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Original

The diagnostic value of dual-phase SPECT/CT scintigraphy based on transport kinetics of ^{99m}Tc-sestamibi confirmed with histopathological findings in patients with secondary hyperparathyroidism — practical consideration

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Abstract

BACKGROUND: Dual phase ^{99m}Tc-sestamibi SPECT/CT preoperative parathyroid scintigraphy (PPS) is seldom discussed in terms of the transport kinetics of the tracer.

Objectives: To assess the relationship between the characteristic type of tracer transport in particular PPS and histopathological findings in patients with secondary hyperparathyroidism (sHPT).

MATERIAL AND METHODS: The study comprised 27 patients (13 females and 14 males) with sHPT. Based on tracer accumulation in early phase (EP) and delayed phase (DP), the following types of accumulation for PPS(+) lesions were identified: EP(–)/DP(+) (type I), EP(+)/DP(+) (type II), EP(+)/DP(–) (type III). EP(–)/DP(–) (type IV) lesions constituted PPS(–) group invisible in SPECT/CT. Overall, 69 lesions 59 PPS(+) and 10 PPS(–) were evaluated histopathologically.

RESULTS: Among SPECT/CT PPS(+), types I, II and III occurred in 9 (15%), 49 (83%), and 1 (2%) lesions, respectively. The frequency of histopathological diagnosis of normal and abnormal (APG — adenoma or hyperplasia) parathyroid gland, as well as non-parathyroid (thyroid, lymph nodes, or fat) lesions differed significantly between type I, II, and III lesions ($p = 0.036$). APG histopathological diagnosis was significantly more frequent in lesions with type II uptake than in lesions with type I uptake (76% vs. 33%, $p = 0.0197$). Type II lesions had significantly higher odds for histopathological diagnosis of APG or NPG than type IV, PPS(–) lesions [odds ratio = 13.1 (95% CI: 2.75 to 63.27)].

CONCLUSIONS: For SHP patients evaluated with SPECT/CT PPS accumulation type I is a weak premise for surgeon to find parathyroid pathology. Only persistent ^{99m}Tc-sestamibi accumulation in both phases - equivocal with accumulation type II — effectively differentiates parathyroid and non-parathyroid lesions as well as indicates with high probability the presence of adenoma or hyperplasia. Type III consistent with washout pattern is rare in sHPT.

KEY words: secondary hyperparathyroidism; single photon emission computed tomography; technetium-99m sestamibi; parathyroid hormone; parathyroid adenoma; hyperplasia

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Introduction

Secondary hyperparathyroidism (sHPT) is usually caused by chronic kidney disease in response to hypocalcaemia, which leads to diffused or nodular hyperplasia of the parathyroid glands. Even after successful renal replacement therapy, this condition can be difficult to control using conservative treatments, and hence require parathyroid surgery [1–3]. If surgical intervention is not performed in the optimal time, some patients can develop autonomic adenoma with a constant elevation of PTH [4, 5]. Among various preoperative imaging techniques, single-photon emission computed tomography (SPECT) is an accurate method used for the localization of abnormal parathyroid gland method. Recently, new hybrid imaging using SPECT in combination with computed tomography (CT) has improved precision in the morphological and metabolic assessment of focal lesions [6].

^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-sestamibi) SPECT/CT preoperative parathyroid scintigraphy (PPS) can be performed as dual-phase single-tracer scintigraphy (washout method). There are two patterns of washout from the parathyroid glands: delayed (parathyroid gland retention of radiopharmaceutical on delayed images, usually accompanied by normal washout from the thyroid) and early (minimal or no retention of the radiotracer in the parathyroid gland on delayed-phase images). It was shown that the metabolic activity of the thyroid tissue diminishes with time while in the parathyroid tissue is more protracted; hence, early phase (EP) in SPECT/CT refers to the thyroid washout and the delayed phase (DP) to the parathyroid washout [7, 8]. Accumulation of ^{99m}Tc-sestamibi may be visible either in one phase only or both phases, thus leading to three different types of trace patterns [9].

The purpose of this study was to evaluate the relationship between the transport kinetics of ^{99m}Tc-sestamibi in SPECT/CT PPS and histopathological findings in patients with sHPT who underwent parathyroid surgery.

