Original article

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Functional evaluation of parathyroid adenoma using ^{99m}Tc-MIBI parathyroid SPECT/CT: correlation with functional markers and disease severity

Hyung-Jun Im[a,c], In Ki Lee[a], Jin Chul Paeng[a], Kyu Eun Lee[b], Gi Jeong Cheon[a], Keon Wook Kang[a], June-Key Chung[a] and Dong Soo Lee[a,c]

Objectives **In parathyroid adenoma, uptake of technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) has been suggested to have a correlation with functional markers. The purpose of this study was to evaluate the feasibility of ^{99m}Tc-MIBI parathyroid single photon emission computed tomography/computed tomography (SPECT/CT) in evaluating the function and disease severity of parathyroid adenoma.**

Patients and methods **Twenty-three patients with surgically confirmed parathyroid adenoma were retrospectively enrolled. A parathyroid planar scan and SPECT/CT were performed before parathyroidectomy. Functional and clinical makers reflecting the disease severity of parathyroid adenoma were also evaluated, including serum intact parathyroid hormone, calcium, bone mineral density, and creatinine clearance. The pathologic volume (V_P) of the adenoma was measured after parathyroidectomy. On parathyroid SPECT/CT, metabolic volume (V_M) was measured using an isocontour method. Maximum uptakes of parathyroid adenoma and mean uptakes of contralateral thyroid tissue were measured to calculate the parathyroid adenoma-to-background ratio on parathyroid SPECT/CT (PBR_{SCT}) and planar scan (PBR_{PL}).**

Results **V_M significantly correlated with V_P ($r=0.669$, $P=0.0005$). Serum intact parathyroid hormone level significantly correlated with PBR_{PL}, PBR_{SCT}, V_M, and V_P ($P=0.0004$, 0.005, 0.003, and 0.025, respectively). However, serum calcium level correlated only with V_M ($P=0.012$). Regarding the surgical indication criteria, PBR_{SCT} and PBR_{PL} were significantly higher in the young-aged group ($P=0.0004$ and 0.024, respectively) and V_M was significantly higher in the high calcium level group ($P=0.049$), whereas V_P was not different between groups on the basis of any criteria.**

Conclusion **Quantitative indices of parathyroid SPECT/CT closely correlate with laboratory functional markers and disease severity of parathyroid adenoma. Thus, parathyroid SPECT/CT could be used for evaluation of the underlying functional state and disease severity of parathyroid adenoma, particularly for decision pertaining to surgical treatment.** ***Nucl Med Commun*** **35:649–654 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Departments of [a]Nuclear Medicine, [b]Surgery, Seoul National University Hospital and [c]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, Korea

Correspondence to Jin Chul Paeng, MD, PhD, Department of Nuclear Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82 2 2072 3341; fax: +82 2 745 7690; e-mail: paengjc@snu.ac.kr

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Introduction

Primary hyperparathyroidism (PHPT) is caused by parathyroid adenoma in about 85% of patients with hyperparathyroidism [1], and 20–25% of PHPT patients present with overt symptoms [2]. Currently, parathyroidectomy is the standard mode of treatment for symptomatic parathyroid adenoma, and it is often recommended for asymptomatic patients because the underlying risk of adverse events such as fracture or renal stone can be reduced with effective surgery [1]. In guidelines of consensus, parathyroidectomy is recommended for asymptomatic PHPT when a patient meets surgical indication criteria that are associated with a high risk for complications [3].

Parathyroid scan using dual-phase technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) imaging is one of the most effective methods for detecting functional parathyroid adenoma [4]. Recently, a hybrid imaging modality of single photon emission computed tomography/computed tomography (SPECT/CT) has been used in clinical practice, which enables accurate localization of parathyroid adenoma with high diagnostic performance [5]. In addition, the parathyroid scan and SPECT/CT can be used for functional evaluation. ^{99m}Tc-MIBI binds to the mitochondria by virtue of its membrane potential [6,7], and thus uptake of ^{99m}Tc-MIBI is related to mitochondrial activity or to

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the metabolic state of cells [8]. On the basis of this relationship, several studies have demonstrated correlations between ^{99m}Tc-MIBI uptake and functional markers such as intact parathyroid hormone (iPTH) and calcium levels [7–9], despite some discrepant results [10,11].

