Validity of dual tracer $^{99m}$Tc-tetrofosmin and $^{99m}$Tc-pertechnetate subtraction parathyroid scintigraphy in patients with primary and secondary hyperparathyroidism

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Abstract

Background/Aim. Primary hyperparathyroidism (pHPT) is an endocrine disease with the third highest incidence of all endocrine disorders after diabetes mellitus and hyperthyroidism. pHPT is typically caused by a solitary parathyroid adenoma, less frequently by multiple parathyroid gland disease (MGD) and rarely by parathyroid carcinoma. Secondary hyperparathyroidism (sHPT) is a common complication in patients with chronic renal failure. The aim of this study was to estimate sensitivity of dual tracer $^{99m}$Tc-tetrofosmin and $^{99m}$Tc-pertechnetate subtraction scintigraphy in detection of abnormal parathyroid glands in patients with pHPT and sHPT confirmed by histopathology.

Methods. In 46 patients, (77 abnormal parathyroid glands), 30 with pHPT and 16 with sHPT parathyroid scintigraphy was done preoperatively. All the patients had histopathological confirmation of diagnosis. Abnormal parathyroid glands weighted from 0.1 to 7 g. After injection dynamic scintigraphy during 25 minutes (one frame-one minute) using 555 MBq of $^{99m}$Tc-tetrofosmin, and three hours latter using 111 MBq of $^{99m}$Tc/pertechnetate was performed. $^{99m}$Tc-tetrofosmin dynamic study was followed by static scintigraphy of the neck and chest 30 minutes, 1, 2 and 3 hours after iv injection. Results. An abnormal scintigraphic finding was found in 44 of 46 patients with sensitivity of 96%. In pHPT sensitivity was 93% (28 of 30 patients, and 28 of 30 glands). In sHPT scintigraphy was abnormal in all the patients (sensitivity 100%). In the patients with sHPT scintigraphy detected 30 of 47 abnormal parathyroid glands (sensitivity 64%). An overall sensitivity of scintigraphy per gland, for pHPT and sHPT in detecting 58 of 77 abnormal parathyroid glands was 75%. Conclusion. An abnormal scintigraphic result per patient was found in 44 patients (sensitivity 96%) and 58 of 77 abnormal parathyroid glands were detected (sensitivity 75%). A high sensitivity of dual tracer subtraction $^{99m}$Tc-tetrofosmin/$^{99m}$Tc-pertechnetate parathyroid scintigraphy in detecting abnormal parathyroid glands in primary and secondary hyperparathyroidism was achieved.

Key words: parathyroid diseases; parathyroid hormones; hyperparathyroidism; radionuclide imaging; organoatechnetium compounds; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Primarni hiperparatiroidizam (pHPT) je endokrinološko oboljenje čija je incidenca na trećem mestu posle dijabetesa melitusa. Najčešće nastaje kao posledica solitarnog paratiroidnog adenoma, zatim zbog multijle bolesti paratiroidnih žležda te retko zbog paratiroidnog karcinoma. Sekundarni hiperparatiroidizam (sHPT) je česta komplikacija kod bolesnika sa kroničnom renalnom insuficijencijom. Cilj ovog rada bio je da odredi osetljivost suptrakcione scintigrafije paratiroidnih žležda $^{99m}$Tc-tetrofosminom i $^{99m}$Tc-pertechnetatom u detekciji patološki izmenjenih paratiroidnih žležda kod bolesnika sa pHPT i sHPT, dokazanim patohistološki.

Methode. Scintigrafiija paratiroidnih žležda urađena je preoperativno kod 46 bolesnika, (77 patološki izmenjenih i uvećanih paratiroidnih žležda), 30 sa primarnim i 16 sa sekundarnim hiperparatiroidizmom. Svi bolesnici imali su patohistološku potvrdu dijagnoze. Patološki izmenjene paratiroidne žleže težile su od 0,1 do 7 g. Posle iv injekcije 555 MBq $^{99m}$Tc-tetrofosmin i 111 MBq $^{99m}$Tc/pertechnetate bilo je primarnog i sekundarnog hiperparatiroidizma. Patološki izmenjene paratiroidne žleže kod bolesnika sa pHPT i sHPT, dokazanim patohistološki.

