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Is dual-phase SPECT/CT with ^{99m}Tc-sestamibi better than single-phase SPECT/CT for lesion localization in patients with hyperparathyroidism?

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Abstract

This study aimed to establish an optimal protocol for ^{99m}Tc-sestamibi parathyroid imaging for lesion localization in patients with hyperparathyroidism (HPT).

We retrospectively enrolled 35 consecutive patients who underwent dual-phase (at 10 minutes and 120 minutes) ^{99m}Tc-sestamibi parathyroid scintigraphy with single-photon emission computed tomography (SPECT)/computed tomography (CT). Twenty seven patients had primary HPT, and 8 had secondary or tertiary HPT. Three nuclear medicine physicians independently analyzed the parathyroid images for lesion localization at 9 predefined parathyroid locations using the following 4 different image sets blinded to the clinical information:

1. dual-phase SPECT,
2. early SPECT/CT,
3. delayed SPECT/CT,
4. dual-phase SPECT/CT.

All SPECT or SPECT/CT image sets were analyzed with dual-phase planar images. The image results were compared with the histopathological results after surgery.

Dual-phase SPECT/CT showed the highest positive rate of 85.7% in the patient-based analysis and 13.7% in the location-based analysis. Of 35 patients, surgical pathological results were available in 21 (16 adenomas in 16 primary HPTs and 16 hyperplasias in 5 secondary or tertiary HPTs). Dual-phase SPECT/CT showed the sensitivity values of 100% and 84.4% in the patient-based and location-based analysis, respectively, which were the highest sensitivity values among all image sets. In the primary HPT subgroup, dual-phase SPECT/CT showed the highest sensitivity value of 93.8% in the location-based analyses, whereas dual-phase SPECT, early SPECT/CT, and delayed SPECT/CT showed the sensitivity values of 62.5%, 81.3%, and 81.3%, respectively. In the secondary or tertiary HPT subgroup, dual-phase SPECT/CT also showed the highest sensitivity value of 75.0%, whereas early SPECT/CT, delayed SPECT/CT, and dual-phase SPECT showed the sensitivity values of 43.8%, 56.3%, and 68.8%, respectively.

Compared with dual-phase SPECT or single-phase SPECT/CT, the dual-phase SPECT/CT imaging protocol for ^{99m}Tc-sestamibi scintigraphy showed the highest positive rate and sensitivity, and was optimal for parathyroid lesion localization.

Abbreviations: CT = computed tomography, HPT = hyperparathyroidism, PPV = positive predictive value, PTH = parathyroid hormone, SPECT = single-photon emission computed tomography.

Keywords: ^{99m}Tc-sestamibi, hyperparathyroidism, parathyroid scintigraphy, SPECT, SPECT/CT

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors of this work have nothing to disclose.

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1. Introduction

Parathyroid scintigraphy is performed to localize a hyperfunctioning parathyroid tissue in patients with hyperparathyroidism (HPT) prior to surgery.[1,2] ^{99m}Tc-sestamibi is the principal tracer used in parathyroid scintigraphy because it retains in the mitochondria after passive diffusion and can be used for parathyroid imaging because it can be washed out more rapidly in the thyroid than in the parathyroid.[3,4]

Guidelines for parathyroid imaging suggest various protocols, including single-photon emission computed tomography (SPECT) and SPECT/computed tomography (CT).[5–7] Parallel-hole imaging is the standard method for parathyroid imaging to evaluate the neck and mediastinum, but pin-hole imaging can provide better resolution.[6] SPECT and SPECT/CT can be performed immediately after planar imaging. According to Lavely et al, early SPECT/CT combined with any kind of delayed imaging (planar imaging, SPECT, or SPECT/CT) provides the highest accuracy[8] because ^{99m}Tc-sestamibi can be washed out more rapidly in some adenomas.[5,6] Therefore, recent guidelines suggest that early SPECT or early SPECT/CT may improve sensitivity.[5,6]

An additional SPECT/CT provides improved detection rate and localization of parathyroid lesions compared with planar parathyroid scintigraphy alone.[8–10] However, the timing of SPECT/CT remains controversial because both early and delayed SPECT/CT seem optimal in primary HPT.[11] Unlike the SPECT/CT used in the study of Lavely et al.,[8] which had low CT resolution (140 kVp, 2.5 mA, 10-mm slices) ("early" generation SPECT/CT that lacks anatomical information), SPECT/CT with better CT resolution (higher mAs) ("later"-generation SPECT/CT[12]) has recently become available to allow visualization of an adenoma on CT images. According to Ciapuccini et al, dual-phase ^{99m}Tc-sestamibi parathyroid scintigraphy with delayed SPECT/CT using later-generation SPECT/CT showed diagnostic performance comparable to that of early or dual-phase SPECT/CT.[12,13]

The study of Lavely et al only evaluated biopsy-confirmed adenomas,[8] although parathyroid imaging is used in both primary and secondary HPT.[14] Yang et al reported that both early and delayed SPECT/CT should be performed in patients with secondary HPT because 16.3% of these patients had positive findings in either early (n = 6/80, 7.5%) or delayed (n = 7/80, 8.8%) SPECT/CT only.[15] However, no study has compared the diagnostic performance of early and delayed ^{99m}Tc-sestamibi SPECT/CT regardless of HPT type.

The study aimed to establish an optimal protocol by comparing the positive rate and diagnostic accuracy of various protocols, including dual-phase SPECT/CT, for parathyroid imaging with ^{99m}Tc-sestamibi for lesion localization in patients with HPT using a later-generation SPECT/CT with improved CT resolution.