However, to the best of our knowledge, there is no report on the functional evaluation of parathyroid adenoma using SPECT/CT. A ^{99m}Tc-MIBI parathyroid SPECT/CT can be an effective imaging method for evaluating the functional state of parathyroid adenoma because of higher sensitivity compared with a planar scan or radiological images, production of a three-dimensional image, and ability of attenuation correction and quantitative analysis. In this study, we evaluated the feasibility of ^{99m}Tc-MIBI parathyroid SPECT/CT in the functional evaluation of parathyroid adenoma.

Patients and methods

Patients and surgery

Patients who underwent parathyroid SPECT/CT were retrieved from the image database of our institution. From them, those patients fulfilling the following criteria were selected: (i) parathyroidectomy had been performed within 2 months of the acquisition date of parathyroid SPECT/CT; (ii) pathologically confirmed presence of a parathyroid adenoma after parathyroidectomy; and (iii) no prior use of calcium-lowering medications. All patients underwent focused parathyroidectomy with intraoperative monitoring of iPTH levels, using the Miami criterion (iPTH decrease more than 50% from the highest level 10 min after parathyroid excision) [12]. After parathyroidectomy, resected parathyroid tissues were reviewed by experienced pathologists. The size of a parathyroid adenoma was measured in terms of the diameters of the major axis, minor axis, and height, from which a pathologic volume (V_P) was calculated using the volume formula for a spherical object.

The study design and exemption of informed consent were approved by the institutional review board of our institution.

Image acquisition

Dual-phase parathyroid planar scans of the neck area were taken 15 min (early phase) and 150 min (delayed phase) after intravenous injection of ^{99m}Tc-MIBI (555 MBq), using a hybrid SPECT/CT scanner equipped with low-energy high-resolution collimators (Discovery NM/CT 670; GE Healthcare, Milwaukee, Wisconsin, USA). Images were acquired by count-setting mode (700 kcounts) using 256×256 matrices. The energy window was open by 20% with the photopeak centered at 140 keV.

Parathyroid SPECT/CT was performed immediately after a delayed parathyroid planar scan using the same scanner. SPECT images were acquired using a step-and-shoot protocol (60 steps with a 3° interval and 20-s acquisition per step). SPECT images were reconstructed on 128×128 matrices using a Butterworth postprocessing filter (cutoff 0.48, order 10) and an iterative algorithm (ordered-subset expectation maximization; two iterations and 10 subsets). After SPECT acquisition, a helical CT scan was taken for anatomical localization and attenuation correction without contrast enhancement (60–100 mA, 120 kVp). CT images were reconstructed into 3.75-mm slices with 512×512 matrices. SPECT, CT, and their fusion images were displayed on transverse, coronal, and sagittal planes.

Image analysis and quantification

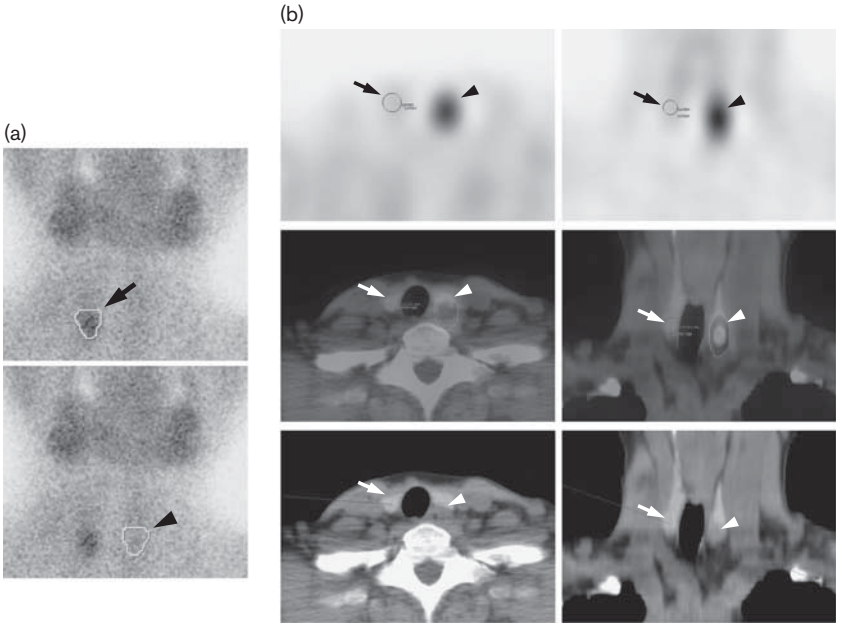
Images were reviewed and analyzed by consensus between two experienced nuclear medicine physicians. Early and delayed parathyroid planar scans were compared, and focal retention of uptake in the parathyroid was regarded as the presence of a lesion. On the delayed scan, a region of interest (ROI) was manually drawn for the uptake lesion using an image analysis tool (Maroview 5.4; Infinitt, Seoul, Korea). Another ROI of the same size and shape was copied to the contralateral thyroid area as a background area (Fig. 1a). When there was no discernible focal uptake in the parathyroid area, a circular ROI was drawn at the location of the adenoma based on the pathologic examination. A parathyroid adenoma-to-background ratio on the parathyroid planar scan (PBR_{PL}) was calculated as the ratio between the maximum count of parathyroid ROI and the mean count of background ROI.