Material and methods

We included 78 patients with sHPT (30 females, 48 males; mean age of 49.9 years, range: 22–86 years). Patients were examined with planar and SPECT/CT PPS (GE INFINIA Hawkeye 4 with a low-energy high-resolution collimator and 2.0 zoom) following intravenous administration of ^{99m} Tc-sestamibi 762 ± 60.7 MBq (range: 600–850) with washout technique (dual-phase, single-tracer), in accordance with EANM guidelines [8]. The SPECT/CT study in EP was started following thorax planar acquisition (but not later than 20 min after administration of the tracer), and DP was performed 127 ± 28 min after tracer administration.

Pathological lesions on SPECT/CT were observed in 73 patients, and negative results in 5 patients. Among them, 27 patients (14 males and 13 females; mean age 46.3 years, range: 22–77 years) with abnormal lesions seen in the SPECT/CT study and inadequately controlled sHPT despite standard medical therapy were qualified for parathyroid surgery. PTH plasma concentration exceeding 600 pg/ml was an eligibility criterion for surgery. Among 26 patients with renal sHPT, 25 received kidney replacement therapy. Coeliac disease was diagnosed in one patient with sHPT. Two patients required second parathyroid surgery 4 and 19 months after the first operation.

Sonography of the neck was performed parallel to the scintigraphy at the same department in all cases, but results of the study had only a supportive function in terms of the results of the study [10]. Measurements to estimate accurately their volume were performed in 18.8% of all histopathologically assessed lesions.

We defined a positive result in early and delayed SPECT/CT as the presence of identifiable focus of increased ^{99m}Tc-sestamibi accumulation in the vicinity of the thyroid gland, or localized outside of the thyroid gland in the neck or mediastinum.

The SPECT/CT method of PPS allowed positioning the anatomic localization of metabolically active lesions in three-dimensional projections. Separate sets of fusion images were delivered to the surgeon to facilitate surgical treatment planning. Removed tissue specimen were secured and, after recording their location, transferred to the pathology lab for histopathological examination.

The specific histopathological diagnoses were correlated with the type of ^{99m}Tc-sestamibi uptake in the lesions, serum PTH, phosphate, total, and ionized calcium.

In surgical centres, PTH measurements were performed postoperatively. Direct, postoperative PTH assays were performed in 22 patients.

SPECT/CT results were considered true positive (TP) if a lesion was SPECT/CT PPS(+) and diagnosed as an abnormal parathyroid gland (APG — parathyroid adenoma and parathyroid hyperplasia) or normal parathyroid gland (NPG) on histopathological diagnosis; false positive (FP) if a lesion was SPECT/CT PPS(+) but not parathyroid lesions (lymph nodes, fat, thyroid tissue) (Non-PL) on histopathological diagnosis, true negative (TN) was characterized as SPECT/CT PPS(–) and confirmed as not of parathyroid origin on histopathological diagnosis and false negative (FN) as SPECT/CT PPS(–) and diagnosed as APG or NPG histopathologically.

The study was approved by the Pomeranian Medical University Ethics Committee and all patients gave their written consent.

Statistical analysis

Normality of distribution for serum PTH concentration was examined by the Kolmogorov-Smirnov test. Since the PTH distribution was significantly different from normal, the Kruskal-Wallis test was used to compare PTH between independent groups. Fisher's exact test was used for assessing the significance of the association between types of accumulation and histopathological diagnosis. Statistical analysis was performed with IBM SPSS 23. The threshold for statistical significance was $p < 0.05$.

Results

In 27 patients 65 lesions SPECT/CT PPS(+) on SPECT/CT were detected, but 6 of them were not found during surgery. During operations on 7 patients from this group, the surgeon additionally removed 10 lesions not indicated on SPECT/CT, and then we called it SPECT/CT PPS(–). As a result, 69 lesions were validated on the histopathological diagnosis. In total, 5 patients had a single lesion, 9 patients had 2 lesions, 7 patients had 3 lesions, 5 patients had 4 lesions, and 1 patient had 5 lesions.

The group of 59 lesions SPECT/CT PPS(+) with an additional 10 lesions SPECT/CT PPS(-) had the following histopathological diagnoses: 28 + 0 (40.6%) — parathyroid adenoma, 12 + 2 (20.3%) — parathyroid hyperplasia, 10 + 2 (17.4%) — NPG, 3 + 1

Table 1. Baseline biochemical analyses before surgery

Serum concentration (reference range)	Mean (± SD)	Median (Q25–Q75)
Ionized calcium (1.05–1.35 mmol/L)	1.49 ± 0.47	1.35 (1.15–1.9)
Total calcium (2.1–2.6 mmol/L)	2.29 ± 0.23	2.32 (2.08–2.51)
Phosphorus (0.87–1.45 mmol/L)	1.90 ± 0.63	1.76 (1.33–2.54)
PTH (16–65 pg/mL)	1701.92 ± 763.40	1600.00 (1272–2500)
Creatinine (0.7–1.5 mg/dL)	5.71 ± 2.18	5.92 (4.90–6.93)
Urea (15–40 mg/dL)	74.18 ± 37.69	71 (51–91.15)

Q25–Q75 — interquartile range; SD — standard deviation

(5.8%) — lymph node and 6 + 4 (14.5%) — normal thyroid gland tissue, 0 + 1 (1.4%) — fatty tissue.

