Original paper

Cite as: Kobylecka M, Płazińska MT, Chudziński W, Fronczewska-Wieniawska K, Mączewska J, Bajera A, Karlińska M, Królicki L: Comparison of scintigraphy and ultrasound imaging in patients with primary, secondary and tertiary hyperparathyroidism – own experience. J Ultrason 2017; 17: 17–22.

Submitted: 19.05.2016
Accepted: 23.09.2016
Published: 31.03.2017

Comparison of scintigraphy and ultrasound imaging in patients with primary, secondary and tertiary hyperparathyroidism – own experience

Małgorzata Kobylecka[1], Maria Teresa Płazińska[1], Witold Chudziński[2], Katarzyna Fronczewska-Wieniawska[1], Joanna Mączewska[1], Adam Bajera[1], Maria Karlińska[3], Leszek Królicki[1]

[1] Nuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland
[2] Department of General and Endocrinological Surgery, Medical University of Warsaw, Warsaw, Poland
[3] Department of Medical Informatics and Telemedicine, Medical University of Warsaw, Warsaw, Poland

Correspondence: Maria Teresa Płazińska MD, PhD, Nuclear Medicine Department, Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland, tel. +48 22 599 22 70, fax +48 25 99 11 70, e-mail: m.plazinska@wum.edu.pl

DOI: 10.15557/JoU.2017.0002

Key words
parathyroids, MIBI, parathyroid scintigraphy, hyperparathyroidism, ultrasound of the nec

Abstract

Background: The imaging techniques most commonly used in the diagnosis of hyperparathyroidisms are ultrasound and scintigraphy. The diagnostic algorithms vary, depending mainly on the population, and experience of physicians. **Aim:** Aim of the present research was to determine the usefulness of parathyroid scintigraphy and ultrasonography in patients diagnosed for hyperparathyroidism in own material. **Material and method:** In the present research, 96 operated patients with documented primary, secondary and tertiary hyperparathyroidism were retrospectively analyzed. All patients underwent a ^{99m}Tc hexakis-2-methoxyisobutylisonitrile scintigraphy of the neck with the use of subtraction and two-phase examinations. Ultrasonography of the neck was performed in all the patients in B mode 2D presentation. A total number of 172 parathyroid glands were analyzed. **Results:** The sensitivity and specificity of scintigraphy was 68% and 60%, respectively. The sensitivity of ultrasound was 49% and specificity 85%. Both techniques allowed visualization of 76 parathyroid glands. Ultrasound revealed 19 glands that were not visible in scintigraphy. Scintigraphy showed 76 parathyroid glands that were not visualized on ultrasound. Having combined the results of scintigraphy and ultrasound, the sensitivity of 76% and specificity of 50% were obtained. Considering the ability to locate the parathyroid glands in both techniques as a positive result, the sensitivity decreased to 37% and specificity rose to 95%. **Conclusions:** Scintigraphy showed greater sensitivity than ultrasound in the localization of enlarged parathyroid glands. Ultrasound, in turn, was characterized by a higher specificity. The combined use of scintigraphy and ultrasonography allowed to obtain the specificity of 95%. In the light of obtained results, scintigraphy and ultrasonography are complementary and should be used together.

Introduction

Despite the development of imaging techniques, controversy concerning how to determine the diagnostic algorithm in patients with hyperparathyroidism still remains. Due to their small size and varying location, normal parathyroid glands are not visible in any of the imaging techniques; it is possible to visualize parathyroids only when they are enlarged and/or hyperfunctioning.

The decision whether imaging will bring any benefit to the patients affects nearly every step of the diagnostic process: patient selection, type of imaging techniques to be used as well as interpretation of results[1–4]. In many cases, an imaging examination before the first surgery is not needed. Only in cases of hyperthyroidism recurrence or unsuccessful operations does the visualization of the parathyroid glands become necessary. However since in the recent years minimally invasive parathyroidectomy has become the treatment of choice, it is believed that the majority of surgeons prefer to have a localization study conducted before operation[5].

Diagnostic imaging techniques routinely used include ultrasound (US), scintigraphy (SC), computed tomography (CT) and magnetic resonance imaging (MRI). The most commonly used techniques are US and SC[6-8]. In the literature, the authors are unanimous in the opinion that the sensitivity and specificity of scintigraphy are superior to other imaging techniques. They also agree that ultrasonography is the most available. However, an algorithm for using different imaging methods as well as their sensitivity and specificity vary depending on the population of patients, experience of physicians and protocols used. The aim of the present research was to determine the usefulness of parathyroid scintigraphy and ultrasonography in patients diagnosed for hyperparathyroidism in own material.