On parathyroid SPECT/CT, a spherical volume of interest (VOI) was manually drawn exclusively in the contralateral thyroid tissue as large as possible, for which the maximum, mean, and SD of voxel counts were measured using a vendor-supplied image analysis tool (Syngo.via; Siemens Healthcare, Berlin, Germany). The VOI values were used as background. For the parathyroid adenoma, an isocontour VOI was automatically drawn around the focal uptake, using mean ± 2 SDs of background counts as the margin threshold (Fig. 1b). For the VOI for parathyroid adenoma, the maximum and mean counts were measured, and a parathyroid adenoma-to-background ratio on parathyroid SPECT/CT (PBR_{SCT}) was calculated as the ratio between the maximum counts of VOIs for the parathyroid adenoma and mean counts of VOIs for the background. In addition, the volume of VOI for parathyroid adenoma was measured and defined as the metabolic volume (V_M).

Disease severity

Serum iPTH, calcium, and creatinine levels were measured before parathyroidectomy. Serum iPTH was measured using a chemiluminescence immunoassay analyzer (Nichols Institute Diagnostics, San Juan Capistrano, California, USA), and creatinine level was measured using an automatic chemical analyzer (TBA-200FR; Toshiba, Tokyo, Japan). Creatinine clearance (C_{Cr}) was calculated by the equation of the Modification of Diet in Renal

Fig. 1



Measurement of parathyroid and background counts on parathyroid planar scan and single photon emission computed tomography/computed tomography (SPECT/CT). (a) On delayed parathyroid planar scan, regions of interest were drawn for parathyroid adenoma (arrow) and background (arrowhead). (b) On parathyroid SPECT/CT images (left row: transaxial SPECT, fusion, CT; right row: coronal SPECT, fusion, CT) of a patient, a volume of interest (VOI) of a lesion (arrowhead) was drawn on parathyroid adenoma using the isocontour method. A VOI for background (arrow) was drawn exclusively on contralateral thyroid tissue using a spherical VOI.

Disease Study. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DEXA, Discovery-W; Hologic, Waltham, Massachusetts, USA) in the L1–L4 spine and femur, of which the lowest *T*-score was used for the analysis.

To evaluate correlations between disease severity and image indices, severity of disease manifestation was evaluated on the basis of commonly used guidelines for parathyroid surgery in asymptomatic PHPT [3], in terms of high calcium level (> 1.0 mg/dl above upper normal limit), low C_{Cr} (< 60 ml/min), low BMD (*T*-score < −2.5 at any site), and young age (< 50 years). The correlations between these criteria and image indices including PBR_{PL}, PBR_{SCT}, and V_M were evaluated.

Statistical analysis

Statistical analysis was performed using SPSS (ver. 18.0; IBM Software, Chicago, Illinois, USA) and a *P*-value of less than 0.05 was considered statistically significant. Correlations were analyzed using Pearson's correlation coefficients. Unpaired Student's *t*-tests were carried out to evaluate differences between two groups.

Results

Patients

Among a total of 114 patients who underwent parathyroid SPECT/CT during the study period, 29 patients were pathologically diagnosed with solitary parathyroid adenoma after parathyroidectomy. Among them, six patients were excluded because of having taken calcium-lowering medications such as cholecalciferol, calcitonin, and bisphosphonate earlier. Thus, 23 patients were included in the final analysis [six men and 17 women; median age 53 (range 33–76) years].

Preoperative serum iPTH, calcium levels, and C_{Cr} were 214.8 ± 134.7 (range 67.6–577.3) pg/ml, 11.38 ± 0.43 (range 10.7–12.5) mg/dl, and 86.36 ± 20.39 (range 40.4–123.6) ml/min, respectively. BMD was evaluated in 20 patients and the lowest *T*-score on BMD was −1.77 ± 1.14 (range −4.3 to 0.1). All patients met the Miami criterion during the focused parathyroidectomy, and all serum iPTH and calcium levels were normalized after surgery. In the pathologic evaluation, V_P of the parathyroid adenoma was measured as 1.07 ± 1.09 (range 0.04–3.90) ml.