Biochemistry data obtained before surgery are presented in Table 1.

To analyze the association between PTH and the histopathological diagnosis we compared PTH concentrations between three groups of patients: 1) 16 patients with parathyroid adenoma in histopathological diagnosis for at least one location, 2) 7 patients with parathyroid hyperplasia in histopathological diagnosis for at least one location, and 3) 4 patients with NPG or other histopathological diagnosis but without parathyroid adenoma or parathyroid hyperplasia at any location. There was no single patient with both parathyroid adenoma and parathyroid hyperplasia in different locations. There was no significant difference between those groups as regards PTH concentration ($p = 0.18$, Kruskal-Wallis test).

In a positive SPECT/CT PPS (PPS+), we identified three types of the uptake accumulation: Type I with the absence of accumulation in the early phase and retention in the delayed phase (EP-/DP+), Type 2 with accumulation in both phases (EP+/DP+), Type III with the uptake observed only in the EP(EP+/DP–).

Additionally, we identified Type IV, in which the lesions were not detected by SPECT/CT but were found and removed during surgery (Type IV EP-/DP–). The parathyroid lesion was defined if it was localized dorsally to the thyroid lobe and the uptake in SPECT/CT was classified either as type I or type II [11]. In the type III uptake, the localization criterion was decisive. None of the patients had ectopic localization of lesions.

In the lesion-based analysis, there were 9 (15.3%), 49 (83%) and 1 (1.7%) lesions SPECT/CT PPS(+) characterized as types I, II and III, respectively (Fig 1).