Age (years)	48.8 (17–79); *SD* 15.07		
Female pts (%)	81/96 (84.4%)		
Primary hyperparathyroidism	76 (79.2%)		
Secondary hyperparathyroidism	15 (15.63%)		
Tertiary hyperparathyroidism	5 (5.21%)		
Persistent/recurrent hyperparathyroidism	26 (27.1%)		
Serum PTH (pg/ml)	718.7 (60.7–3000); *SD* 792.3		
Serum Ca (mmol/l)	3.06 (2.14–6.2); *SD* 0.55		
Serum PO4 (mg/dl)	1.26 (0.5–3.2); *SD* 0.75		
Nodular goiter	41	–	42.70%
Nephrolithiasis	22	–	22.90%
Osteporosis complicated with fracture	9	–	9.40%
Peptic ulcer disease	4	–	4.20%
Hashimoto disease	3	–	3.10%
Osteitis fibrosa	2	–	2.10%
Renal insufficiency treated with hemodialysis	15	–	15.60%
Cholelithiasis	1	–	1.04%
Renal transplant	5	–	5.20%

Tab. 1. *Clinical characteristics of the patients*

Material and method

The results of US and SC examinations in 96 operated patients with clinically and biochemically documented primary (70), secondary (15), tertiary (5) hyperparathyroidism and MEN1 syndrome (6) were retrospectively analyzed. Patients gave their informed consent to the study. Radioisotope studies were performed in the Department of Nuclear Medicine, SP CSK, Medical University in Warsaw. The diagnosis of hyperparathyroidism was determined based on serum calcium, phosphate and parathyroid hormone levels. The clinical characteristics are listed in the Tab. 1.

The patients were clinically evaluated, which included taking medical history, physical examination, laboratory tests, neck ultrasonography and scintigraphy of the neck and upper mediastinum.

Scintigraphy

All patients underwent a ^{99m}Tc hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) scintigraphy with the use of a double head VariCam (Elscint) gamma camera. Parallel hole, LEHR (low energy high resolution) collimators were used. Images were registered with a 128 × 128 matrix. A combined subtraction and two-phase acquisition protocol was used, with the initial part of the study being equivalent to the subtraction examination. Firstly, 60–74 MBq (1,6–2,0 mCi) of $Na^{99m}TcO_4$ was administered, and a thyroid image was obtained 10 minutes thereafter. Subsequently, 555÷740 MBq (15÷20 mCi) ^{99m}Tc-MIBI was injected intravenously. The image of the neck was obtained after 20 minutes. Subtraction was performed by subtracting thyroid images from the ^{99m}Tc-MIBI image. Further stages of the examination proceeded according to the standard two-phase study protocol. The ^{99m}Tc-MIBI image obtained 20 minutes after administration of a radiopharmaceutical was regarded as "early" two-phase examination. The "late" neck acquisition was performed 120 minutes after ^{99m}Tc-MIBI administration (Fig. 1). The detailed description of the study protocol and home-made computer program for analysis of parathyroid scintigraphy examinations were presented elsewhere[6].

Parathyroid scintigraphy was considered positive when the focus of tracer accumulation met the criteria of positive two-phase and/or subtraction study. Two-phase scintigraphy was considered positive when the focus of increased, abnormal accumulation of the radiopharmaceutical was found in the early image and its intensity increased in comparison to the surrounding tissues in the late image