2. Methods

2.1. Study participants

We retrospectively enrolled 35 consecutive adult patients (24 women; mean age = 53.3 ± 15.5 years) with HPT who underwent dual-phase parathyroid planar scintigraphy and SPECT/CT between June 2017 and August 2017 in our institution. Among 35 patients, 27, 4, and 4 patients had primary, secondary, and tertiary HPT (persistent HPT with hypercalcemia after renal transplantation), respectively.

Data regarding age, sex, serum calcium level, serum intact parathyroid hormone level, surgery, and pathological results after SPECT/CT were collected through a review of medical records. This study was approved by our institutional review board (IRB no. 2018–0051), and the requirement to obtain an informed consent was waived.

2.2. Parathyroid imaging protocol

The patients were given approximately 740 MBq (20 mCi) of ^{99m}Tc-sestamibi intravenously. Dual-phase planar imaging followed by immediate SPECT/CT image acquisitions was initiated at 10 minutes (early phase) and 120 minutes (delayed phase) after injection. An integrated SPECT/CT scanner (Symbia Intevo 16; Siemens Medical Solutions, Erlangen, Germany) was used. Anterior neck planar images were obtained for 3 minutes in a 256 × 256 matrix using a low-energy high-resolution collimator post-filtered with a commercial package (Oncoflash; Siemens Medical Solutions, Erlangen, Germany). SPECT images were acquired with 128 projections, 20 seconds per projection, over 360° in a 256 × 256 matrix. The SPECT data were reconstructed using a Flash 3D (Siemens Medical Solutions, Forchheim, Germany) reconstruction algorithm (24 iterations and 2 subsets) without a smoothing filter. Both CT-based attenuation-corrected and non-attenuation-corrected SPECT images were reconstructed. The CT images were taken from the angle of the mandible to the subcarina, which is approximately half of the SPECT field. The CT acquisition parameters were as follows: voltage, 110 kV; tube current, 80 mA for early phase and 25 mA for delayed phase with tube current modulation (CARE Dose 4D; Siemens Medical Solutions, Forchheim, Germany); collimation, 16 × 0.6 mm; and pitch, 1. The CT data were reconstructed from the acquired slices with a 1-mm slice thickness at 1-mm slice increments. The SPECT images were registered with the CT images of the same phase.

2.3. Image analysis

An image analysis was performed on the following 5 image sets:

1. dual-phase planar images,
2. dual-phase SPECT,
3. early SPECT/CT,
4. delayed SPECT/CT,
5. dual-phase SPECT/CT.

In all SPECT or SPECT/CT image sets, dual-phase planar images were also reviewed. When analyzing the images, the order of patients was randomly arranged for each image set, and all 35 patients were analyzed for each image set. A dedicated software package (Syngo.via, Siemens Medical Solutions, Forchheim, Germany) was used to analyze all images.

The interpretation of parathyroid imaging was independently performed by 3 nuclear medicine physicians (S.H.L., E.S., and S. H.) blinded to the clinical data of the patients. ^{99m}Tc-sestamibi uptakes were evaluated according to 9 different predefined locations: right superior, left superior, right inferior, left inferior, right inferior-posterior, left inferior-posterior, right intrathyroidal, left intrathyroidal, and mediastinum. ^{99m}Tc-sestamibi uptake was visually categorized as positive if there was an unequivocal focal ^{99m}Tc-sestamibi uptake compared with the background. The absence of visually discernable or equivocal ^{99m}Tc-sestamibi uptake was categorized as negative. If the results

of all 3 observers were different, 2 matched results were treated as the final result. Positive rate was defined as the number of patients who showed at least 1 positive lesion among all patients in the patient-based analysis and the number of positive lesions among all locations in the location-based analysis. Diagnostic accuracy was calculated in patients with available reference standards and surgical results.

2.4. Statistical analysis

Of the 5 image sets, the previous 4 image sets were compared with the dual-phase SPECT/CT image set by performing the McNemar test and Cohen kappa statistics. The interobserver agreement of visual analysis was estimated by calculating the Fleiss kappa for 3 observers. Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 21.0.; IBM Corp., Armonk, NY, USA) and Excel sheet (macro) from http://www.ccitonline.org/jking/homepage. Statistical tests were 2 sided and considered to be statistically significant at a P value of $\leq .05$.

3. Results

The clinical characteristics of the patients are summarized in Table 1. Tables 2 and 3 show the positive rate results of the image sets and concordance rates of 4 different sets of images from dual-phase SPECT/CT for the detection of abnormal parathyroid lesions. In the patient-based analysis (Table 2), dual-phase SPECT/CT showed the highest positive rate (85.7%) among the 5 different sets. Compared with dual-phase SPECT/CT, delayed SPECT/CT showed a nearly significant difference ($P = .083$), and the other 3 image sets showed significant differences.

In the location-based analysis (Table 3), dual-phase SPECT/CT showed the highest positive rate (13.7%). In the subgroup of patients with primary HPT, the positive rate decreased in the order of dual-phase SPECT/CT (9.9%), delayed SPECT/CT (9.1%), and early SPECT/CT (8.6%). Compared with dual-phase SPECT/CT, delayed SPECT/CT showed the highest positive concordance rate (91.7%) followed by early SPECT/CT (87.5%). The results of early SPECT/CT and delayed SPECT/CT were not significantly different ($P = .250$; $P = .500$, respectively) from those of dual-phase SPECT/CT and showed very good agreement (kappa = 0.927 and kappa = 0.952, respectively). In the subgroup of patients with secondary or tertiary HPT, dual-phase SPECT showed the highest positive rate (27.8%) followed by dual-phase SPECT/CT (26.4%). Compared with dual-phase SPECT/CT, dual-phase SPECT had the highest positive concordance rate (89.5%) followed by delayed SPECT/CT (84.2%). The results of dual-phase SPECT and delayed SPECT/CT were not statistically different ($P = 1.000$; $P = .250$, respectively) from those of dual-phase SPECT/CT and showed very good agreement (kappa = 0.824 and kappa = 0.887, respectively).