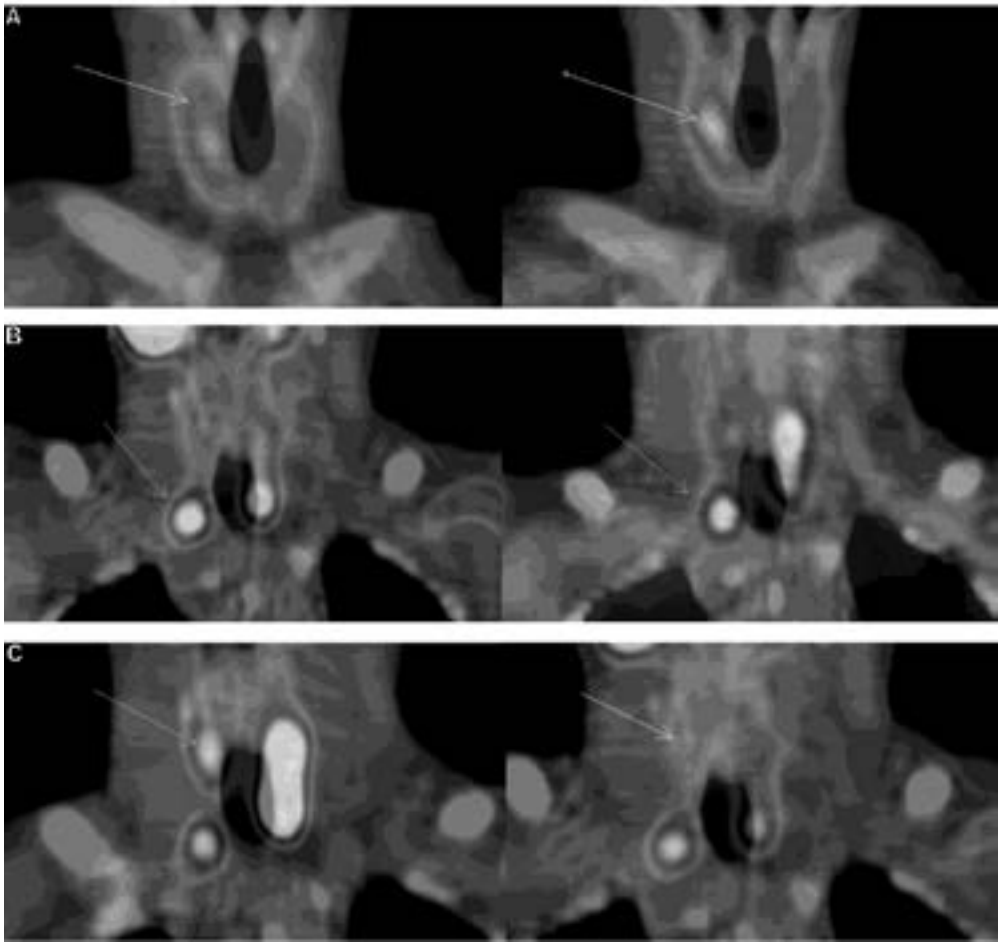

Figure 1. Three types of 99mTc-sestamibi SPECT/CT uptake in fusion coronal cross-sections; **A.** Type I — the tracer is visible in the delayed phase for right upper parathyroid gland. HP proved as adenoma (patient ZG, 56 y.o.); **B.** Type II — tracer is visible in both phases for right lower parathyroid gland. HP proved as adenoma (patient LM, 57 y.o.); **C.** Type III — the tracer is visible in the early phase for right upper parathyroid gland HP proved as NPT (patient LM, 57 y.o.). White arrows show lesions with or without uptake in corresponding phases of SPECT/CT PPS

Table 2. Association of SPECT/CT ^{99m}Tc-sestamibi results and type of uptake with parathyroid or non-parathyroid lesions in histopathological evaluation

Type of uptake	Parathyroid lesions (n)	Non-parathyroid lesions (n)	P value
TYPE I (EP–/DP+)[a]	5	4	
TYPE II (EP+/DP+)[a]	44	5	0.036*
TYPE III (EP+/DP–)[a]	1	0	
TYPE IV (EP–/DP–)[b]	4	6	N/A
Total	54	15	69

*Fisher exact test for types I–III; EP — early phase; DP — delayed phase; N/A — not applicable ; [a]SPECT/CT PPS(+) for types I–III lesions visible in SPECT/CT preoperative parathyroid scintigraphy; [b]SPECT/CT PPS(–) for type IV lesions not visible in SPECT/CT preoperative parathyroid scintigraphy.

Among 69 removed lesions 50 were acknowledged as TP, 9 lesions as FP, 4 lesions as FN, 6 lesions as TN. In type I the rate of TP achieved 5(55%) lesions, in type II — 44 (90%), in type III — 1(100%) lesion, whereas in type IV SPECT/CT PPS(–) achieved 4 (40%) lesions (Tab. 2).

In 13 (18.8%) lesions removed by the surgeon in 3 hyperplasia and 7 adenomas the average volume was 0.38 mL and 0.41 mL, respectively. All those lesions presented as type II on PPS SPECT/CT study.

The statistical analysis for the whole PPS(+) group showed significant differences between accumulation types I, II or III and results of histopathological examination ($p = 0.036$). A comparison between types I and II of ^{99m}Tc-sestamibi accumulation showed significant ($p = 0.025$) differences in histopathological diagnosis (Tab. 2).

The association of detailed histopathological diagnosis with SPECT/CT uptake type is shown in Table 3.

There were no significant differences between lesions with type I and type II uptake as regards proportions of parathyroid adenomas (33% vs. 51%, $p = 0.473$) and parathyroid hyperplasia (0% vs. 24%, $p = 0.181$) in relation to histopathological diagnosis. However, when parathyroid adenomas and parathyroid hyperplasia were combined as APG, this diagnosis was significantly more frequent in lesions with type II uptake than in lesions with type I uptake (76% vs. 33%, $p = 0.0197$). The frequency of APG was significantly different between types II and IV (76% vs. 20%, respectively, $p = 0.0016$), but not between types I and IV (33% vs. 20%. $p = 0.628$).

Combined lesions with positive uptake (types I, II and III) had significantly higher odds for combined histopathological diagnosis of APG and NPG than lesions with negative uptake (type IV) [OR = 8.33 (95% CI: 1.95–35.54), $p = 0.004$]. Type II lesions had the highest odds ratio for APG or NPG when compared to type IV lesions [OR = 13.1 (95% CI: 2.75 to 63.27), $p = 0.001$], while type I lesions did not have significantly higher odds for APG or NPG than type IV lesions [OR = 1.88 (95% CI: 0.30 to 11.63), $p = 0.499$].