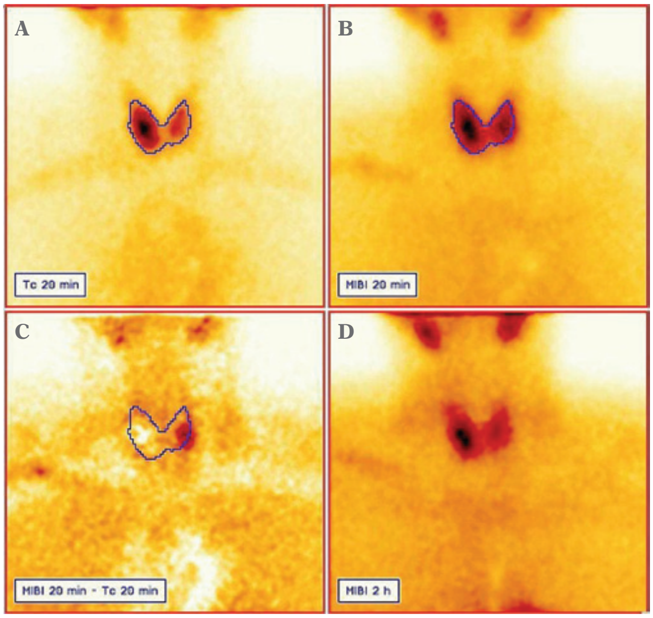

Fig. 1. *An example of combined subtraction and two phase scintigraphy. Positive result:* **A.** *Na^{99m}TcO$_4$ thyroid scan;* **B.** *^{99m}Tc-MIBI scan 20 min after tracer injection;* **C.** *Subtraction scan;* **D.** *^{99m}Tc-MIBI scan 120 min after tracer injection*

(Fig. 2). Subtraction scintigraphy was considered positive whenever the focus of tracer accumulation was found regardless of its intensity (Fig. 3).

Ultrasound

The ultrasound examination of the neck was performed with the use of Aloka 680 ultrasound scanner equipped with a linear probe of 7.5 MHz, in 2D B mode presentation. The location of the parathyroid glands, their size and echostructure were assessed. Cross-sectional and longitudinal images of the anterior region of the neck were obtained. The bilateral assessment was performed in the region from the common carotid artery bifurcation to the midline and down to the sternum. An attempt to visualize the superior part of the mediastinum was performed.

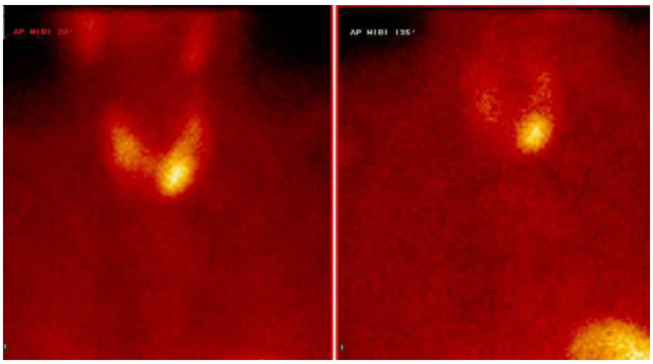

Fig. 2. *Two phase scintigraphy. Positive result. Extended retention of the radiopharmaceutical in the enlarged parathyroid*

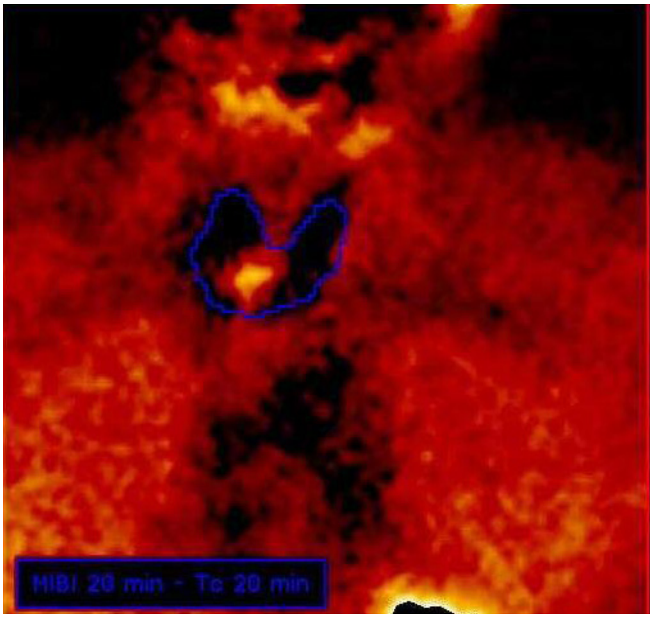

Fig. 3. *Subtraction scintigraphy. Positive result. A focus of increased radiopharmaceutical accumulation is visible as a result of subtraction*

Statistical analysis

The usefulness of scintigraphy and US in detecting abnormal parathyroid glands was expressed as: (1) sensitivity – the probability of obtaining a positive result in a patient with confirmed pathology, (2) specificity – the probability of obtaining a negative result in a healthy patient. As both diagnostic tests were performed in eachpatient, McNemar's test was used to compare the proportions of correct results. A p value of <0.05 was considered statistically significant. Calculations were carried out using the STATISTICA 10 package (StatSoft Inc., Tulsa, USA, 2011) and Confidence Interval Analysis (University of Southampton, Southampton, UK, 2009).