Image findings and quantification

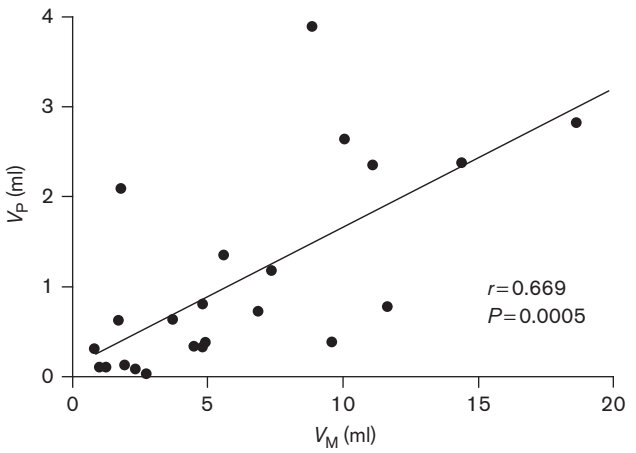
On parathyroid planar scans, focal uptake in the parathyroid gland was seen in 20 (87%) patients, whereas three (13%) patients showed no discernible uptake. On parathyroid SPECT/CT, all 23 (100%) patients exhibited discernible focal uptake in the parathyroid. There was no patient with multifocal lesions in the ipsilateral parathyroid or with an abnormal focal lesion in the contralateral thyroid. PBR_{SCT} on parathyroid SPECT/CT was

3.47±1.96 (range 1.51–8.42), and it was significantly higher than PBR_{PL} on parathyroid planar scans (2.64±0.64, range 1.67–4.25, $P = 0.01$). On parathyroid SPECT/CT, V_M was measured as 6.1±4.7 (range 0.8–18.6) ml, which significantly correlated with V_P ($r = 0.669$, $P < 0.001$; Fig. 2).

Correlations between image indices and disease severity

Serum iPTH level correlated significantly with image indices of PBR_{PL}, PBR_{SCT}, and V_M ($P = 0.0004$, 0.005, and 0.003, respectively), as well as with V_P ($P = 0.025$; Table 1). However, serum calcium level correlated significantly with V_M only ($P = 0.012$), whereas it did not correlate significantly with PBR_{PL}, PBR_{SCT}, and V_P

Fig. 2



Correlation between V_M measured in parathyroid single photon emission computed tomography/computed tomography and V_P. Significant correlation was found between V_P and V_M. V_M, metabolic volume of parathyroid adenoma; V_P, pathologic volume of parathyroid adenoma.

Table 1 Correlations of functional markers with image parameters and pathologic volume

Parameters	PBR_{PL}	PBR_{SCT}	V_M	V_P
iPTH				
r	0.675	0.562	0.592	0.465
P	0.0004	0.005	0.003	0.025
Ca				
r	0.363	0.308	0.513	0.218
P	0.089	0.152	0.012	0.319
C_{Cr}				
r	0.367	0.188	0.307	0.342
P	0.085	0.391	0.155	0.110
T-score[a]				
r	−0.319	−0.349	−0.153	0.014
P	0.170	0.131	0.520	0.954

C_{Cr}, creatinine clearance; iPTH, intact parathyroid hormone; PBR_{PL}, parathyroid adenoma-to-background ratio on parathyroid planar scan; PBR_{SCT}, parathyroid adenoma-to-background ratio on single photon emission computed tomography/computed tomography; V_M, metabolic volume; V_P, pathologic volume.
[a]Analyzed in 20 patients.

C_{Cr} and *T*-score on BMD did not correlate with any of the tested indices. The results of correlation tests are summarized in Table 1.

When patients were evaluated according to the guidelines for parathyroid surgery in asymptomatic PHPT [3], five patients met no criterion, 14 met one criterion, and four met two criteria; eight patients exhibited high serum calcium level, two exhibited low C_{Cr}, six exhibited low *T*-score on BMD, and six were young-aged. V_M was significantly larger in patients with high calcium level ($P = 0.049$), and PBR_{PL} and PBR_{SCT} were significantly higher in young-aged patients ($P = 0.004$ and 0.024, respectively). In contrast, V_P was not significantly different according to any of the criteria. None of the tested indices were different between two groups on the basis of low C_{Cr} and *T*-score on BMD (Table 2).

