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The role of ^{99m}Tc-MIBI SPECT/low dose CT with 3D subtraction in patients with secondary hyperparathyroidism due to chronic kidney disease

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Objective. The aim of the present work was to assess the incidence of parathyroid glands hyperplasia or adenoma in patients with various stages of chronic renal insufficiency using ^{99m}Tc-methoxyisobutylisonitrile (MIBI) SPECT and 3D subtraction technique with ^{99m}Tc-pertechnetate (Tc).

Subjects and methods. Sixty one patients underwent hybrid SPECT with low-dose CT of the parathyroid glands and thyroid SPECT scintigraphy. Thirty six patients were with chronic kidney disease (CKD) without renal failure (RF) and 25 patients underwent peritoneal dialysis or hemodialysis. In each patient, two SPECT studies were performed - an early and a late one with low dose of CT with MIBI injection. Additional SPECT was performed on another day with Tc. SPECT studies were evaluated visually using volume rendering method and semi-quantitatively by 3D subtraction of Tc SPECT from early MIBI SPECT.

Results. From all 61 patients, 40/61 (66%) findings were positive, 7/61 (12%) inconclusive, and 14/61 (23%) negative. Solitary lesions were detected in 22 patients. More than one lesion was found in 18 patients.

Conclusion. The incidence of secondary hyperparathyroidism was detected in 40/61 patients (66%) with chronic kidney disease using scintigraphy and 16 patients (40%) from them underwent surgery. MIBI SPECT/low dose CT with 3D dual - tracer subtraction (MIBI-Tc) method is an effective tool for preoperative detection of the parathyroid glands hyperplasia or adenoma.

Key Words: hyperparathyroidism, chronic renal insufficiency, parathyroid ^{99m}Tc-MIBI SPECT/low dose CT, 3D dual -tracer subtraction analysis

Secondary hyperparathyroidism is one of the most common and serious complications due to excessive secretion of parathyroid hormone (PTH) by the parathyroid glands in patients with CKD. The main factors responsible for excessive synthesis and secretion of PTH include phosphate retention, leading to hypocalcaemia, which in turn stimulates PTH secretion and calcitrion deficiency resulting from a decreased kidney function. Sustained hypersecretion of PTH is associated with an increase in the parathyroid gland size, initially leading to diffuse parathyroid hyperplasia (Rubello et al. 2007; Komata and Fukagawa 2009).

Maintaining relatively normal concentrations of calcium and phosphorus in the serum by hemodialysis and vitamin D therapy reduces the incidence of bone changes. Most patients with secondary hyperparathyroidism can be treated medically. The need for surgical treatment of secondary hyperparathyroidism increases

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with chronic kidney disease (CKD) duration and the number of years the patient is dialyzed. Calcium-phosphate metabolism failure and an increased PTH serum level ≥ 88 pmol/l (National Kidney Foundation, NKF 2003) indicate the need for surgery. The determination of parathyroid glands localization is essential in selective surgical procedures.

Normal parathyroid glands measure approximately 6 mm in length, 3-4 mm in transverse diameter, and 1-2 mm in anteroposterior diameter. They weigh 29.5 mg ± 17.8 (mean ± SD) (NKF 2003; Vaz and Griffiths 2011). Normally, there are two superior and two inferior parathyroid glands located within the visceral space of the neck, posterior to the thyroid gland, near the tracheoesophageal groove. They may be either inside or outside the thyroid capsule. Ectopic inferior parathyroid glands may be located in the neck, inferior to the lower pole of thyroid lobe, either in the thyrothymic ligament or associated with the cervical portion of the thymus (Vaz and Griffiths 2011).

^{99m}Tc-methoxyisobutylisonitrile (MIBI) can be used as the sole imaging agent in a parathyroid scan. It relies on the fact that this radiotracer washes out of normal thyroid tissue faster than from abnormal parathyroid adenomas and hyperplasia (Rubello et al. 2007; Taieb et al. 2012). This difference increases with the time, so delayed images are usually compared to the early ones. Nevertheless, the washout of the radiotracer from the hyperplastic parathyroid gland can be as fast as from thyroid gland and that is why it is need to perform a second study with Tc and subtraction MIBI-Tc method as well. Combination of washout technique and 3D subtraction technique, both on the basis of SPECT studies, results in better sensitivity of the localization of the hyperproducing parathyroid glands.