Among all 35 patients, 22 (17 primary, 3 secondary, and 2 tertiary HPT patients) had undergone exploratory parathyroid surgery (interval between SPECT/CT and surgery, 65.2 ± 45.9 days; median, 56 days; range, 1–169 days). In 16 of 17 patients with primary HPT, minimally invasive focused parathyroidectomy was performed according to the patients preoperative imaging findings. In 1 patient with primary HPT, all parathyroid glands were explored, and a 4.6-cm parathyroid mass was resected after performing a conventional transverse incision. In secondary and tertiary HPT patients, 3½ gland subtotal parathyroidectomy was performed in 4 patients after the exploration of all parathyroid glands. In 1 patient with secondary PTH who had coexisting thyroid papillary microcarcinoma, 1 enlarged parathyroid gland was resected after the exploration of all parathyroid glands including lesions shown in the imaging findings.

Among 17 primary HPT patients, adenomas were pathologically confirmed in 16 patients. In the remaining patient, a small benign parathyroid tissue was found with a thyroid tissue although parathyroid adenoma or hyperplasia was not pathologically discriminated, and the postoperative serum calcium and

Table 1

Patient characteristics.

Characteristics	Total (n = 35)	Primary HPT (n = 27)	Secondary or tertiary HPT (n = 8)
Age, years (median, range)	58 (25–87)	60 (25–87)	38 (26–51)
Sex			
Male, n (%)	11 (31%)	5 (19%)	6 (75%)
Female, n (%)	24 (69%)	22 (81%)	2 (25%)
Serum calcium, mg/dL (median, range)*	10.7 (7.0–13.3)	10.8 (8.8–13.3)	10.1 (7.0–12.9)
Intact PTH, pg/mL (median, range)*	150 (5–1860)	123 (5–690)	1065 (136–1860)
Surgery, n (%)	22 (62.9%)	17 (63.0%)	5 (62.5%)

* The normal reference range of serum calcium is 8.6 to 10.2 mg/dl, and the normal reference range of PTH is 10 to 65 pg/ml.
HPT = hyperparathyroidism, PTH = parathyroid hormone.

Table 2

Positive rate for the set of images in the patient-based analysis (n = 35).

		Comparison with dual-phase SPECT/CT				
		Concordance, n (%)				
Protocol	Positive, n (%)	Total	Positive	Negative	kappa	*P* value
Dual-phase planar	18 (51.4%)	23 (65.7%)	18 (60.0%)	5 (100%)	0.300	.001
Dual-phase SPECT	24 (68.6%)	29 (82.9%)	24 (80.0%)	5 (100%)	0.533	.014
Early SPECT/CT	26 (74.3%)	31 (88.6%)	26 (86.7%)	5 (100%)	0.650	.046
Delayed SPECT/CT	27 (77.1%)	32 (91.4%)	27 (90.0%)	5 (100%)	0.720	.083
Dual-phase SPECT/CT	30 (85.7%)	N/A	N/A	N/A	N/A	N/A

CT = computed tomography, N/A = not applicable, SPECT = single-photon emission computed tomography.

Table 3

Positive rate for each set of images in the location-based analysis (n = 315).

Protocol	Positive, n (%)	Comparison with dual-phase SPECT/CT Concordance, n (%)			kappa	*P* value
		Total	Positive	Negative		
Total locations (n = 315)						
Dual-phase planar	24 (7.6%)	290 (92.1%)	21 (48.8%)	269 (98.9%)	0.586	<.001
Dual-phase SPECT	38 (12.1%)	296 (94.0%)	31 (72.1%)	265 (97.4%)	0.731	.359
Early SPECT/CT	34 (10.8%)	306 (97.1%)	34 (79.1%)	272 (100%)	0.867	.004
Delayed SPECT/CT	38 (12.1%)	310 (98.4%)	38 (88.4%)	272 (100%)	0.929	.063
Dual-phase SPECT/CT	43 (13.7%)	N/A	N/A	N/A	N/A	N/A
Locations in primary hyperparathyroidism (n = 243)						
Dual-phase planar	14 (5.8%)	227 (93.4%)	11 (45.8%)	216 (98.6%)	0.546	.021
Dual-phase SPECT	18 (7.4%)	229 (94.2%)	14 (58.3%)	215 (98.2%)	0.636	.180
Early SPECT/CT	21 (8.6%)	230 (98.8%)	21 (87.5%)	219 (100%)	0.927	.250
Delayed SPECT/CT	22 (9.1%)	231 (99.2%)	22 (91.7%)	219 (100%)	0.952	.500
Dual-phase SPECT/CT	24 (9.9%)	N/A	N/A	N/A	N/A	N/A
Locations in secondary or tertiary hyperparathyroidism (n = 72)						
Dual-phase planar	10 (13.9%)	63 (87.5%)	10 (52.6%)	53 (100%)	0.621	.004
Dual-phase SPECT	20 (27.8%)	67 (93.1%)	17 (89.5%)	50 (94.3%)	0.824	1.000
Early SPECT/CT	13 (18.1%)	66 (91.7%)	13 (68.4%)	53 (100%)	0.761	.031
Delayed SPECT/CT	16 (22.2%)	69 (95.8%)	16 (84.2%)	53 (100%)	0.887	.250
Dual-phase SPECT/CT	19 (26.4%)	N/A	N/A	N/A	N/A	N/A