The SPECT/CT ^{99m}Tc-sestamibi PPS quality parameters for detecting APG or NPG on the basis of positive (type I-III) uptake were sensitivity 92.6%, specificity 40.0%, accuracy 81.2%, positive predictive value 84.7% and negative predictive value 60.0% was achieved.

Discussion

Even if some articles are focused on parathyroid scanning with ^{99m}Tc-sestamibi in sHPT, there is limited data about its correlation with histopathology [12, 13]. SPECT/CT PPS has lately been regarded as the method of choice [6, 14, 15]. The main purpose of the study was to find pathological lesions, and the next one was to apply the best procedure to find them effectively. The method of washout analysis was rarely correlated with particular types of uptake and the final results of the study [16]. However, Carpertier, in one of the first articles about the utility of ^{99m}Tc-sestamibi in preoperative diagnosis of hyperparathyroidism, wrote about the EP and DP phases of the study [17]. Yang compared EP and DP results and pointed out the importance of dual-phase analysis methodology on final results [9].

In our study special attention was paid to the presence or absence of tracer accumulation in particular phases of the study. In this context, our approach is quite innovative. In the current paper, lesions were assessed according to their visibility in both phases of PPS and compared with histopathology.

To our knowledge, this is the first comparison performed between the transport kinetics of ^{99m}Tc-sestamibi and histopathological results in particular lesions for sHPT patients.

In our material type, I turned out not to be diagnostic for discrimination of whether the lesion is or is not of parathyroid origin. This is depicted by significantly lower odds for histopathological diagnosis of APG or NPG for type I in comparison to type II.

Table 3. Association of SPECT/CT ^{99m}Tc-sestamibi results and uptake types with histopathological diagnosis in sHPT

Histopathological findings			SPECT/CT PPS(+)			SPECT/CT PPS(–)	Total
			Type I EP–/DP+	Type II EP+/DP+	Type III EP+/DP–	Type IV EP–/DP–	
Positive	APG	Parathyroid adenoma	3[a]	25[a]	–	-	28
		Parathyroid hyperplasia	–	12[a]	–	2[c]	14
	NPG	Normal parathyroid gland	2[a]	7[a]	1[a]	2[c]	12
Negative	Non–PL	Thyroid tissue	2[b]	4[b]	–	4[d]	10
		Lymph node	2[b]	1[b]	–	1[d]	4
		Fatty tissue	–	–	–	1[d]	1
Total			9	49	1	10	69

[a]TP — true positive; [b]FP — false positive; [c]FN — false negative; [d]TN — true negative; APG — abnormal parathyroid gland, NPG — normal parathyroid gland; SPECT/CT PPS(+) — lesions visible in SPECT/CT preoperative parathyroid scintigraphy; SPECT/CT PPS(-) — lesions not visible in SPECT/CT preoperative parathyroid scintigraphy; EP — early phase; DP — delayed phase

Type II uptake was predominant in the examined group. As a practical remark, it might be valuable to point out in the report of the PPS study the type ^{99m}Tc-sestamibi uptake. Such lesions would have higher odds of being APG or NPG. The explanation might be the greater number of mitochondrias, and the ability of parathyroid cells to persistently capture ^{99m}Tc-sestamibi in comparison with Non-PL.

For parathyroid adenomas and parathyroid hyperplasias, type II accumulation was observed in 90% and 86%, respectively, while type I accumulation was noted in 10% of adenoma lesions. The examined group consisted of patients with relatively high ratios of parathyroid adenoma to hyperplasia (ratio 2:1) and was different compared with data obtained by Yuan [6]. The explanation for this fact might be the relatively long waiting time for kidney transplantation in our country [18]. This fact in patients with sHPT refractory to medical treatment promoted the evolution of parathyroid gland hyperplasia into adenoma [2, 19, 20]. This happens because of alternation in parathyroid tissue growth pattern from polyclonal to monoclonal or multiclonal proliferation [21].

