadvantages. While, single parathyroid adenomas are localized with greater precision, hyperfunctioning parathyroid hyperplastic cells represent a real challenge to the imaging modalities.

Several factors can influence the radionuclide uptake in pathologically changed parathyroid cells:

a. biochemical factors

- Total calcium levels—higher preoperative calcium levels are more frequently seen in patients with positive scans.
- Parathyroid hormone levels.
- A significant correlation between radiopharmaceutical uptake and preoperative levels of PTH is observed. As higher PTH is, as higher is the possibility for positive scans.
- Vitamin D levels.

- Patents with vitamin D deficiency are more likely to have positive scans.
- Suboptimal levels of vitamin D, can stimulate the growth of the parathyroid adenomas independently from hypocalcemia and 1,25-dihydroxyvitamin D_3 deficit can change the set-point of calcium suppressive effect upon PTH secretion [59].
- Calcium-channel blockers.
- The use of calcium-channel blockers can influence the uptake of the radiopharmaceutical in the parathyroid cells diminishing the sensitivity of the method.

b. biological factors

- Size—although considered to be very important, it is not the only determining factor.
- Type of cells of the parathyroid adenoma—because oxyphilic cells contain more mitochondria, they uptake radionuclides to a larger extent.
- P glycoprotein and MDR gene products.

Uptake of ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin in the cells of the parathyroid adenomas depends on the activity of the P glycoprotein coded by MDR gene, which is functioning as an ATP dependent efflux pump, protecting against accumulation of lipophilic cationic radiopharmaceuticals, including ^{99m}Tc-tetrofosmin [60]. The expression of P glycoprotein in the parathyroid adenomas appears to be important factor determining radiopharmaceutical uptake. In one study 71% (10 out of 14) of adenomas with high P glycoprotein membrane activity have shown negative scans, 70% (45 out of 64) with negative P glycoprotein expression ($p = 0.006$) have shown positive scans [61].

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