CT = computed tomography, N/A = not applicable, SPECT = single-photon emission computed tomography.

parathyroid hormone levels returned to normal. The size of the lesion ranged from 0.6 to 4.6 cm (median, 1.2 cm), and the weight ranged from 80 to 7850 mg (median, 420 mg). In 5 patients with secondary or tertiary HPT, 13 parathyroid hyperplasias (size, 1.82 ± 0.66 cm; median, 1.6 cm; range, 1.1–3.0 cm; weight, 1185 ± 1140 mg; median, 620 mg; range, 270–3920 mg) were totally resected, while 3 parathyroid hyperplasias (size 0.9 cm, 1.0 cm, and 1.0 cm, respectively) were partially resected. In all patients except 3, the serum parathyroid hormone level returned to normal after surgery. In 3 patients (2 with secondary HPT and 1 with primary HPT), the serum parathyroid hormone level was markedly decreased, the serum calcium level was normal, but the parathyroid hormone level was elevated above the normal range.

Diagnostic performance was calculated from 21 patients whose pathology was confirmed. In the patient-based analysis, the sensitivity of each image set was as follows:

1. dual-phase planar images, 61.9%
2. dual-phase SPECT, 81.0%
3. early SPECT/CT, 85.7%
4. delayed SPECT/CT, 85.7%;
5. dual-phase SPECT/CT, 100%.

The representative images were shown in Figures 1–3.

Table 4 shows the location-based analysis of the diagnostic accuracy of 16 pathologically proven parathyroid adenomas and 16 parathyroid hyperplasias in 21 patients. The dual-phase

Table 4

Diagnostic performance based on the location of the lesion (n = 189) in the patients with surgical results.

Protocol	Accuracy	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV
Total locations (n = 189)									
Dual-phase planar	88.9%	14	3	18	154	43.8%	98.1%	82.4%	89.5%
Dual-phase SPECT	92.1%	21	4	11	153	65.6%	97.5%	84.0%	93.3%
Early SPECT/CT	92.1%	20	3	12	154	62.5%	98.1%	87.0%	92.8%
Delayed SPECT/CT	93.1%	22	3	10	154	68.8%	98.1%	88.0%	93.9%
Dual-phase SPECT/CT	95.8%	27	3	5	154	84.4%	98.1%	90.0%	96.9%
Locations in primary hyperparathyroidism (n = 144)									
Dual-phase planar	92.4%	8	3	8	125	50.0%	97.7%	72.7%	94.0%
Dual-phase SPECT	93.1%	10	4	6	124	62.5%	96.9%	71.4%	95.4%
Early SPECT/CT	95.8%	13	3	3	125	81.3%	97.7%	81.3%	97.7%
Delayed SPECT/CT	95.8%	13	3	3	125	81.3%	97.7%	81.3%	97.7%
Dual-phase SPECT/CT	97.2%	15	3	1	125	93.8%	97.7%	83.3%	99.2%
Locations in secondary or tertiary hyperparathyroidism (n = 45)									
Dual-phase planar	77.8%	6	0	10	29	37.5%	100%	100%	74.4%
Dual-phase SPECT	88.9%	11	0	5	29	68.8%	100%	100%	85.3%
Early SPECT/CT	80.0%	7	0	9	29	43.8%	100%	100%	76.3%
Delayed SPECT/CT	84.4%	9	0	7	29	56.3%	100%	100%	80.6%
Dual-phase SPECT/CT	91.1%	12	0	4	29	75.0%	100%	100%	87.9%

CT = computed tomography, FN = false negative, FP = false positive, NPV = negative predictive value, PPV = positive predictive value, SPECT = single-photon emission computed tomography, TN = true negative, TP = true positive.

Table 5

Interobserver agreement in the location-based analysis.

Protocol	Agreement (%)	Fleiss' kappa
Total locations (n = 315)		
Dual-phase planar	95.3 (94.0–97.1)	0.677 (0.614–0.741)
Dual-phase SPECT	92.1 (91.4–93.3)	0.644 (0.581–0.708)
Early SPECT/CT	94.7 (93.0–96.8)	0.723 (0.659–0.787)
Delayed SPECT/CT	94.7 (92.4–96.8)	0.749 (0.685–0.812)
Dual-phase SPECT/CT	93.0 (91.4–96.2)	0.702 (0.638–0.766)
Locations in primary hyperparathyroidism (n = 243)		
Dual-phase planar	95.9 (95.1–96.3)	0.659 (0.586–0.731)
Dual-phase SPECT	93.1 (92.2–94.2)	0.589 (0.517–0.662)
Early SPECT/CT	95.3 (93.8–97.5)	0.691 (0.619–0.764)
Delayed SPECT/CT	95.1 (93.0–97.9)	0.692 (0.619–0.764)
Dual-phase SPECT/CT	93.4 (90.9–97.1)	0.639 (0.566–0.712)
Locations in secondary or tertiary hyperparathyroidism (n = 72)		
Dual-phase planar	93.5 (90.3–100)	0.704 (0.570–0.837)
Dual-phase SPECT	88.9 (83.3–97.2)	0.696 (0.563–0.829)
Early SPECT/CT	92.6 (90.3–94.4)	0.759 (0.626–0.893)
Delayed SPECT/CT	93.5 (90.3–97.2)	0.815 (0.682–0.949)
Dual-phase SPECT/CT	91.7 (88.9–93.1)	0.778 (0.644–0.911)

Data are expressed as mean (range) for pairwise agreement and point estimate (95% confidence interval) for Fleiss' kappa.

CT = computed tomography, SPECT = single-photon emission computed tomography.