Results

A total of 172 parathyroids glands were analyzed. Scintigraphy was true positive in 104, false positive in 8, true negative in 12 and false negative in 48 cases. The sensitivity and specificity of scintigraphy was 68% and 60%, respectively. Ultrasound results were true positive in 75, false positive in 3, true negative in 17 and false negative in 77 cases. The sensitivity of ultrasound was 49% and specificity 85%. Differences between scintigraphy and ultrasonography were statistically significant (p = 0.00001) for all analyzed parameters.

Both techniques allowed visualization of 76 parathyroid glands. Ultrasound revealed additional 19 glands that were not visible in scintigraphy. However, 76 parathyroid glands that were not visualized on ultrasound were found in scintigraphy. Having combined the results of

Diagnostic method	Sensitivity	Specificity
US	27%[7]	65%[7]
CT	44÷63%[8] 13%[7]	39%[7]
MR	17%[7]	65%[7]
Scintigraphy	83%[8] 57%[7]	85%[7]

Tab. 2. *Comparison of sensitivity of various diagnostic methods in locating hyperfunctioning parathyroid gland*

scintigraphy and ultrasound, the sensitivity of 76% and specificity of 50% was obtained. Considering the ability to locate parathyroid glands in both techniques as a positive result, the sensitivity decreased to 37% and specificity rose to 95%.

Discussion

In the published literature, the results of SC are usually compared with the results of US, rarely with CT or MR (Tab. 2).

Differences in their sensitivity and specificity in the published literature result from a number of factors affecting the results of the examination: studied group, equipment used, technique of examination and experience of a physician evaluating the results. Compared with the literature, the sensitivity of US and SC in the current study was moderate, which in our opinion is related to the mixed group of patients, including not only primary but also a high number of secondary and tertiary hyperparathyroidism. By contrast with US, CT or MRI, radionuclide techniques reflect the function of the assessed glands, not their anatomical structure. Functional imaging is especially important in ectopic parathyroid glands which appear approx. in 6–16% of patients[9] and in cases of additional parathyroid glands (10 to 15%). Most commonly, the "errant" lower parathyroid gland is located in the thymus[9,10] and the upper gland behind the esophagus, in the upper mediastinum or within the thyroid gland parenchyma[10]. The intraoperative location of all abnormal parathyroid glands can then cause considerable difficulties and may lead to ineffective operation.

Finding abnormal parathyroid glands is especially important in patients with a history of parathyroid operations and recurrent hyperparathyroidism, which occurs in approximately 1–4% of cases[1]. The number of reoperated patients (first operation performed in other centers) in the analyzed group was 26. Changed anatomical conditions and presence of adhesions make it significantly harder to find the abnormal gland. These factors also increase the risk of recurrent laryngeal nerve injury.

Parathyroid scintigraphy is most commonly performed using MIBI (methoxyisobutylisonitrile radiopharmaceutical labeled with technetium-99m, which is a monovalent lipophilic cation, passively diffusing through the cell membrane. Coackley *et al*.[11] was the first to notice accidental accumulation of ^{99m}Tc-MIBI in the enlarged parathyroid glands. ^{99m}Tc-MIBI is nowadays a reference radiopharmaceutical in the diagnosis of hyperparathyroidism. However the uniform protocol of parathyroid scintigraphy is still not established.

Parathyroid scintigraphy with ^{99m}Tc-MIBI uses two main techniques: subtraction and two-phase scintigraphy.

Subtraction scintigraphy with the use of ^{99m}Tc-MIBI involves comparing the ^{99m}Tc-MIBI images with images obtained after administration of another radiopharmaceutical, which has affinity to the thyroid gland tissue, namely sodium iodide ($Na^{123}I$, $Na^{131}I$) or pertechnetate ($Na^{99m}TcO_4$).

The two-phase examination with ^{99m}Tc-MIBI was introduced into routine practice by Taillefer *et al*., 1992[12]. It is based on differences in the pharmacokinetics of the radiopharmaceutical within the thyroid and parathyroid gland: initially it accumulates in both the thyroid and enlarged parathyroid glands. As time passes, the distribution of the radiopharmaceutical changes: intense accumulation of the tracer in enlarged parathyroid glands is still observed (the phenomenon of prolonged retention), while the accumulation in the thyroid gland and muscles gradually decreases. To this day, it is the most widely used technique in the imaging of parathyroid glands.