Discussion

In this study, we evaluated the functional significance of quantitative indices acquired from a parathyroid scan and SPECT/CT images in terms of correlations with laboratory functional markers and disease severity criteria, and it was demonstrated that image indices of PBR_{PL}, PBR_{SCT}, and V_M closely correlate with serum iPTH, calcium level, and age, which are disease severity criteria.

In the diagnosis of functional parathyroid adenoma, the parathyroid scan using ^{99m}Tc-MIBI is the most effective image for detecting the lesion. In a meta-analysis, sensitivity of the parathyroid scan for a single parathyroid adenoma was reported to be 88.4% [13], which is similar to that of the present study (87%). With a higher image quality, SPECT exhibited higher diagnostic performance compared with a parathyroid planar scan. SPECT/CT is a fusion imaging modality combining SPECT and high-resolution CT and can

Table 2 Image parameters and pathologic volume according to the disease severity criteria

Parameters	*N*	PBR_{PL}	PBR_{SCT}	V_M	V_P
Ca (mg/dl)					
>11.5	8	2.84±0.79	4.07±2.6	8.72±5.39	1.32±1.13
≤ 11.5	15	2.53±0.55	3.15±1.54	4.71±3.82	0.94±1.08
P		0.285	0.298	0.049	0.441
C_{Cr} (ml/min)					
<60	2	1.87±0.29	1.51±0.01	1.30±0.70	1.20±1.26
≥ 60	21	2.71±0.62	3.66±1.96	6.56±4.69	1.06±1.10
P		0.077	0.144	0.135	0.865
T-score[a]					
< −2.5	6	2.92±0.45	4.12±1.62	6.66±4.17	0.99±0.85
≥ −2.5	14	2.54±0.68	3.23±2.07	5.91±5.01	1.1±1.18
P		0.216	0.357	0.746	0.832
Age (years)					
<50	6	3.25±0.60	4.99±2.50	8.75±5.35	1.98±1.36
≥ 50	17	2.42±0.52	2.93±1.48	5.17±4.27	0.75±0.79
P		0.004	0.024	0.113	0.079

C_{Cr}, creatinine clearance; PBR_{PL}, parathyroid adenoma-to-background ratio on parathyroid planar scan; PBR_{SCT}, parathyroid adenoma-to-background ratio on parathyroid single photon emission computed tomography/computed tomography; V_M, metabolic volume; V_P, pathologic volume.
[a]Analyzed in 20 patients because three were not assessable.

be used for specific localization of parathyroid adenoma based on fusion images. Thus, SPECT/CT is effective for minimally invasive surgery and selective parathyroidectomy [5,14]. Several studies reported higher sensitivities of parathyroid SPECT/CT, ranging from 88 to 100% [5,13,15]. In the present study, uptake in the parathyroid adenoma was more evident on SPECT/CT than on a planar scan, and the lesion-to-background ratio was significantly higher on SPECT/CT. Therefore, the sensitivity of SPECT/CT was higher than that of the planar scan (100 vs. 87%), although it was not statistically significant, and hence the confidence in the diagnosis based on its results is higher.

In addition to the diagnosis of a lesion, the parathyroid scan can be used for functional evaluation of a parathyroid adenoma because ^{99m}Tc-MIBI uptake is related to the metabolic state of the parathyroid [8]. Piga *et al.* [16] reported that serum iPTH level is significantly higher in patients with ^{99m}Tc-MIBI-positive adenoma, and Melloul *et al.* [7] reported that ^{99m}Tc-MIBI uptake correlates with serum iPTH and calcium levels. Biertho *et al.* [9] also reported that the degree of ^{99m}Tc-MIBI uptake is associated with serum iPTH level. In accordance with these studies, PBR_{PL} in the present study significantly correlated with serum iPTH level. However, parathyroid SPECT/CT can provide additional quantitative indices including metabolic volume and uptake ratio, based on three-dimensional images. We tested the functional significance of various indices of a parathyroid scan and SPECT/CT in terms of the correlation with serum markers and disease severity criteria. All the image indices of PBR_{PL}, PBR_{SCT}, and V_M exhibited functional significance; in particular, V_M was significantly related to the serum calcium level.