SPECT/CT had the highest sensitivity (84.4%) and positive predictive value (PPV, 90.0%) among all imaging protocols. In the subgroup of patients with primary HPT, the highest sensitivity (93.8%) and PPV (83.3%) were shown for dual-phase SPECT/CT, followed by early SPECT/CT (81.3% and 81.3%, respectively) and delayed SPECT/CT (81.3% and 81.3%, respectively). In the subgroup of patients with secondary or tertiary HPT, the sensitivity decreased in the order of dual-phase SPECT/CT (75.0%), dual-phase SPECT (68.8%), and delayed SPECT/CT (56.3%).

Table 5 shows the interobserver agreement of the image analysis. In the location-based analysis of all locations, all image sets showed good agreement.

4. Discussion

As expected, the study results revealed that dual-phase SPECT/CT had the highest accuracy in all patients, including primary, secondary, and tertiary HPT, among the imaging protocols compared. Therefore, we compared the results of dual-phase SPECT/CT with the results of the other 4 protocols to obtain the concordance rates. In patients with primary HPT, SPECT/CT at any phase showed higher sensitivity (81.3%–93.8% vs 62.5%, Table 4) and positive rate (8.6%–9.9% vs 7.4%, Table 3) than dual-phase SPECT. However, in patients with secondary and tertiary HPT, dual-phase SPECT and delayed or dual-phase SPECT/CT showed higher sensitivity (56.3%–75.0% vs 43.8%, Table 4) and positive rate (22.2%–27.8% vs 18.1%, Table 3) than early SPECT/CT. Compared with dual-phase SPECT/CT, delayed SPECT/CT showed nearly a significant difference ($P = .083$), and the other 3 image sets showed significant differences, which implies that dual-phase SPECT/CT is more advantageous than dual-phase planar imaging, dual-phase SPECT, and single-phase SPECT/CT. The interobserver agreement among the protocols was good for most image sets, including those in the subgroup analyses.

Parathyroids are small glands with subcentimeter size and weigh approximately 30 to 50 mg, which are generally located adjacent to the thyroid.[16] Although parathyroid adenoma tends to be larger than normal,[17] the weight and size of the adenomas were as small as 80 mg and 0.6 cm, respectively, in this study. Considering the small size of parathyroids, we carefully set the appropriate parameters in our examinations. SPECT data were obtained with a 256×256 matrix, which led to a pixel size of 2.4 mm $\times$ 2.4 mm, instead of one with a 128×128 matrix, which is used in most studies of ^{99m}Tc-sestamibi parathyroid SPECT/CT.[12] We did not use any smoothing filter because contrast loss can make it difficult to interpret the images of small lesions.[18] The slice thickness and increment of CT were each set to 1 mm. Using our protocol, we detected 8 adenomas (50%) < 500 mg, with a minimum detectability of 80 mg (Fig. 1). The radiation exposure was reduced while increasing the resolution. Although the SPECT field was 38 cm, considering the ectopic location of the parathyroid, the CT field was limited from the angle of the mandible to the subcarina, which was approximately 20 cm. We also used tube current modulation. When the images were acquired using our protocol, the radiation doses in early and delayed CT were 0.89 ± 0.24 mSv and 0.45 ± 0.08 mSv, respectively.

In primary HPT, Lavely et al reported that early SPECT/CT combined with any kind of delayed imaging was accurate for parathyroid adenoma localization.[8] However, dual-phase SPECT/CT was the most accurate protocol in this study, and accuracy of early SPECT/CT was similar to that of delayed SPECT/CT even after reviewing the dual-phase planar images together in all protocols. In this study, a parathyroid adenoma showed uptake only in the early phase and was washed out in the delayed phase, as previously known (Fig. 2). However, another parathyroid adenoma was detected only in the delayed phase (Fig. 1); it was the smallest parathyroid adenoma (size, 0.7 cm; weight, 80 mg) in this study and was not detectable in the early phase due to the high uptake of the adjacent thyroid. However, it was detectable in the delayed phase because the contrast was better. As this lesion was extremely small, it might not have been detected if the SPECT and CT parameters were inadequate. Unlike Lavely et al, we acquired the SPECT data in a larger matrix (256×256 vs 128×128); performed CT using a later-generation SPECT/CT, which has higher CT resolution; and reviewed the images in thinner slices (1 mm vs 10 mm). These 2 cases (Figs. 1 and 2) suggest that early SPECT/CT and delayed SPECT/CT are complementary because early SPECT/CT has the advantage in evaluating parathyroid tissue with rapid washout, whereas delayed SPECT/CT has the advantage in evaluating small parathyroid tissue adjacent to the thyroid. Both dual-phase and single-phase SPECT/CT showed better performance than dual-phase SPECT and dual-phase planar imaging.

Because recent guidelines suggest that early-phase SPECT/CT is more advantageous than delayed-phase SPECT/CT, we performed early-phase CT for anatomical localization and delayed-phase CT for attenuation correction. However, anatomical localization may be more important in delayed-phase SPECT/CT, because it seems more valuable in evaluating small lesions. If CT scan should only be carried out once to reduce the radiation dosage, a delayed-phase CT is recommended, because the registration of small lesions is difficult. Because the thyroid can be used as a reference organ for registration in early-phase SPECT, the registration of early-phase SPECT on delayed-phase CT would be easier than that of delayed-phase SPECT on early-phase CT.