Own observations and published literature show that the two-phase technique can lead to false negative results: some of the affected parathyroid glands are characterized by rapid leaching of ^{99m}Tc-MIBI[13,14]. False positive results, in turn, may be caused by thyroid tumors, which may have enhanced and prolonged retention of the radiopharmaceutical. This problem is of particular importance in areas of endemic goiter[8,15,16]. The presented results do not differ from those reported in the literature: Ishibashi *et al*.[17], in a group of 26 patients with primary and secondary hyperparathyroidism, compared the results of tetrofosmin scintigraphy, US and MRI. The reported sensitivity of scintigraphy of 77.3% was superior to other imaging techniques: sensitivity of US was 45.5% and 68.2% for MRI. Yao *et al*.[18], based on 37 patients with primary hyperparathyroidism, reported slightly lower sensitivity of scintigraphy (67%), similar results for US (44%) and only 36% for MRI.

In another study, Wakamatsu *et al*.[19] obtained 51% sensitivity for US as well as 43% and 56% for MRI and scintigraphy, respectively. On the basis of these reports, we can say that the sensitivity of scintigraphy is significantly higher than that of other imaging techniques.

Different results were obtained by Lemmi *et al*.[20] The sensitivity of US and CT in a group of 119 patients was 72% and 80%, respectively. Having combined the results of CT and ultrasound, the authors obtained a sensitivity of 87%.

On the other hand, Geatti *et al*.[8], in 43 patients, compared the scintigraphic ^{99m}Tc-MIBI two-phase and subtraction 201 Tl / ^{99m}Tc examination with US and CT. The highest obtained sensitivity was 95% for ^{99m}Tc-MIBI scintigraphy. The authors stressed better image quality, lower ^{99m}Tc-MIBI cost than thallium and its easier availability. They pointed out that thanks to these factors ^{99m}Tc-MIBI is a radiopharmaceutical of choice in the diagnosis of hyperparathyroidism.

In our material, the results of scintigraphy were comparable to those obtained by Yao *et al*.[18] and the results of ultrasound were similar to the results of Wakamatsu *et al*.[19]. The most important fact was that, as in the literature, SC had higher sensitivity than US.

Having compared the results of ultrasound and scintigraphy in our own material, we obtained the highest sensitivity in the group of patients who had a positive result of at least one test; the sensitivity was 76% and specificity of 50%.

When analyzing the published data, it can be stated that ultrasound diagnosis of parathyroid glands encounters two main limitations: firstly, abnormal parathyroid glands are not visualized in many cases; secondly, normal anatomical structures or thyroid nodules are misinterpreted as enlarged parathyroids. The problem of misinterpretation of the nature of visualized structures largely depends on the experience of the reading physician. In the case of an abnormal ultrasound image or unusual location, ultrasound-guided biopsy or the use of Doppler technique enable correct diagnosis[20,21].

In the analyzed material, the specificity of ultrasound was greater than that of scintigraphy. Lower specificity of scintigraphy was mostly affected by false positive results due to thyroid gland abnormalities in more than 60% of patients. Ultrasound examination along with scintigraphy determined the nature of the visualized lesions and influenced specificity in a positive manner: in a group of patients where both studies were positive, it amounted to 95%, while the sensitivity was only 37%. The results showed that ultrasound should be performed along with scintigraphy, in order to improve specificity.

Conclusions

Scintigraphy showed greater sensitivity than ultrasound in establishing the location of enlarged parathyroid glands; ultrasound was characterized by a higher specificity. The combined use of scintigraphy and ultrasonography allowed to obtain 95% specificity in the diagnosis of enlarged parathyroid glands. In the light of obtained results, scintigraphy and ultrasonography are complementary and should be used together.

Conflict of interest

Authors do not report any financial or personal links with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

A financial model is constructed by our own resources from hospital researchers fund.