Rezultati. Patološki izmenjene paratiroidne žleže našene su scintigrafski kod 44 od 46 bolesnika, sa osetljivosti 96%. Kod bolesnika sa pHPT osetljivost scintigrafije bila je 93% (28 od 30 bolesnika, tj. 28 od 30 žležda). Kod bolesnika sa sHPT svi bolesnici imali su patološki scintigrafski nalaz (osetljivost 100%). Kod bolesnika sa sHPT scintigra-
fija je otkrila 30 od 47 patološki izmenjenih paratirojidijskih žlezda (osećljivost 64%). Ukupna osetljivost, izračunata po žledzi, za pHPT i sHPHT bila je 75% (otkrijeo 58 od 77 patološki izmenjenih paratirojidijskih žlezda). Zaključak. Patološki scintigrafski nalaz naden je kod 44 od 46 bolesnika (osećljivost 96%). Otkriveno je 58 od 77 patološki izmenjenih paratirojidijskih žlezda (osećljivost 75%). Dobijena je visoka osetljivost supstrukcione scintigrafije paratirojidijskih žlezda 99mTc-tetrofosminim i 99mTc-pertechnetatom u otkrivanju patološki izmenjenih i uvećanih paratirojidijskih žlezda kod bolesnika sa primarnim i sekundarnim hiperparatirozidmom.

Ključne reči: paratirojidijske žlezde, bolesti; paratirojidi hormoni; hiperparatirozidizam; scintigrafija; organotnecijumska jedinjenja; osetljivost i specifičnost.

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**Introduction**

Primary hyperparathyroidism (pHPT) is an endocrine disease with the third highest incidence of all endocrine disorders after diabetes mellitus and hyperthyroidism. Primary hyperparathyroidism is caused by secretion of excessive amounts of parathyroid hormone (PTH) by one or more enlarged diseased parathyroid gland(s). Two normal pairs of parathyroid glands are located in the neck posterior to the thyroid gland. pHPT is typically caused by a solitary parathyroid adenoma, less frequently (about 15% of cases) by multiple parathyroid gland disease (MGD) and rarely (about 1% of cases) by parathyroid carcinoma. Patients with MGD have either double adenomas or hyperplasia of three or all four parathyroid glands. Secondary hyperparathyroidism (sHPT) is a common complication in patients with chronic renal failure. Hypocalcemia, accumulation of phosphate and a decrease in the active form of vitamin D lead to increased secretion of PTH. When medical therapy fails, surgery becomes necessary. Successful parathyroidectomy depends on recognition and excision of all hyperfunctional parathyroid glands. Unguided bilateral exploration, dissecting all potential sites in the neck lead to remedy in 90–95% of patients. Two main reasons for surgery failure are ectopic glands (para-oesophageal, mediastinal, intrathyroid, in the sheat of the carotid artery, or undescended) and undetected MGD. The first neck exploration is optimal to intrathyroid, in the sheat of the carotid artery, or undescended) surgery failure are ectopic glands (retro-oesophageal, mediastinal, undescended))