The presence of increased uptake of ^{99m}Tc-sestamibi only in DP or increased activity of a tracer in both phases (EP and DP) are the main principles of the washout protocol [22, 23]. The ^{99m}Tc-sestamibi clearance from the lesion is a well-known phenomenon in the case of pHPT patients, and it is assessed as from 17% to 40% of all cases of parathyroid scintigraphy [24–27]. In our material type III uptake was presented only in one case, perhaps because there is a different aetiology of primary hyperparathyroidsim (pHPT) and sHP [6, 28]. The lesion with this kind of uptake misleads nuclear medicine practitioners suggesting the thyroid origin of the lesion. Quick clearance typical of thyroid tissue is a cause of false-negative findings, and researchers overcome it by performing thyroid scans with ^{123}I after the ^{99m}Tc-sestamibi scan [14]. On the other hand, it leads to a disadvantage in image interpretation because of the "shine through" phenomenon [29]. In our opinion, it is not necessary when the SPECT- CT technique is applied. Localization of the lesion behind the thyroid gland indicates its parathyroid rather than thyroid origin regardless of the type of transport kinetics type [14, 30]. Furthermore, the better technical possibilities related to the use of hybrid techniques and structural imaging have resulted in better sensitivity compared to previous planar or SPECT modality, even if in sHPT lesions are multiple and smaller [6, 14, 31, 32].

Surgeons removed 12 (17.4%) lesions of NPT because they were visible in parathyroid scintigraphy. These findings are similar to the 15.8% noted in the publication by Yuan [6]. High PTH plasma concentration (greater than in pHPT) might influence and stimulate to some extend NPG [7, 33]. However, Bolasco found one case of sHPT treated with cinacalcet where despite the lowering PTH plasma level ^{99m}Tc-sestamibi uptake in APG was unchanged [34].

SPECT/CT PPS helped in choosing lesions to be removed. Nowadays, it is believed that if four glands exploration parathyroid surgery is necessary, surgeons should remove three glands and a half of the fourth with the most normal appearance, leaving the remaining half in situ [6]. For the 27 patients, the estimated number of removed parathyroid glands should have been minimum 81 glands, but 69 glands were removed. So, SPECT/CT PPS results helped to limit the number of resected glands, shortened the duration time of the surgery, and diminished the failure rate. However, it is possible that in the operating theatre lesions suspected of pathology by the surgeon would be removed during the exploration, even if there is no indication in preoperative diagnosis. It is important to admit this in terms of the limitation of our study. The study was conducted in just one university centre. The surgeons' skills, preoperative assessment, and the experience of nuclear medicine specialists will affect the outcome of the study.

A sensitivity of 92.6% and accuracy of 81.2% is comparable with the literature data [2, 30]. A specificity of 40% is much lower than that achieved by other authors [2, 6, 9, 30, 35]. This could have been affected by including Type IV lesions in the calculation. Type IV consisted of lesions removed by the surgeon despite the lack of accumulation of the tracer in scintigraphy. It is worth mentioning in this context that our study provides additional quality parameters not available in other papers as the odds ratio for successful surgery in particular transport kinetics types in patients with sHPT.

In the current study as well as in the literature there was no statistical relation between histopathological diagnosis and PTH level. The explanation may be that pharmacological treatment in sHPT patients influences their PTH level [36]. In our study, the recommendation for surgery was PTH level of more than 600 pg/mL. The same criteria were applied by Souberbielle and Rosato [33, 37].

Separation into three groups of tracer uptake was used in previous studies with ^{99m}Tc-sestamibi performed for different indications. For example, the kinetics of the tracer was used as a predictor of tumour response to chemotherapy treatment. It combined imaging findings with prognostic value in patients with breast cancer, lymphoma, and small and non-small cell lung cancer [38]. Different kinetics of ^{99m}Tc-sestamibi depicted a multidrug resistance phenotype prior to preoperative diagnosis or any treatment. The above idea inspired us to perform the comparison between ^{99m}Tc-sestamibi uptake in SPECT/CT PPS and different histopathological diagnosis in sHPT.

The genetic factors influencing parathyroid uptake in patients with hyperparathyroidism were postulated in some publications [39–41]. But there is still a limited number of genetics studies investigating the background of the transport kinetics of ^{99m}Tc-sestamibi in patients with sHPT. Also, different mathematical models of transport kinetics have been created but there is a lack of clinical studies [42]. The authors of the presented study performed genetic studies in patients with hyperparathyroidism and proved the significant negative correlation of mRNA expression for the *ABCC1* gene with maximal ^{99m}Tc-sestamibi uptake values in patients with hyperparathyroidism [43, 44]. There is a need for further investigation in this field.

Conclusions

For sHPT patients evaluated with SPECT/CT PPS accumulation type, I is a weak premise for a surgeon to find parathyroid pathology. Only persistent ^{99m}Tc-sestamibi accumulation in both phases — equivocal with accumulation type II — effectively differentiates parathyroid and non-parathyroid lesions as well as indicates with high probability the presence of adenoma or hyperplasia. Type III, consistent with washout pattern, is rare in sHPT.

Conflict of interest

The authors declare no conflicts of interest.

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