Material and Methods

Sixty one patients (34 males and 27 females) aged 23-86 (mean 55) years underwent MIBI hybrid SPECT with low-dose CT of the parathyroid glands and Tc SPECT of the thyroid, 12 of them were examined repeatedly. All patients had high levels of iPTH. In our patient group, 36 patients (pts.). were with CKD without RF and 25 pts. underwent peritoneal dialysis or hemodialysis.

In CKD group of patients, 7 pts. were with vascular nephrosclerosis, 6 pts. with diabetic nephropathy, 6 pts. with tubulointersticial nephropathy, 4 pts. after genitourinary system tumors surgery, 3 pts. with glomerulonephritis, 2 pts. with Wegener granulomatosis, congenital anomalies, polycystic kidneys and lupus erythematosus, 1 patient with amyloidosis and 1 patient with lithiasis. In these patients, different stages of CKD were present: serum creatinine values varied from 90 to 1094 μmol/l, mean 302 μmol/l.

In the group of the dialysed patients, there were 10 pts. with glomerulonephritis, 6 pts. with tubulointersticial nephropathy, 5 pts. with vascular nephrosclerosis and 1 patient with Alport syndrome, chronic hydronephrosis, reflux nephropathy, and nephrocalcinosis. Only 5 pts. in each group had high levels of serum calcium, the others had normal values.

In each patient, two SPECT studies were performed - early (5-10 min) and late (2-2.5 h) with low dose CT after 700 MBq /average) MIBI injection (Fig. 1A, B). Additional SPECT was performed on another day after 200 MBq (average) Tc injections. The data were recorded with double head gamma camera Infinia-Hawkeye and reconstructed with Xeleris workstation (GE) using standard acquisition and reconstruction protocols. Digital SPECT data were acquired in 120 projections with 3^{o} angular step in a 128 x128 matrix at 20 s per view using a low energy, high-resolution parallel hole collimator with a broad field of view of the neck and mediastinum extending from the parotid glands to the diaphragm. The low dose CT parameters included a current of 2.5 mA, a voltage of 140 kV and 10 mm slides reconstructed in 256 x 256 matrixes. The CT rotated at 2.6 rotations per minute. The evaluation of the late (or early) MIBI SPECT/CT determined localization and anatomical details on ectopic foci (Fig. 1C).

SPECT images were evaluated visually (Fig. 2A, B) using volume rendering method and semi-quantitatively by 3D subtraction of early MIBI minus Tc SPECT data. Having both as SPECT studies, we can compare tomographic data by 3D (voxel by voxel) subtraction analysis. It requires very precise and objective registration of the SPECT images and also proper normalization. For registration purposes, the images have to cover a region from the top of the salivary glands to the bottom of the thyroid gland, and the head has to be oriented equally in regard to the chest in both images. The process is semi-automatic, using a number of user-defined normalization parameters, which depend on the thyroid shape, size, and overall activity trapped in the gland. There are 1) activity mask with user-defined activity threshold to separate background, 2) spherical geometry mask with user-defined center and radius to separate salivary glands and other undesirable objects. After the registration and normalization, the images are subtracted.

