

# Diagnostic accuracy of planar, SPECT, and SPECT/CT parathyroid scintigraphy protocols in patients with hyperparathyroidism

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## Abstract

**BACKGROUND:** Several parathyroid scintigraphy protocols have been used for preoperative localization of hyperfunctioning parathyroid glands in patients with hyperparathyroidism. The aim of this study is to compare the diagnostic accuracy of various parathyroid scintigraphy protocols.

**MATERIAL AND METHODS:** A retrospective diagnostic accuracy study with histopathology as the reference standard was done. Five imaging protocols were investigated including planar dual tracer Tc-99m pertechnetate/Tc-99m sestamibi (DT), planar dual phase Tc-99m sestamibi (DP), and combined dual tracer dual phase (DTDP) protocols, as well as add-on single photon emission computed tomography (SPECT), and single photon emission computed tomography/computed tomography (SPECT/CT).

**RESULTS:** A total of 63 patients underwent parathyroid scintigraphy and subsequent parathyroid surgery with a total of 106 excised lesions with histopathological diagnosis. On a lesion-based analysis, sensitivity and specificity (with 95% confidence interval) of protocols were as follows. DT protocol: 69.4% (53.1–82.0%) and 80.0% (49.0–94.3%); DP protocol: 78.6% (52.4–92.4%) and 33.3% (9.7–70.0%); DTDP protocol: 64.7% (47.9–78.5%) and 50.0% (18.8–81.2%); SPECT: 92.3% (66.7–98.6%) and 75.0% (30.1–95.4%); SPECT/CT: 80.0% (49.0–94.3%) and 75.0% (30.1–95.4%). All protocols had perfect sensitivity for detection of parathyroid adenoma whereas SPECT was the most sensitive method for detection of hyperplastic parathyroid glands.

**CONCLUSION:** Planar parathyroid scintigraphy using the DT protocol has a trend towards being more accurate than DP and DTDP protocols. Additional imaging with SPECT and SPECT/CT had a trend towards being more accurate than planar imaging.

**KEY words:** radionuclide imaging; parathyroid scintigraphy; SPECT; SPECT/CT; parathyroid glands; hyperparathyroidism

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## Background

Hyperparathyroidism is characterized by excessive parathyroid hormone secretion by parathyroid glands. The incidence of primary hyperparathyroidism ranges from 34 to 120 per 100,000 in women and 13 to 36 per 100,000 in men [1] and may be caused by parathyroid adenoma, hyperplasia, or rarely, parathyroid carcinoma [2]. Secondary and tertiary hyperparathyroidism are mostly found in patients with chronic kidney disease with prevalence inversely proportional to renal function [3]. Sequela of chronic hyperparathyroidism include bone loss and symptoms related to hypercalcemia as well as increased risk of cardiac death [4].

Management includes medical treatment and surgical removal of hyperfunctioning parathyroid glands. Preoperative localization of hyperfunctioning parathyroid glands can be done by various imaging modalities including ultrasound [5–8], magnetic resonance imaging [5, 9, 10], and computed tomography [5]. However, the modality most utilized is nuclear medicine isotopic imaging using various radiopharmaceuticals. Although newer positron emission tomography radiopharmaceuticals including C-11 methionine [11, 12], and F-18 fluorocholine [13, 14] have been investigated, the mainstay of radionuclide imaging in hyperparathyroidism relies on Tc-99m sestamibi which localizes in hyperfunctioning parathyroid glands. Several imaging protocols have been used. Planar imaging can be done using the dual tracer (DT) protocol where the image using Tc-99m sestamibi which localizes in both the thyroid and hyperfunctioning parathyroid lesions is compared with an image using Tc-99m pertechnetate or I-123 sodium iodide which localizes solely in the thyroid. The dual phase (DP) protocol compares two or more Tc-99m sestamibi images obtained at

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different time points and diagnosis is based on the observation that Tc-99m sestamibi washes out of the thyroid more rapidly than from hyperfunctioning parathyroid lesions [15]. Tomographic imaging including single photon emission computed tomography (SPECT) and single photon emission computed tomography/computed tomography (SPECT/CT) has been suggested to provide improved diagnostic accuracy over planar imaging [16–19]. The purpose of this study was to determine the diagnostic accuracy of various nuclear medicine parathyroid imaging techniques for preoperative localization of hyperfunctioning parathyroid glands.

