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Imaging diagnostics for primary hyperparathyroidism

Diagnostyka obrazowa pierwotnej nadczynności przytarczyc

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Abstract

Primary hyperparathyroidism (PHP) is a benign condition characterised by malignant potential. Even in specialist wards, 5–10% of operations for PHP are unsuccessful. The main reasons seem to be ectopy of the parathyroid gland, numerous adenomas, multiglandular parathyroid hyperplasia, and intrathyroid location of the parathyroid. The last three decades have witnessed a rapid progression in imaging diagnostics. **(Endokrynol Pol 2013; 64 (5): 404–408)**

Key words: *primary hyperparathyroidism, ultrasonography, scintigraphy MIBI*

Streszczenie

Pierwotna nadczynność przytarczyc (PNP) jest chorobą łagodną o złośliwym potencjale. Nawet w ośrodkach specjalistycznych 5–10% operacji z powodu pierwotnej nadczynności przytarczyc (PNP) kończy się niepowodzeniem. Główną tego przyczyną wydają się być ektopia przytarczyc, obecność mnogich gruczolaków, przerost guzkowy przytarczyc oraz wewnątrztarczycowa lokalizacja przytarczyc. Ostatnie trzy dekady przyniosły gwałtowny postęp diagnostyki obrazowej. **(Endokrynol Pol 2013; 64 (5): 404–408)**

Słowa kluczowe: *pierwotna nadczynność przytarczyc, ultrasonografia, scyntygrafia MIBI*

Primary hyperparathyroidism (PHP) is a benign condition characterised by malignant potential. If left untreated, it will double the risk of developing a cancer of the breast, prostate or large intestine. It will also cause an increase in heart diseases, hypertensive diseases and osteoporosis. Roughly one third of patients with primary hyperparathyroidism suffer from nephrolithiasis, and most of them complain of a reduction in their quality of life. It is important to note that patients with a 15 year-long history are seen very rarely, and over that time practically never [1].

Why then do surgeons try to avoid operations on patients with the disease diagnosed biochemically but showing a negative result of imaging examinations? Based on experience, lack of disease imaging is not a contraindication to operative treatment. On the other hand, such patients are often a very grateful subject of said management [2]. However, it is widely known that the picture of parathyroid glands correlates well with the clinical severity of the disease [3].

Even in specialist wards, 5–10% of operations for PHP are unsuccessful [4]. The main reasons seem to be ectopy of the parathyroid gland, numerous adenomas, multiglandular parathyroid hyperplasia, and intrathyroid location of the parathyroid [5–8].

The statement of the radiologist J.Doppman in 1968 that "the only localisation study needed by a patient undergoing initial parathyroid surgery is to locate an experienced parathyroid surgeon" [9] was still valid in 1986 during the conference held by the National Institutes of Health on the diagnostics of parathyroid glands.

Since that time, a rapid progression of imaging diagnostics has taken place. Now it is quite easy to define a highly accurate location of disease-transformed parathyroid glands. The advantages of such accurate localisation are obvious.

First of all it is very important to shorten the length of the operation and to reduce the number of unsuccessful operations. Also, a limited preparation area allows a reduced risk of complications, which shortens the time of postoperative care and helps to lower the costs of treatment [10–12].

In light of the above, imaging examinations of parathyroid glands should be:
— highly sensitive
— highly specific
— as minimally invasive as possible
— cost-effective
— available [13].

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Table I. *Examinations enabling identification of disease-transformed parathyroid glands*
Tabela I. *Badania pozwalające na identyfikację chorobowo zmienionych przytarczyc*

Examinations		
Preoperative		Intraoperative
Non-invasive	Invasive	
1. USG	1. BAC	1. USG
2. CT	2. Selective arteriography/thyrocervicaltrunk, internal thoracic artery, cervical arteries, superior thyroid arteries	2. Scintillating probe
3. MR	3. SVS selective venous blood sampling for PTH determination	3. OPTH
4. Scintigraphy		4. Methylene blue
— subtraction (thallium technetium)		5. Histopathological examination
— 'washout' (SPECT)/Tc99m sestamibi		
5. PET		

High sensitivity and specificity of the examination are closely related to the experience of the examiner. It is also important that the requisition form has been properly completed, giving full information not only on the history but also on laboratory findings. The quality of the picture is important too [13–16].

It is definitely true that imaging diagnostics can enable the surgeon to perform a minimally invasive parathyroidectomy (MIP) in a safe way [1, 17].