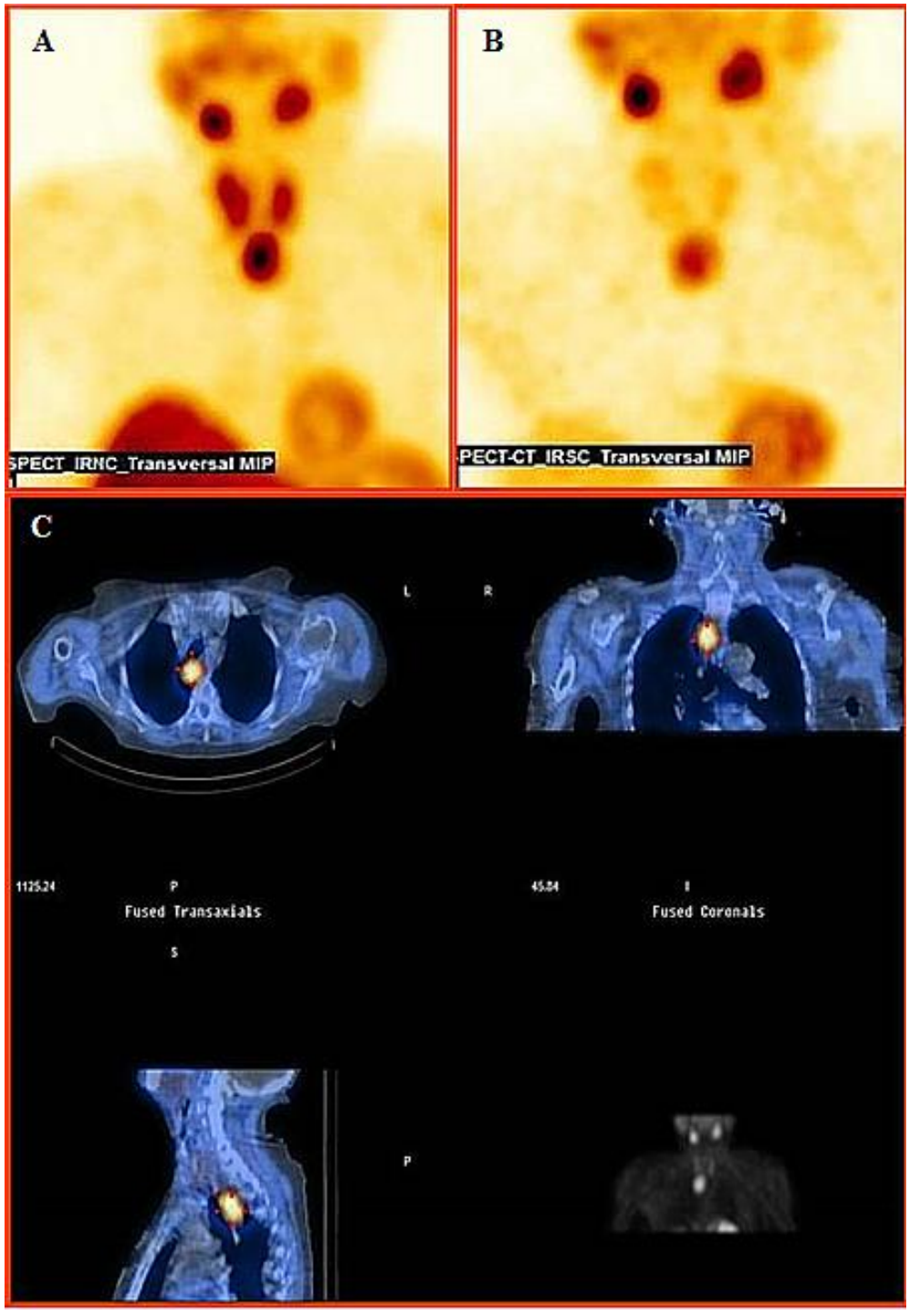

Figure 1. Typical finding of retrotracheal localization of parathyroid gland adenoma in 70 year old woman with tertiary hyperparathyroidism: A) early ^{99m}Tc-MIBI SPECT; B) late ^{99m}Tc-MIBI SPECT; C) evaluation of the late ^{99m}Tc-MIBI SPECT/CT with accurate imaging of retrotracheal localization of the parathyroid gland.

The suspicious foci consist of a small group of voxels which are visible in the contrast image. 3D dual tracer subtraction was essential in many cases of our group of patients (Fig. 2C).

Results

1) Total: 40/61 (66%) positive, 7/61 (12%) inconclusive and 14/61 (23.9%) negative findings were detected.