## Materials and methods

This single center, retrospective, diagnostic accuracy study was approved by the authors' institutional review board (reference no. HE581328). Inclusion criteria were 1) patients diagnosed with hyperparathyroidism who 2) underwent preoperative parathyroid scintigraphy, and 3) have histopathological diagnosis of surgically excised lesions. Patients who underwent previous neck surgery were excluded.

### Parathyroid scintigraphy

Several parathyroid scintigraphy protocols are done at the authors' center. Planar imaging was done using either Vertex V60 EPIC HP dual headed gamma camera (ADAC, CA, USA), Genesys single headed gamma camera (ADAC, CA, USA), or Discovery NM/CT 670 (GE Healthcare, IL, USA) equipped with low energy high-resolution collimator with a  $128 \times 128$  imaging matrix with an energy peak set at  $140 \text{ keV} \pm 10\%$ . Patients were examined using one of the following protocols.

#### Dual tracer protocol (DT)

The patient was first intravenously injected with 130 MBq of Tc-99m pertechnetate and anterior static planar image of the neck and chest was obtained 20 minutes later. Then the patient was injected with 555 MBq of Tc-99m sestamibi, and without changing patient position another static planar image was obtained 15 minutes later.

#### Dual phase protocol (DP)

After the patient was injected with 555 MBq of Tc-99m sestamibi, an early static planar image of the neck and chest was obtained at 15 minutes. Delayed image at 60 minutes was later obtained. In some patients, further delayed images were obtained at 120 minutes and/or 180 minutes depending on the discretion of the nuclear medicine physician on duty that day.

#### Combined dual tracer dual phase protocol (DTDP)

This is a continuation of the DT protocol. In some instances, after reviewing the initial planar Tc-99m pertechnetate and Tc-99m sestamibi images, the nuclear medicine may deem that the initial images were not yet sufficient for diagnosis and may order an additional set of delayed planar Tc-99m sestamibi image to possibly provide additional information.

#### SPECT and SPECT/CT

SPECT or SPECT/CT were done in some patients in addition to planar imaging, up to the discretion of the nuclear medicine physician

on duty. The timing of SPECT or SPECT acquisition varied from 15 minutes to 120 minutes after Tc-99m sestamibi injection. SPECT and SPECT/CT may be done regardless of the initial planar protocol the patient underwent. SPECT was acquired using a  $128 \times 128$  imaging matrix in step-and-shoot mode (25 seconds/shoot, 6 degrees/step). For SPECT/CT, the non-contrast CT portion of the study was done using 120 kV, 80 mA, and 2.5 mm slice thickness.

### Image interpretation

All images were independently interpreted by two experienced nuclear medicine physicians blinded to clinical information. A third nuclear medicine physician resolved any discrepant readings. Readings included positivity of the scan, number, and location of the focal uptake (right upper, right lower, left upper, and left lower). For the DT protocol, Tc-99m pertechnetate and Tc-99m sestamibi images were visually assessed side by side, as well as by using parathyroid subtraction software included in the Xeleris 3 software suite provided by the vendor (GE Healthcare, IL, USA). For the DP protocol, early and delayed Tc-99m sestamibi images were visually assessed side by side. For the DTDP protocol, all available images including the Tc-99m pertechnetate, early Tc-99m sestamibi, subtracted image, and delayed Tc-99m sestamibi images were interpreted side by side. In patients who had additional SPECT and SPECT/CT examination, the SPECT and SPECT/CT images were interpreted separately after interpretation of the planar images.

### Reference standard

Histopathological examination was used as the reference standard. Positive lesions include parathyroid adenoma, parathyroid hyperplasia, and parathyroid carcinoma. All other histopathological readings were considered negative. The location of lesions noted in pathological reports was compared with location of focal uptake in parathyroid scintigraphy.