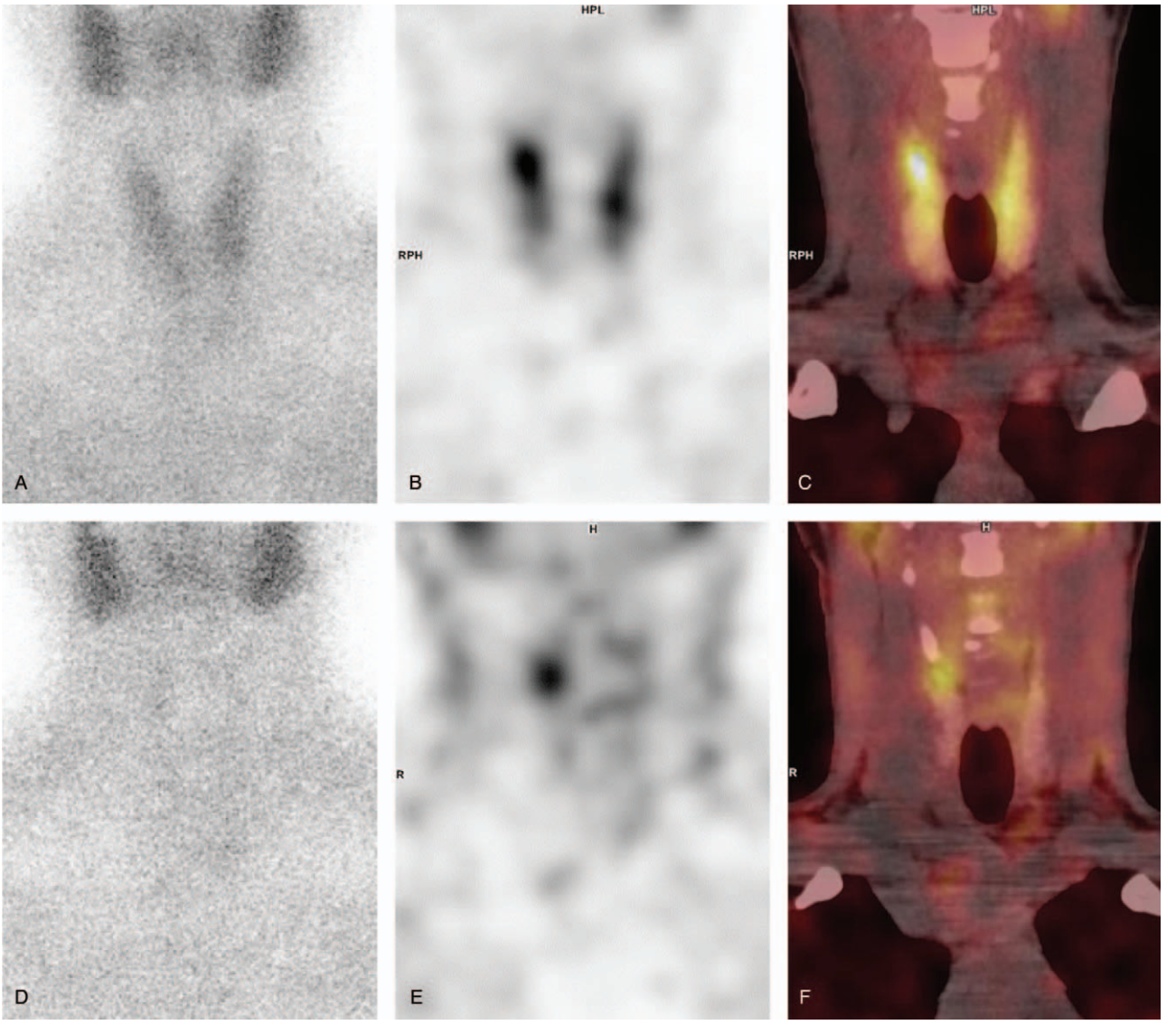

Figure 1. Parathyroid images (a: early planar, b: early SPECT, c: early SPECT/CT, d: delayed planar, e: delayed SPECT, f: delayed SPECT/CT) of a 34-year-old woman with primary hyperparathyroidism. A parathyroid adenoma (0.7 cm, 80 mg) was identified after the surgery. The lesion is considered to be positive in dual-phase SPECT, delayed SPECT/CT, and dual-phase SPECT/CT.

Secondary HPT results from vitamin D deficiency in chronic renal failure and thereby induces parathyroid hyperplasia.[19] Among patients with secondary HPT, tertiary HPT may occur that does not resolve even if chronic renal failure is corrected after kidney transplantation. Tertiary HPT is mainly caused by parathyroid hyperplasia.[20,21] The same subgroup was categorized as secondary and tertiary HPT as they may have the same pathology. Parathyroidectomy is indicated in patients with both refractory secondary and tertiary HPT,[22,23] and 3% to 8% of the patients required reoperation due to persistence or recurrence of HPT.[24,25] According to Andrade et al, patients with secondary and tertiary HPT had 91 (13.6%) out of 664 parathyroid glands located in the ectopic locations.[26] Therefore, parathyroid tissue localization before surgery is important in patients with secondary and tertiary HPT.