2) Solitary lesions (parathyroid hyperplasia or adenoma) were detected in 22 patients.

3) More than one lesion was found in 18 patients.

4) From 40 patients with positive findings, 16 underwent surgery (5 patients with CKD and 11 patients with RF) Table 1.

One patient died. Several patients refused surgery or could not be operated due to serious complications. These non operable patients were usually treated medically, most often with Cinacalceti hydrochloridum (Mimpara) as a tool for symptomatic therapy in patients with CKD.

Histological findings of the operated patients confirmed parathyroid glands hyperplasia in 7 patients as the secondary hyperparathyroidism; 3 patients with SPECT a solitary lesion had the histological signs of adenoma.

In 2 patients with scintigraphic multifocal lesions and normal calcium values adenoma was found as well.

Two patients with multifocal lesions and high levels of calcium were confirmed as the tertiary hyperparathyroidism.

Two patients, with calcium value at the upper limit and the histological signs of adenoma, were confirmed as the tertiary hyperparathyroidism as well.

Discussion

Secondary hyperparathyroidism is the result of an extraparathyroidal disorder, causing hypocalcemia, which subsequently becomes the stimulus for oversecretion of the hormone from all parathyroid glands present, resulting in parathyroid hyperplasia. In patients with renal failure, PTH secretion is stimulated by hypocalcemia, which results from low concentrations of 1,25-dihydroxy-vitamin D caused by decreased renal production and hyperphosphathemia. Prolonged hypocalcemia and hyperphosphathemia may evolve into a state of autonomous PTH secretion and hypercalcemia referred to as tertiary hyperparathyroidism (Eslamy and Ziessman 2008; Thomas et al. 2009). The parathyroid glands produce PTH, which is a key molecule important for maintaining calcium, phosphate and vitamin D homeostasis, and ultimately bone health. Many patients who acquire the CKD diagnosis often have had chronic exposure to reductions in vitamin D and serum calcium and elevations in PTH and phosphorus, and may manifest significant skeletal or cardiovascular sequels (Joy et al. 2007). The continuous stimulus to produce and to secrete PTH results in parathyroid hyperplasia.

Parathyroid glands can be imaged with multiple modalities, including ultrasonography, CT, MRI, scintigraphy and methods using intraoperative gamma probe (O´Doherty and Kettle 2003; Garcia-Talavera et al. 2010).

Ultrasound is a widely available technique with the advantage of no radiation, but it is operator-dependent and is not able to evaluate ectopic mediastinal foci (Rubello et al. 2003; Taylor et al. 2006). CT is a good tool especially in confirming mediastinal ectopia, but it is neither sensitive nor specific for juxtathyroidal or thyroidal parathyroid tumors, and requires iodinated contrast. MRI is more expensive than nuclear scanning and is often used if the nuclear study is equivocal. Whereas the sensitivity of MRI is similar to MIBI scanning, the specificity is lower (Taylor et al. 2006). Scintigraphy is considered to be a very useful technique for the detection of parathyroid hyperplasia or adenoma in many articles (Billotey et al. 1996; O´Doherty and Kettle 2003; Rubello et al. 2003; Rubello et al. 2006, 2007; Taylor et al. 2006; Gasparri et al. 2009). The optimal methodology for parathyroid scintigraphy was not clear from a review of medical literature (Lavely et al. 2007).

Nuclear medicine examination is very often provided with MIBI, which consists of lipophilic cationic molecules. After intravenous injection, the molecules are distributed by means of blood flow in the body cross the cell membranes by passive diffusion, and become concentrated intracellularly in the region of the mitochondria (Eslamy and Ziessman 2008). MIBI is accumulated by thyroid and parathyroid tissue in proportion to blood flow after intravenous application, though the activity in normal parathyroid glands is too low to be seen on an image. Dual-tracer and single-tracer parathyroid scintigraphy investigations were discussed as the various modalities of image acquisition (Rubello et al. 2007; Neumann et al. 2008). The kinetics of MIBI could be different in the thyroid and parathyroid tissues. The uptake of MIBI remained constant (possibly