An analysis of data from 15 American hospital centres revealed that the costs of an operation for PHP with bilateral neck exploration were $1,773 USD and with unilateral neck exploration $1,123 USD including the costs of scintigraphy (sestamibi). Total costs including the description were $429 USD (examination — $305 USD, description — $124 USD). Reducing the costs is undoubtedly connected to the length of the operation. A bilateral exploration takes usually 109.3 ± 29 min., and a unilateral 49.29 min. [17–20].

Examinations performed to enable identification of disease-transformed parathyroid glands are shown in Table I.

One of the most generally available and relatively cheap examinations is ultrasonography (USG) [21–23]. Unfortunately, the sensitivity of this examination, usually 71-80%, is to a great degree dependent on the experience of the examiner [24, 25]. So USG can be more or less sensitive (30-90%) depending on the experience and skill of the examiner [6, 23, 26, 27] (Table II). USG does not enable localisation of parathyroid glands placed in the mediastinum or in retrotracheal or retro-oesophageal regions due to acoustic shadows from bones or air spaces. On the other hand, the latter region can be excellently shown by transoesophageal USG [21, 26, 28, 29]. Moreover, USG enables better imaging of an adenoma located within the thyroid gland [30], in spite of the ease with which a thyroid tuberculum can be confused with an adenoma.

It is well known that a nodular goitre is detected in 6–15% of PHP patients. Generally, PHP is estimated to coexist with other thyroid diseases in 18–84% of patients [1, 31, 32].

Massive nodular goitres restrict the visualisation of structures located backwards of the thyroid gland through:

reducing the sound wave,
displacing adjacent structures by mass effect,
overlapping acoustic shadows [33, 34].

If USG is performed by a surgeon (adequately experienced of course), sensitivity and accuracy of such examination are 87% and 88% respectively [10]. If the result has been assessed as 'atypical' or negative, PTH level in jugular vein blood is measured.

The term 'atypical' refers to the picture in which the examiner:

— is not able to differentiate an ectopic parathyroid gland from a transformed lymph node in jugular region;
— suspects a parathyroid gland as the lesion is only partially visualized;
— is not able to differentiate a hypoechogenic lesion from a thyroid tuberculum or a cyst located in posterior part of the neck;
— has found a bilateral suspicious lesion, 'atypical' with reference to a parathyroid gland [10].

Therefore, an 'atypical' result of a USG examination does not mean a negative result.

USG does not seem very useful for the evaluation of hyperplastic parathyroid glands [25]. In secondary parathyroidism, sensitivity of the examination is 60% and specificity 64%. If the lesions are connected with more than one parathyroid gland, false diagnoses cover nearly 30% of patients [34].

If a parathyroid gland is ectopically located in the anterior mediastinum or retro-oesophageal region, computed tomography is a great help [35]. Sensitivity

Table II. *Characteristics of non-invasive methods to localise disease-transformed parathyroid glands*
Tabela II. *Charakterystyka nieinwazyjnych metod obrazowych w diagnostyce chorobowo zmienionych przytarczyc*

Factor	Localization method				
	USG	CT with contrast	MR	Scintigraphy	
				Tl/Tc	Tc99m sestamibi
Sensitivity (%)	71–80 /range 30–90/	46–80	64–88	75	90.7
Specificity (%)	80–89	80	88–95	73–82	98.8
Reoperation Sensitivity (%)	40		50–88	50	
Falsely positive (%)	15–20	50	18	25	Low
Dependent on examiner's skill	+++	+	++	No	No
Exposure to radiation	No	++	No	+	+
Costs	+	+++	++++	++	++

of this examination can be as high as 92% [36, 37]. However, it is less sensitive than magnetic resonance (MR), and a high percentage of false positive results (up to 50%) is also involved. For this reason, and also due to the necessary contrast, a far better method to examine ectopic parathyroid glands seems to be MR, in spite of the higher costs [30].

In a CT picture, a parathyroid adenoma can be difficult to differentiate from lymph nodes, normal vessel structures or an exophytic thyroid tuberculum, particularly in patients who have previously undergone an operation within the neck [38,39].

The characteristics of non-invasive methods for localising transformed parathyroid glands indicate that the best of them is isotopic radiodiagnostics, particularly technet scintigraphy Tc99m sestamibi [15, 17, 40]. This radiotracer is easily assimilated both by the thyroid gland and by the parathyroid. However, it is soon washed out from the thyroid, whereas parathyroid glands have the ability to store it [41]. Compared to scintigraphy based on isotope Thal201, Technet99m sestamibi is safer when administered in higher doses and has closer affinity with parathyroid tissues. Sensitivity of this examination ranges from 85% to 100%, the latter in the case of parathyroid adenoma [42, 43]. But Technet99m sestamibi is less useful for diagnosing parathyroid hyperplasia as only one gland is identified. Advantages and disadvantages of non-invasive methods used to localise disease-transformed parathyroid glands are shown in Table III.