In parathyroid adenoma, the serum iPTH level has been reported to correlate with the volume of adenoma [9,17,18]. In the present study serum iPTH was significantly related to V_P in line with previous studies. However, the correlation between serum calcium level and volume of adenoma has been controversial [7,12,18], and we observed no significant correlation between serum calcium level and V_P. In addition, V_P was not related to *T*-score on BMD, in accordance with a previous report [12]. In contrast, V_M exhibited a significant correlation with serum calcium and iPTH levels, which suggests that the volume of metabolically active tissue may be a more effective marker than the simple pathologic volume. It is speculated that PBR_{PL} or PBR_{SCT} is related to the metabolic activity of parathyroid adenoma cells, and V_M is related to the functional burden of the whole adenoma.

To the best of our knowledge, the present study is the first to measure metabolic volume on parathyroid SPECT/CT, and thus there is no standard method to measure the metabolic volume of parathyroid adenoma. We measured V_M with varying thresholds to determine the most appropriate one. In the case of ^{18}F-fluorodeoxyglucose PET, metabolic volume is measured with a margin threshold based on the maximum value of a lesion or a certain fixed value [5,19,20]. We measured V_M using various methods including those applied for PET analysis, and selected mean $\pm$ 2 SDs of background count for the margin threshold because V_M exhibited the highest correlation with V_P (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/NMC/A20*) at this threshold. However, further studies are required to determine the optimal method for quantification of parathyroid SPECT/CT.

The quantitative functional indices of parathyroid SPECT/CT may be used as effective complementary criteria to the current ones in determining disease severity and surgery. Although the functional index using a parathyroid planar scan has been shown to have the ability to reflect the functional aspect of parathyroid adenoma, it is not used in routine clinical management, probably because of insufficient diagnostic certainty and anatomical information. However, the localization and quantification of parathyroid adenoma using SPECT/CT is objective and reliable because of the high sensitivity (100% in the present study) and detailed anatomical information of SPECT/CT, and thus functional evaluation using parathyroid SPECT/CT could be a part of standard clinical management. In addition, these image indices can provide cross-sectional information on the present parathyroid function, whereas C_{Cr} and BMD reflect the cumulative effect of hyperfunctioning parathyroid adenoma. Therefore, the image indices may be more sensitive or earlier markers for disease progression compared with C_{Cr} and BMD. In addition, the image indices of SPECT/CT are presumably less prone to diurnal or endocrinological variations than serum iPTH and calcium levels are. Although we demonstrated only the correlations between the image indices and the current criteria of disease severity and surgical indication criteria, further studies are required to determine whether the image indices are independent risk factors for adverse events or disease progression. Because disease progression is not rare in asymptomatic patients even with normal C_{Cr} and BMD [21], accurate prognostic markers for disease progression are still required.

In the present study, only the patients who were free from previous calcium-lowering medication were included, because hyperparathyroidism is suppressed after calcitriol therapy in primary and secondary hyperparathyroidism according to previous reports [22,23]. Ambrosoni *et al.* [23] reported that ^{99m}Tc-MIBI uptake and iPTH level can be downregulated within 10 days after calcitriol pulse therapy. In addition, other medications for hyperparathyroidism, such as calcitonin and bisphosphonate, can reduce the serum level of calcium. Accordingly, the original characteristics of a parathyroid adenoma cannot be reliably reflected on ^{99m}Tc-MIBI

imaging and biochemical parameters after calcium-lowering treatment. In the six patients who were excluded from the present study because of previous calcium-lowering medication, no significant correlation was observed between serum markers and V_P or other image indices. For example, in a patient who was medically treated before parathyroid SPECT/CT, ^{99m}Tc-MIBI uptake and iPTH were very low (PBR_{SCT} 1.28, iPTH 66 pg/ml) despite a very large pathologic volume (2.09 ml). Therefore, the history of calcium-lowering medication should be considered in the analysis of parathyroid SPECT/CT.

This study has several limitations. It is a retrospective study in a single institution, and a possibility of selection bias cannot be excluded, although the images were analyzed by readers blind to other clinical and pathologic information. In addition, the results of the present study could have been underpowered because of the relatively small number of patients. Thus, further prospective studies with a larger number of patients are required to determine the efficacy of and the optimal analysis method for parathyroid SPECT/CT in the functional evaluation of parathyroid adenoma.

Conclusion

Quantitative indices of parathyroid SPECT/CT closely correlate with laboratory functional markers and disease severity of parathyroid adenoma. Thus, parathyroid SPECT/CT could be used for evaluation of the underlying functional state and disease severity of parathyroid adenoma, particularly for decisions pertaining to surgical treatment.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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