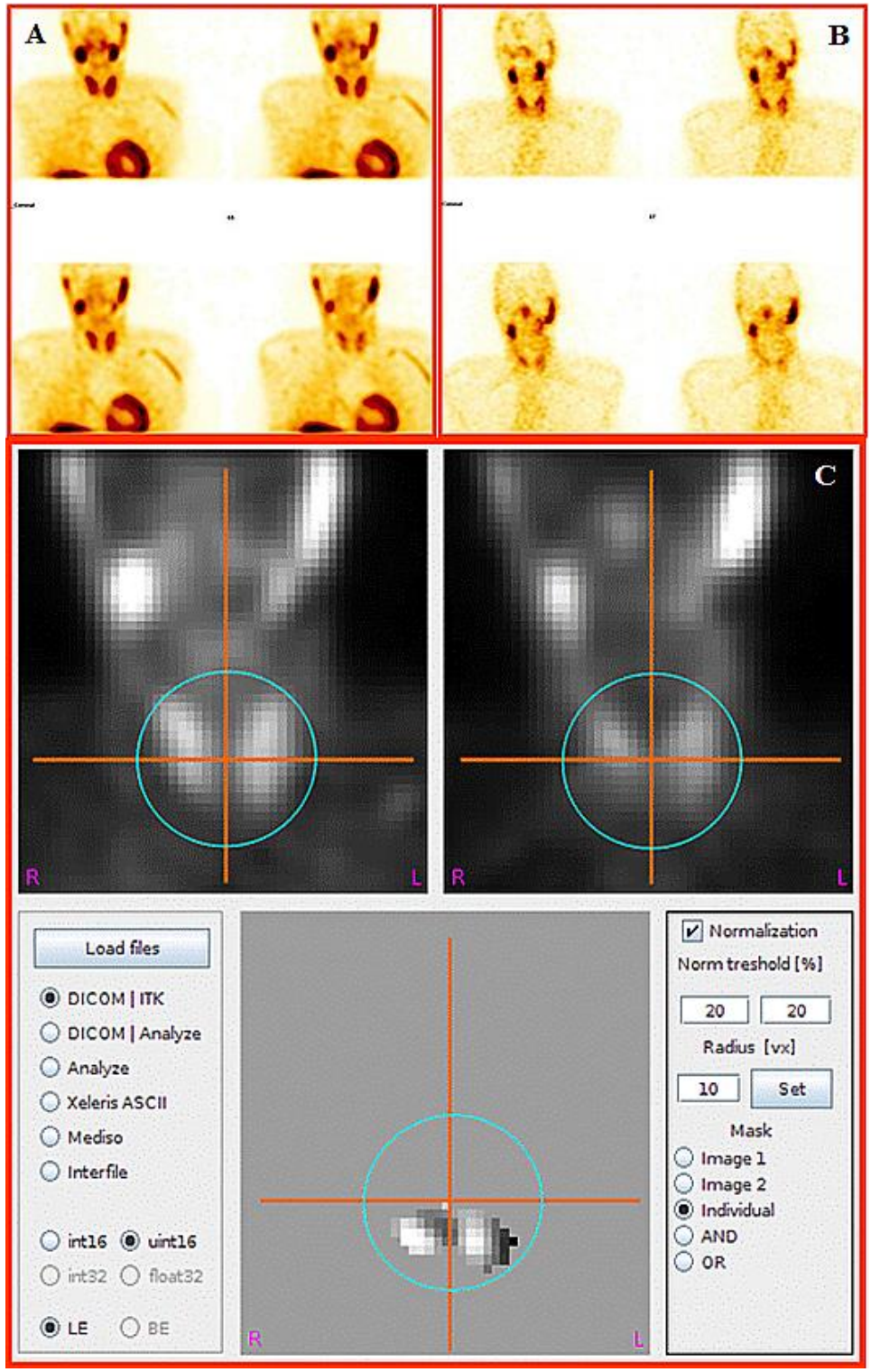

Fig. 2. A) Coronal slide of ^{99m}Tc-MIBI SPECT in a dialyzed 41 year old man with positive finding of hyperplasia of the left and right lower parathyroid glands. B) Coronal slide of ^{99m}Tc- pertechnetate SPECT, where the dual tracer subtraction is essential. C) 3D dual tracer subtraction: After registration and normalization, the images are subtracted (^{99m}Tc-MIBI minus ^{99m}Tc-pertechnetate). A suspicious finding consists of a small group of voxels, which is visible in the contrast image as a residue of ^{99m}Tc-MIBI and records a difference in an order of tens or hundreds of percent.