When medical therapy fails, surgery becomes necessary. Unsuccessful parathyroidectomy depends on recognition and excision of all hyperfunctional parathyroid glands. Uncoupled bilateral exploration, dissecting all potential sites in the neck lead to remedy in 90–95% of patients. Two main reasons for surgery failure are ectopic glands (retro-oesophageal, mediastinal, intrathyroid, in the sheat of the carotid artery, or undescended) and undetected MGD. The first neck exploration is optimal to cure hyperparathyroidism. Reoperation is associated with the dramatic reduction in the success rate and an increase in surgical complications. Scintigraphic imaging is, therefore, mandatory before reoperation of persistent or recurrent hyperparathyroidism. Because of that, most surgeons would now appreciate having information of localization of abnormal parathyroid tissue. This would minimize the need for reoperation and shorten operation time by avoiding unnecessary surgery. The most common preoperative localization methods for hyperparathyroidism are scintigraphy and ultrasonography. High resolution ultrasound is sensitive enough for localization of abnormal parathyroid glands in the neck, but is unable for mediastinal ectopic enlarged parathyroid masses. Scintigraphy can visualize enlarged parathyroid glands in the neck and parathyroid glands with ectopic localization. The two normal pairs of parathyroid glands are located in the neck posterior to the thyroid gland. They are very small, weighing between 20 and 50 mg. 99mTc-sestamibi and 99mTc-tetrofosmin are intracellular tracers, and both go into thyroid and parathyroid tissue allowing visualization of enlarged parathyroid glands. Critical mass of parathyroid tissue for scintigraphic visualization is about 300 mg. Technetium-99m alone in the form of pertechnetate (99mTcO4-) and I-123-sodium iodide are specific tracers for thyroid tissue and they are in use as second tracer for subtraction technique of parathroid scintigraphy. Ectopic localization of parathyroid glands can be diagnosed by planar scintigraphy, SPECT and SPECT-CT scintigraphy techniques, magnetic resonance imaging (MRI) and computed tomography (CT).

The aim of this study was to estimate sensitivity of dual tracer 99mTc-tetrofosmin and 99mTc-pertechnetate subtraction scintigraphy, in detection of abnormal parathyroid glands in patients with primary and secondary hyperparathyroidism confirmed by histopathology.

**Methods**

Parathyroid scintigraphy was done preoperatively in 46 patients (77 abnormal parathyroid glands). There were 34 female and 12 male patients, 24 to 78 years old, mean age was 54 years. Thirty patients had primary and sixteen secondary hyperparathyroidism. The patients with pHPT had iPTH values from 65 to 837 pg/mL, mean value 253 pg/mL, and plasmatic calcium levels from 2.4 to 3.89 mmol/L, mean value 2.89 mmol/L. Twenty one patient with pHPT had values of serum anorganic phosphates, ranged from 0.35 to 1.1 mmol/L, mean value 0.76 mmol/L. The patients with sPTH had iPTH values from 518 to 2500 pg/mL, mean value 1547 pg/mL. Normal iPTH values were in the range from 10.0 to 72.0 pg/mL, for plasmatic calcium from 2.13 to 2.65 mmol/L and for anorganic phosphates from 0.81 to 1.53 mmol/L. All the patients had histopathological confirmation of the diagnosis. Abnormal parathyroid glands weighed from 0.1 to 7 g.

Scintigraphy was done using regular field-of-view gamma camera with a high-sensitivity parallel hole collimator centered at 140 keV with 20% window. After iv injection of 555 MBq of 99mTc-tetrofosmin, with a head of gamma camera under the head, neck and chest of a patient, dynamic scintigraphy during 25 minutes (one frame-one minute) was performed. Twenty one patient with pHPT had values of serum anorganic phosphates, ranged from 0.35 to 1.1 mmol/L, mean value 0.76 mmol/L. The patients with sPTH had iPTH values from 518 to 2500 pg/mL, mean value 1547 pg/mL. Normal iPTH values were in the range from 10.0 to 72.0 pg/mL, for plasmatic calcium from 2.13 to 2.65 mmol/L and for anorganic phosphates from 0.81 to 1.53 mmol/L. All the patients had histopathological confirmation of the diagnosis. Abnormal parathyroid glands weighed from 0.1 to 7 g.

Scintigraphic results were graded one to five: grade 1 - normal finding, grade 2 - probably normal finding, grade 3 - suspicious finding, grade 4 - probably abnormal finding and grades 5 - abnormal finding. Scintigraphic findings graded four and five were considered as positive. Sensitivity was calculated using decision matrix formula for sensitivity.