It should be stressed here that MIBI is a function test and not an anatomical examination. Therefore a smaller gland may reduce its sensitivity [28, 44, 45].

There are three types of technet scintigraphy:
— monoisotopic and two-stage type — scintigraphic pictures are interpreted after 15 minutes and with an interval of 2–3 hours; quicker elimination of the tracer from the thyroid than from the parathyroid plays a role;
— subtraction bi-isotopic type — the thyroid is first examined using e.g. iodine J123 or Tc99m pertechnet, and the picture is 'subtracted' from the one obtained upon administration of Technet99m sestamibi [46, 47];
— three-dimensional examinations SPECT (Single Photon Emission Computed Tomography) [5, 38, 48].

Using USG together with Tc99sestamibi enables the examiner to obtain higher sensitivity of the picture from 10% to even 30% [13]. Statistical analyses have revealed that further independent factors affecting the accuracy of the two diagnostic tests are body mass index (BMI) and the size of the thyroid gland [8]. If MIBI and USG give a negative result, it is recommended to perform MRI or stereoscopic computed tomography (4D-CT) [36].

It must be stressed that if a reoperation is necessary in patients with persistent primary hyperparathyroidism, the most sensitive examination (50–88%) among non-invasive types will be magnetic resonance (MR) [49, 50].

Invasive methods used for diagnosing primary hyperparathyroidism are much more sensitive. Selective angiography shows 60% sensitivity, and intra-operative determination of parathormone in venous blood 80%. If both examinations are used, the sensitivity will increase to as much as 91–95% [50–52]. These examinations help to accurately localise an adenoma (angiography) and to identify further adenomas or hyperplasia (PTH in venous blood) [51]. Unfortunately, the methods may involve dangerous complications, including neurological disorders, embolism or renal failure.

Table III. *Advantages and disadvantages of non-invasive methods to localise disease-transformed parathyroid glands*
Tabela III. *Zalety i niedogodności metod obrazowych w diagnostyce chorobowo zmienionych przytarczyc*

Factor	Localisation method				
	USG	CT with contrast	MR	Scintigraphy	
				Tl/Tc	Tc99m sestamibi
Advantages	Cheap Quick Avoids radiation and contrast i.v. Easy to use together with BAC Transoesophageal USG: good evaluation of posteriori neck and perioesophageal	Good evaluation of mediastinum, retro-oesophageal and retrotracheal spaces Easy to use together with BAC	Enables localisation of ectopic dose glands Useful if scintigraphy unsuccessful No need to use ionic contrast	Readily available Minimal dose of radiation	Best available to localise Minimal dose of radiation Readily available Excellent anatomical localisation with SPECT
Disadvantages	Difficult to evaluate to posteriori neck and mediastinum Not possible to recognise lesions nodes < 5 mm Dependent on examiner's skill Transoesophageal USG difficult to evaluate lateral and/or anterior spaces	Difficult to differentiate small lesions (lymph, parathyroid adenoma) in lower neck and periscapular spaces and thyroid	expensive Not to be used together with BAC Limited use because of claustrophobia Not possible to evaluate lesions < 5 mm	Poor topographic evaluation Limited sensitivity	May 4 hyperplastics glands or a few adenomas unidentified

Intra-operative determination of parathormone (IOPTH) helps the examiner to decide whether it is better to extend the operation, or instead to end it, if:

— a suspicious hyperplastic gland has been removed but the hormone level does not go down;
— an abnormal parathyroid gland has been found although not confirmed by imaging examinations (in such a case, bilateral exploration of the neck is avoided to decrease the risk of complications);
— the diseased gland is not clearly recognisable (an answer is given as to which part of the neck should be explored; even a 5% difference can play a decisive role);
— thin-needle biopsy has been performed to examine the tissue in question (bioptate is placed in 1 mL of physiological saline; the presence of the parathyroid tissue is confirmed if PTH level is higher than 1,500 pg/mL) [52, 53].
— In light of the available data, it seems that patients with primary hyperparathyroidism should receive USG of the neck and scintigraphy MIBI in the first place to identify the lesions [54–58]. If any discrepancies occur in the results, MR is recommended. Operation should be decided afterwards. Levels of parathormone should be monitored throughout the operation [59–63].

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