A few previous studies evaluated the accuracy of ^{99m}Tc-sestamibi SPECT/CT in secondary or tertiary HPT. Li et al recently reported that the sensitivity of dual-phase ^{99m}Tc-sestamibi parathyroid SPECT/CT was 98.0% in a patient-based analysis and 59.3% in a lesion-based analysis of 50 secondary HPT patients,[27] which is similar to the results of our study (100% and 75.0%, respectively), although our study evaluated only 5 patients with 16 parathyroid hyperplasia. Yang et al reported that both early- and delayed-phase ^{99m}Tc-sestamibi SPECT/CT should be performed in patients with secondary HPT because 7 of 80 patients only showed positive results in delayed SPECT/CT and 6 of 80 patients only showed positive results in early-phase SPECT/CT.[15] In our study, dual-phase SPECT/CT also showed the highest sensitivity. However, unlike Yang et al, dual-phase SPECT, delayed SPECT/CT, and dual-phase SPECT/CT showed higher sensitivity values (68.8%, 56.3%, 75.0%, respectively) and positive rates (27.8%, 22.2%, 26.4%, respectively) than early SPECT/CT (sensitivity, 43.8%; positive rate, 18.1%). This difference may have resulted from the different

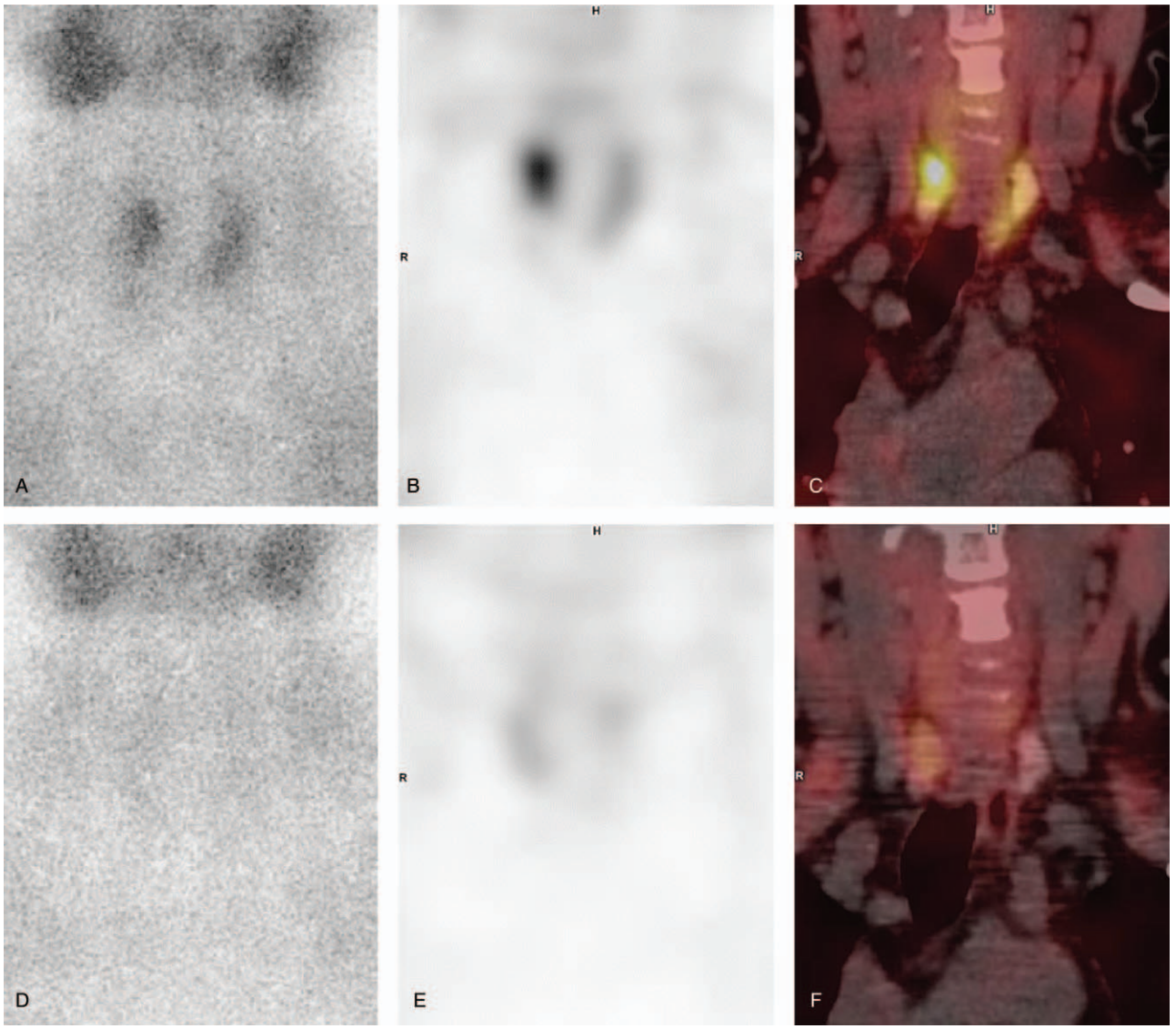

Figure 2. Parathyroid images (a: early planar, b: early SPECT, c: early SPECT/CT, d: delayed planar, e: delayed SPECT, f: delayed SPECT/CT) of a 60-year-old woman with primary hyperparathyroidism. A parathyroid adenoma (1.0 cm, 570 mg) was identified after the surgery. The lesion is considered to be positive in early-phase SPECT/CT and dual-phase SPECT/CT.

imaging acquisition protocols between the study of Yang et al and our study. Yang et al obtained only SPECT data in the delayed phase and registered with the CT data from the early phase, which may increase the chance of misregistration. By contrast, we obtained the CT data in both the early and delayed phases, although the tube current in the delayed phase (25 mA) was reduced relative to that in the early phase (80 mA). Yang et al also acquired SPECT data in a 128×128 matrix, whereas Li et al and our study used a 256×256 matrix. These differences may have led to relatively low sensitivity values in the delayed SPECT/CT and dual-phase SPECT/CT in the study of Yang et al relative to the sensitivity values in the study of Li et al and in our study. Figure 3 shows the representative images of parathyroid hyperplasia in patients with tertiary HPT. Because of the high thyroid uptake in the early phase, only 1 lesion was considered to be positive in the dual-phase planar images, 2 lesions were considered to be positive in early SPECT/CT, while 4 lesions were detected in dual-phase SPECT, delayed SPECT/CT, and dual-phase SPECT/CT.