Results

An abnormal scintigraphic finding was found in 44 of 46 patients, with sensitivity per patient of 96%. One patient with pHPT had scintigraphic finding grade 2 and other one with pHPT scintigraphic finding grade 3. In the patient with scintigraphic finding grade 2, scintigraphic false negative finding was caused by a diffuse enlarged thyroid gland. Scintigraphy was false positive in the patient with scintigraphic finding grade 3, caused by thyroid colloid nodule, on the opposite side from enlarged parathyroid gland. From the remaining 28 patients with pHPT six patients had a scintigraphy finding grade 4, while 22 of them had scintigraphy finding grade 5. Primary hyperparathyroidism showed (Figures 1 and 2) scintigraphic sensitivity per gland of 93% (28

![Fig. 1 – Patient S.M, 65 years of age, Hyperparathyroidismus prim. susp, Osteoporosis sec, PTH-225 pg/mL, CaU-2.83 mmol/L, P-0.84 mmol/L, ALP-159 U/L, Ca and P in urine b.o. Scintigraphy showed enlarged left inferior parathyroid gland](image)

![Fig. 2 – Patient M. N, 46 years of age, Hyperparathyroidismus prim, Calculosis renis bill, CaU-2.91 mmol/L, P-0.72 mmol/L, PTH-267 pg/mL. US finding was hypoechogenic zone in right inferior pole of thyroid gland 10×7 mm in diameter: enlarged parathyroid gland of thyroid node. Scintigraphy showed enlarged right inferior parathyroid gland](image)
of 30 patients, i.e. 28 of 30 glands). All patients with the secondary hyperparathyroidism (Figure 3) had abnormal scintigraphic finding with sensitivity per patient of 100%, but sensitivity per gland, detecting 30 of 47 abnormal glands, was 64%. An overall sensitivity of scintigraphy for primary and secondary hyperparathyroidism per gland (detecting 58 of 77 abnormal parathyroid glands) was 75%.

**Discussion**

In the last decade improvements in sensitivity and specificity of diagnostic techniques for identifying parathyroid pathology in patients with primary and secondary hyperparathyroidism were made. This has increased the need for preoperative parathyroid imaging, because exact localization of abnormal parathyroid glands shortened operation time and allow minimally invasive parathyroid surgery 22, 26, 27.

More than twenty years ago Ferlin et al. 19, 20, 23 introduced double tracer thallium-201/technetium-99m (201Tl/99mTc) subtraction scintigraphy as a very sensitive method for localizing abnormal or aberrantly located parathyroid tissue. Since then parathyroid scintigraphy has been used for localizing enlarged parathyroid glands both in primary and secondary hyperparathyroidism. 99mTc-sestamibi and 99mTc-tetrofosmin were promoted as new radiofarmaceuticals first for myocardial perfusion imaging, about ten years later 13, 14. Because of their high and uniform sensitivity, sestamibi and tetrofosmin are the radionuclides of choice for parathyroid imaging. Earlier papers reported wide range of sensitivity (26–94%) but uniform specificity, more than 95% of 201Tl/99mTc double tracer subtraction scintigraphy 7, 13, 14. Scintigraphy with 99mTc-sestamibi and 99mTc-tetrofosmin reaches sensitivity of 97% 24, 25. Our results are similar reaching as high sensitivity as 96% per patient and 93% per gland, for pHPT, and 100% sensitivity per patient for sHPT. Causes of false negative findings are small weight, localization and kinetics of radionuclid uptake (cellularity and perfusion) of abnormal parathyroid glands, and large thyroid gland (mass > 35 g). Most frequent cause of false negative results is small gland weight. Enlarged hyperplastic parathyroid glands in sHPT have diffuse or nodular hyperplasia, and reach different weight and size in

Fig. 3 – Patient P. J, 44 years of age, Insuff. Ren. Chr, Haemodyalisis 6 years, PTH-1230 pg/mL. Scintigraphy showed Tc99m-TRF activity in projection of left upper half of thyroid gland and smaller amount of TRF activity below left inferior pole of thyroid gland, suggesting enlarged left superior and inferior parathyroid gland

Conclusion

An abnormal scintigraphic result per patient was found in 44 patients (sensitivity 96%) with 58 abnormal glands detected (sensitivity 75%). In this study a high sensitivity of dual tracer subtraction 99mTc-tetrofosmin/99mTc-pertechnetate parathyroid scintigraphy in detecting abnormal parathyroid glands in primary and secondary hyperparathyroidism was achieved.

REFERENCES