### Statistical analysis

Patient demographics and characteristics of histopathological findings were presented using descriptive statistics. Diagnostic performance was derived from  $2 \times 2$  contingency tables of readings from each scintigraphic protocol in relation to the reference standard. Analysis was done on a "per lesion" basis. Shapiro-Wilk test was used to test for distribution normality of continuous variables. Two-sample t-test was used to compare the size of true positive glands and false negative glands across different scintigraphic protocols. A  $p$  value of  $< 0.05$  indicates statistical significance. Accompanying 95% confidence intervals (95% C.I.) were reported appropriate. Confidence intervals for diagnostic accuracy indices were estimated using Wilson's score interval estimation for binomial proportions.

## Results

From 1 May 2006 to 31 May 2015, 290 patients were sent for parathyroid scintigraphy at the authors' center. Among these, 63 patients underwent parathyroidectomy with a total of 106 excised lesions having final histopathological diagnosis that could be compared with parathyroid scintigraphy. Patient characteristics are described in Table 1. The cohort had an average age of 48.2 years with almost equal male to female ratio. Over half of

**Table 1.** Patient characteristics

Characteristic	
Number	63 (100%)
Age (years, mean $\pm$ SD)	48.2 $\pm$ 13.8
Sex	
Male	30 (47.6%)
Female	33 (52.4%)
Type of hyperparathyroidism	
Primary	19 (30.2%)
Secondary	5 (7.9%)
Tertiary	27 (42.9%)
Undetermined	12 (19.0%)
Underlying end-stage renal disease	
Yes	33 (52.4%)
No	18 (28.6%)
Undetermined	12 (19.0%)
Time from scintigraphy to surgery (days)	
Median (IQR)	65 (45–114)
Range	2–596
Parathyroid scintigraphy protocol	
Dual tracer	24 (38.1%)
Dual phase	18 (28.6%)
Combined dual tracer dual phase	21 (33.3%)
Additional SPECT or SPECT/CT	
No	48 (76.2%)
SPECT	15 (23.8%)
SPECT/CT	7 (11.1%)

patients had underlying end-stage renal disease and were clinically diagnosed with secondary or tertiary hyperparathyroidism.

As shown in Table 2, of the 106 excised lesions, 79.2% were positive, with most of the lesions being parathyroid hyperplasia. Parathyroid adenomas accounted for about one-eighth of lesions and two parathyroid carcinomas were found. The most common negative histology was normal parathyroid glands.

Among the 63 patients, 24 patients underwent scintigraphy with the DT protocol and had 46 excised lesions that could be compared with histopathological results, 18 patients were examined with the DP protocol with 20 excised lesions, and 21 patients underwent the DTDP protocol with 40 excised lesions. The DP protocol had the highest sensitivity but poorest specificity while the DT protocol was most accurate for localizing parathyroid lesions. The DTDP protocol yielded the lowest accuracy. In addition to planar imaging, SPECT was also done in 15 patients with a total of 17 excised lesions while SPECT/CT was additionally done in 7 patients with 14 excised lesions. SPECT had a higher sensitivity of 92.3% compared with SPECT/CT which was 80.0% sensitive, while both modalities had equal specificity of 75%. However, confidence intervals of all imaging protocols overlapped, thus superiority of a single protocol over others could not be concluded. A summary of diagnostic performance of the imaging protocols are provided in Table 3.

From the 106 excised lesions, 70 parathyroid lesions had pathological report regarding lesion size. The average diameter

**Table 2.** Histopathological diagnosis of 106 surgically excised lesions

Histopathological diagnosis	Number	Percent
Parathyroid hyperplasia	69	65.1%
Parathyroid adenoma	13	12.3%
Parathyroid carcinoma	2	1.9%
Normal parathyroid gland	13	12.3%
Normal thyroid tissue	4	3.8%
Lymph node	3	2.8%
Other	2	1.9%
All	106	100.0%

was 1.8  $\pm$  0.8 cm. Across different imaging protocols, overall, true positive lesions had a trend towards being larger than false negative ones. Only in the DP technique were truly positive lesions significantly larger than falsely negative ones. Table 4 provides details of size comparison between true positive and false negative lesions.