Table 1

Therapy of positive patients

N	Surgery	Medicament treatment	Total
Solitary findings	7	15	22
Multifocal findings	9	9	18
Total	16	24	40

due to mitochondrial binding or reduced PgP expression) whereas there was washout from the thyroid. This feature is the mainstay of the dual-phase technique. But the washout rate from the thyroid and hyperplastic parathyroid glands can be similar and then parathyroid hyperplasia is missed on the double-phase ^{99m}Tc-MIBI scan (Siegel et al. 2007; Gonzales et al. 2008). Based on our similar experiences with this MIBI phenomenon, early ^{99m}Tc-MIBI SPECT started cca 5 minutes after i.v. ^{99m}Tc-MIBI application in order not to miss parathyroid hyperfunctioning glands with rapid washout.

Tc is trapped but not organified by functioning thyroid tissue and is not taken up by parathyroid glands. Thus subtraction MIBI minus Tc is able to distinguish a parathyroid adenoma/hyperplasia as a difference. In normal cases without adenoma/hyperplasia of the parathyroid the result of subtraction is zero. Moreover, the thyroid scan can be helpful in differentiating a thyroid nodule from a parathyroid glands hyperplasia (Siegel et al. 2007).

The superiority of subtraction technique is especially true regarding detection of parathyroid hyperplasia and diagnosis of multiple parathyroid gland disease (Taieb et al. 2012).

In our study, there was used the method for 3D (voxel) subtraction technique using two SPECT images (^{99m}Tc-MIBI and ^{99m} Tc-pertechnetate), which should represent an alternative to dual-phase ^{99m}Tc-MIBI imaging. Dual-phase ^{99m}Tc-MIBI imaging is unable to detect pathological parathyroid glands with fast washout.

Subtraction 3D scanning of the ^{99m}Tc-MIBI and ^{99m}Tc-pertechnetate has been applied successfully in all our patients with hyperparathyroidism. In our opinion, this 3D analysis is very helpful in the detection of several lesions of the parathyroid glands hyperplasia in loco typico and is useful in patients with thyroid pathology as well. In our experience, 3D subtraction method is very useful in the detection of parathyroid hyperplasia in the neck localization.

^{99m}Tc-MIBI imaging with low dose CT is a simple and reliable modality for parathyroid glands localization. It is the only technique that combines functional information and extensive anatomic coverage, allowing evaluation for hyperplasia or adenomas in the neck and mediastinum. These imaging modalities identified the relation of the mediastinal parathyroid adenomas to the trachea, esophagus, thymus, spine and sternum (Krausz et al. 2006; Akram et al. 2009). The use of volume rendering of parathyroid SPECT images is helpful for good visualization. Combining nuclear imaging with low dose CT gives the highest accuracy. Hybrid SPECT/low dose CT instruments should be most helpful in this setting (Fig. 1C) and play a major role in obtaining anatomical details on ectopic foci, which are very important for surgery and can optimize the surgical procedure (Gayed et al. 2005; Krausz et al. 2006; Lavely et al. 2007; Eslamy and Ziessman 2008; Harris et al. 2008; Neumann et al. 2008; Akram et al. 2009; Wimmer et al. 2010; Taieb et al. 2012). Surgery was planned based on the SPECT / CT data in our patients, which excluded an ectopic focus and determined the most enlarged parathyroid glands in typical localization. The current trend is toward minimally invasive surgery to select patients with hyperparathyroidism for unilateral or focused surgery instead of the conventional bilateral neck exploration. The development of minimally invasive surgery and its application to parathyroidectomy has reduced morbidity, hospital stay and postoperative complications (Rubello et al. 2003; Rubello et al. 2007).