This study had several limitations. First, we only enrolled 35 patients. The number of patients was small, especially in the secondary and tertiary HPT subgroups. Second, parathyroid hyperplasia or double adenomas were not noted in patients with primary HPT, which accounted for approximately 10% of those with primary HPT[28]; therefore, the results of our study may not be applicable in those settings. Third, since not all patients underwent surgery, the diagnostic accuracy might be biased.

In conclusion, dual-phase ^{99m}Tc-sestamibi SPECT/CT showed the highest positive rate and highest sensitivity value among the various tested protocols. As SPECT and CT images have better resolution than those used in previous studies, delayed SPECT/CT was used as complementary to early SPECT/CT in primary HPT, and delayed SPECT/CT appeared to be superior to early SPECT/CT in secondary and tertiary HPT.

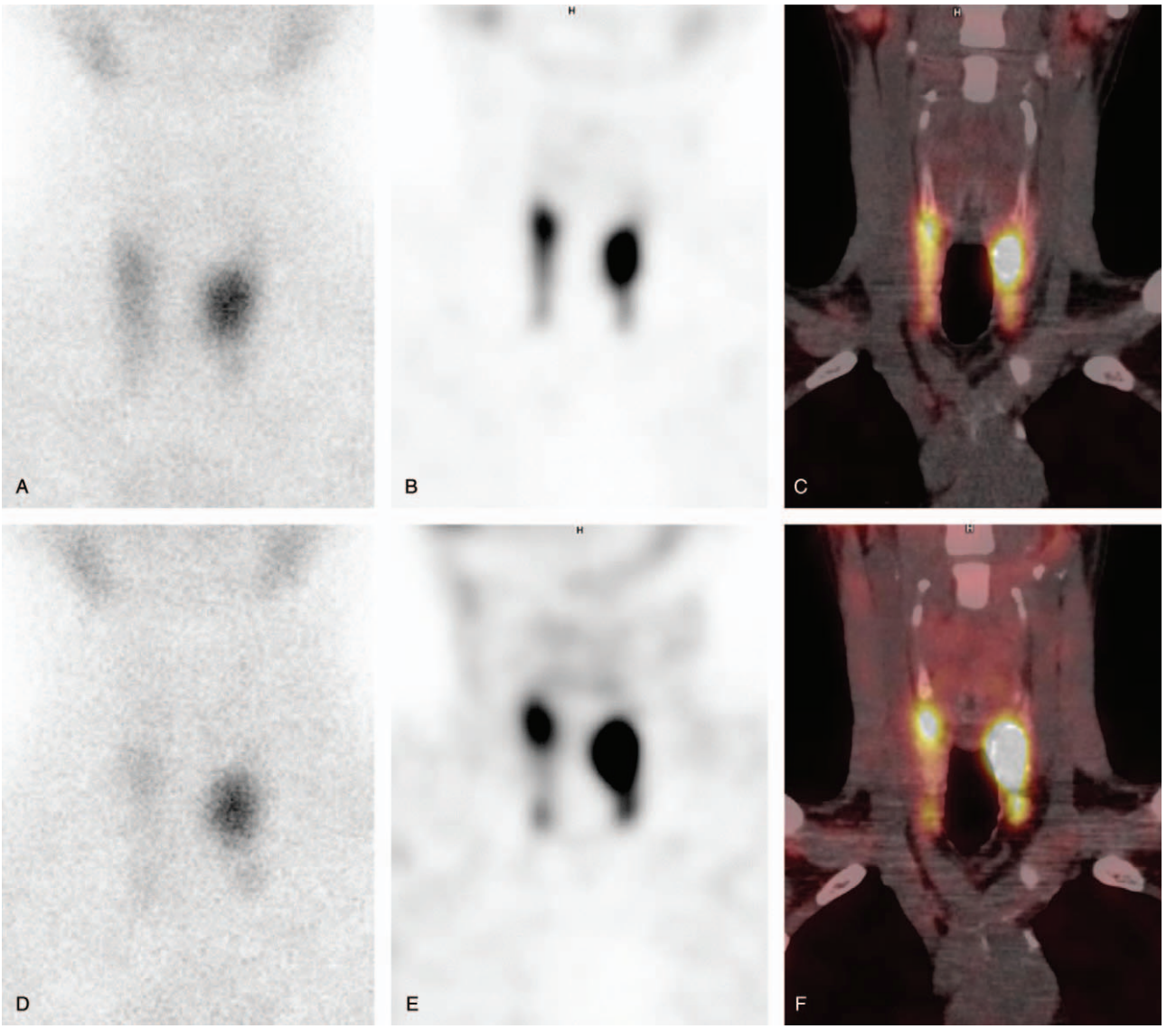

Figure 3. Parathyroid images (a: early planar, b: early SPECT, c: early SPECT/CT, d: delayed planar, e: delayed SPECT, f: delayed SPECT/CT) of a 48-year-old man with tertiary hyperparathyroidism. The patient had persistent hypercalcemia and hyperparathyroidism after renal transplantation for end-stage renal disease. Parathyroid hyperplasia (right superior: 1.5 cm, 800 mg; left superior: 3.0 cm, 3920 mg; right inferior: 1.2 cm, 450 mg; left inferior: 1.0 cm) was identified after a 3½ gland subtotal parathyroidectomy. The preoperative parathyroid hormone level was 1860.0 pg/ml and was decreased to 61.7 pg/ml postoperatively. This patient is considered to be positive in all protocols in the patient-based analysis, but only delayed SPECT/CT, dual-phase SPECT, and dual-phase SPECT/CT showed all 4 lesions in the lesion-based analysis.

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