References

1. Peeler BB, Martin WH, Sandler MP, Goldstein RE: Sestamibi parathyroid scanning and preoperative localization studies for patients with recurrent/persistent hyperparathyroidism or significant comorbid conditions: development of an optimal localization strategy. Am Surg 1997; 63: 37–46.
2. Lumachi F, Tregnaghi A, Zucchetta P, Marzola MC, Cecchin D, Marchesi P *et al*.: Technetium-99m sestamibi scintigraphy and helical CT together in patients with primary hyperparathyroidism: a prospective clinical study. Br J Radiol 2004; 77: 100–103.
3. Glotthardt M, Lohmann B, Hebr TM, Bauhofer A, Franzius C, Schipper ML *et al*.: Clinical value of parathyroid scintigraphy with technetium 99m metoxyisobutylisonitrile: discrepancies in clinical data and systematic metaanalysis of the literature. World J Surg 2004; 28: 100–107.
4. Profanter C, Wetscher GJ, Gabriel M, Sauper T, Rieger M, Kovacs P *et al*.: CT-MIBI image fusion: a new preoperative localization technique for primary, recurrent and persistent hyperparathyroidism. Surgery 2004; 135: 157–162.
5. Minisola S, Cipriani C, Diacinti D, Tartaglia F, Scillitani A, Pepe J *et al*.: Imaging of the parathyroid glands in primary hyperparathyroidism. Eur J Endocrinol 2016; 174: D1–D8.
6. Kobylecka M, Bajera A, Fronczewska-Wieniawska K, Mączewska J, Płazińska MT, Królicki L: Computer program for analysis of parathyroid scintigraphy examinations: combination of dual-tracer (subtraction) and double phase single-tracer washout techniques. Nucl Med Rev 2016; 19: 58–62.
7. De Feo ML, Colagrande S, Biagini C, Tonarelli A, Bisi G, Vaggelli L *et al*.: Parathyroid glands: combination of ^{99m}Tc-MIBI scintigraphy and US for demonstration of parathyroid glands and nodules. Radiology 2000; 214: 393–402.
8. Geatti O, Shapiro B, Orsolon PG, Proto G, Guerra UP, Antonucci F *et al*.: Localization of parathyroid enlargement: experience with technetium-99m methoxyisobutryloisonitrile and thallium201 scintigraphy, ultrasonography and computed tomography. Eur J Nucl Med 1994; 21: 17–22.
9. Hindié E, Zanotti-Fregonara P, Tabarin A, Rubello D, Morelec I, Wagner T *et al*.: The role of radionuclide imaging in the surgical management of primary hyperparathyroidism. J Nucl Med 2015; 56: 737–744.
10. Tołłoczko T: Surgical treatment in patients with MEN1 syndrom. Endokrynol Pol 2003; 54: 73–81.
11. Coackley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins REC: ^{99m}Tc sestamibi: a new agent for parathyroid imaging. Nucl Med Commun 1989; 10: 791–794.
12. Taillefer R, Boucher Y, Potvin C, Lambert R: Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium 99m-sestamibi (double phase study). J Nucl Med 1992; 33: 1801–1807.
13. Benard F, Lefebvre B, Beuvon F, Langlois MF, Bisson G: Rapid washout of technetium-99m-MIBI from a large parathyroid adenoma. J Nucl Med 1995; 36: 241–243.
14. Hindie E, Melliere D: Parathyroid imaging using simultaneous double-window recording of technetium 99m-sestamibi and iodine-123. J Nucl Med 1998; 39: 410–416.
15. Rubello D, Saladini G, Casara D: The role of scintigraphy with dual tracer and potassium perchlorate (^{99m}TcO4 & KClO4/ MIBI) in primary hyperparathyroidism. Minerva Endocrinol 2001; 26: 13–21.
16. Lemmi A, Baroni M, Corneli P, Galuppo C, Malaspina C, Filipponi P *et al*.: Echography and integrated imaging in the diagnosis of hyperparathyroidism. Radiologia Medica 1994; 88: 606–611.
17. Ishibashi M, Nishida H, Strauss HW, Kojima K, Fujito H, Watanabe J *et al*.: Localization of parathyroid glands using technetium-99m-tetrofosmin imaging. J Nucl Med 1997; 38: 706–711.
18. Yao M, Jamieson C, Blend R: Magnetic resonance imaging in preoperative localization of diseased parathyroid glands: a comparison with isotope scanning and ultrasonography. Can J Surg 1993; 36: 241–244.

19. Wakamatsu H, Noguchi S, Yamashita H, Yamashita H, Tamura S, Jinnouchi S *et al.*: Parathyroid scintigraphy with ^{99m}Tc-MIBI and 123I subtraction: a comparison with magnetic resonance imaging and ultrasonography. Nucl Med Commun 2003; 24: 755–762.
20. Wolf RJ, Cronan JJ, Monchik J: Color Doppler sonography: an adjunctive technique in assessment of parathyroid adenomas. J Ultrasound Med 1994; 13: 303–308.
21. Zhang JX, Li JC, Cai S: Ultrasonographic study on primary hyperparathyroidism: evaluation of B-mode and color Doppler ultrasonography in localization. Chin Med J 1994; 74: 598–601, 645.