Unlike the diagnosis of primary hyperparathyroidism, the diagnosis and treatment of the secondary or tertiary hyperparathyroidism in patients with kidney failure is much more complicated. Also the verification of the diagnosis is not always easy to achieve. Only 16 patients were operated on in our study. Many patients could not be operated on due to either preparing for a kidney transplant or other serious complications of the primary or secondary disease, several patients refused surgery. In our group of the operated patients, tertiary hyperparathyroidism in 5 cases, secondary hyperparathyroidism in 7 patients were confirmed. Histological signs of adenoma were found in 5 patients. In cases of adenoma findings, there must also be considered the possibility that the patients had untreated primary hyperparathyroidism, which led to chronic renal failure. In some cases, even an experienced pathologist has difficulty in differentiating the parathyroid adenoma from hyperplasia. In our group of patients, there were 2 patients with scintigraphic multifocal lesions, and

normal calcium values, in whom the adenoma was histologically confirmed.

The success of targeted parathyroid surgery depends not only on an experienced surgeon, but also on a sensitive and accurate imaging technique. The two accepted surgical procedures for the management of secondary hyperparathyroidism are subtotal parathyreoidectomy and total parathyroidectomy with parathyroid autotransplantation. The surgeon should make an exhaustive effort to locate all parathyroid glands, knowing that in 15% of patients a fifth or even a sixth gland may be hidden in an ectopic localization.

The role of scintigraphic imaging before surgery in patients with secondary HPT is discussed in literature (Taieb et al. 2012). However, we believe, that our modification of ^{99m}Tc-MIBI scintigraphy with late ^{99m}Tc-MIBI SPECT/CT and especially 3D subtraction of ^{99m}Tc-MIBI - ^{99m}Tc-pertechnetate can be considered another option for more precise determination of parathyroid hyperplasia lesions and thus choosing the most appropriate procedure for the surgery.

Seven patients from our study had inconclusive finding. A patient follow-up and monitoring is essential, not only in patients with equivocal finding, but in all patients, because in secondary hyperparathyroidism the remaining additional glands can lead to the persistence of hyperparathyroidism. Twenty to thirty precent of patients develop persistent or recurrent parathyroid disease (Papthanassiou et al. 2008; Hindie et al. 2010; Wimmer et al. 2010). In our group, there were 3 patients with recurrent hyperparathyroidism.

The incidence of the parathyroid multiglandular disease prevailed in dialyzed patients, which is related to the severity and duration of chronic renal process. In addition to surgery, the arsenal of medical treatment of secondary hyperparathyroidism includes diet, calcium-containing and calcium-free intestinal phosphate binders, native and active vitamin D analogues and calcimimetics. In our study, there were a few positive patients, who have not undergone surgery and took cinacalcet. Reductions in parathyroid hormone levels are accompanied by significant reductions in serum calcium, serum phosphorus, and Ca x P products (Lindberg and Calcimimetics 2005; Joy et al. 2007; Ichii et al. 2010). Monitoring of calcium, phosphorus, PTH serum levels were performed in all our patients regularly. If the biochemical parameters of PTH or Ca increased, the patients were indicated for a repeated scintigraphic examination.

Conclusion

The localization of hyperplastic parathyroid gland in secondary hyperparathyroidism was detected in 40/61 patients (66%) with chronic kidney disease using scintigraphy and 16 patients (40%) from them underwent surgery. Our study confirmed the fact that the incidence of the parathyroid glands hyperplasia depends on the chronic renal disease duration and pointed to a wide variability in their size and localization.

In our opinion, SPECT only technique with MIBI SPECT/low dose CT and especially 3D dual-tracer subtraction analysis is an effective method for preoperative detection of the parathyroid glands hyperplasia or adenoma. This method helps to avoid an extensive surgery and supports the minimally invasive surgery approach especially in case of ectopic parathyroid adenomas.

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