When comparing between detection rates of various scintigraphic protocols for detection of parathyroid adenoma and parathyroid hyperplasia, all imaging protocols had 100% detection rate for parathyroid adenoma. All three planar protocols had similar sensitivity for detection of hyperplastic parathyroid glands with the DP protocol being the most sensitive. Add-on SPECT imaging improved the detection rate for parathyroid hyperplasia to 90%, but SPECT/CT provided a more modest improvement to 77.8%. Details of sensitivity of different scintigraphic protocols for detection of parathyroid adenoma and hyperplasia are provided in Table 5.

## Discussion

In this study, diagnostic accuracy of different parathyroid scintigraphy protocols was investigated using histopathological diagnosis as the reference standard. The cohort consisted mostly of patients with underlying end-stage renal disease, thus explaining the dominance of parathyroid hyperplasia as the cause of hyperparathyroidism. The DP protocol had higher sensitivity than the DT and DTDP protocols. This finding is contrary to most previous studies that reported that dual tracer had higher sensitivity than single tracer protocols [20–27]. The discrepant finding in the current study could, to some degree, be due to context bias since most of the patients sent for parathyroid scintigraphy at the authors' center have end-stage renal disease with pronounced hyperparathyroidism. It is conceivable that readers are more likely to interpret the findings as anomalies — irregularities in radiotracer uptake in the Tc-99m sestamibi image could have been interpreted as positive because the DP protocol relies only on the Tc-99m sestamibi without Tc-99m pertechnetate images outlining the thyroid for comparison. This is reflected in the specificity of the DP protocol which was the poorest among all protocols. When taking both sensitivity and specificity into account, the DT protocol had the highest accuracy with the DTDP protocol having the poorest accuracy, a finding which is not in line with a previous study which demonstrated that combined dual tracer and dual phase imaging

**Table 3.** Diagnostic performance of planar parathyroid scintigraphy protocols, SPECT and SPECT/CT

	Dual tracer		Dual phase		Combined dual tracer dual phase		Add-on SPECT		Add-on SPECT/CT	
	Value	95% C.I.	Value	95% C.I.	Value	95% C.I.	Value	95% C.I.	Value	95% C.I.
Patients	24		18		21		15		7	
Excised lesions	46		20		40		17		14	
True positive	25		11		22		12		8	
False positive	2		4		3		1		1	
False negative	11		3		12		1		2	
True negative	8		2		3		3		3	
Sensitivity	69.4%	53.1–82.0%	78.6%	52.4–92.4%	64.7%	47.9–78.5%	92.3%	66.7–98.6%	80.0%	49.0–94.3%
Specificity	80.0%	49.0–94.3%	33.3%	9.7–70.0%	50.0%	18.8–81.2%	75.0%	30.1–95.4%	75.0%	30.1–95.4%
Accuracy	71.7%	57.5–82.7%	65.0%	43.3–81.9%	62.5%	47.0–75.8%	88.2%	65.7–96.7%	78.6%	52.4–92.4%
Positive predictive value	92.6%	76.6–97.9%	73.3%	48.0–89.1%	88.0%	70.0–95.8%	92.3%	66.7–98.6%	88.9%	56.5–98.0%
Negative predictive value	42.1%	23.1–63.7%	40.0%	11.8–76.9%	20.0%	7.0–45.2%	75.0%	30.1–95.4%	60.0%	23.1–88.2%
Likelihood ratio positive	3.47	1.55–7.79	1.18	0.96–1.44	1.29	0.90–1.85	3.69	0.84–16.26	3.20	0.70–14.62
Likelihood ratio negative	0.38	0.32–0.45	0.64	0.20–2.06	0.71	0.46–1.09	0.10	0.01–0.74	0.27	0.10–0.69

**Table 4.** Comparison of size between true positive and false negative lesions

Protocol*	True positive			False negative			P-value
	Number of lesions**	Lesion size (cm.)		Number of lesions**	Lesion size (cm.)		
		Mean	S.D.		Mean	S.D.	
DT	23	1.7	0.85	10	1.3	0.71	0.0723
DP	10	2.6	0.96	3	1.2	0.91	0.0241
DTDP	17	1.8	0.57	7	1.7	0.37	0.3327
Add-on SPECT	10	2.2	0.63	1	2.0	—	—
Add-on SPECT/CT	7	2.2	0.75	1	2.0	—	—

\*DT — dual tracer protocol; DP — dual phase protocol; DTDP — dual tracer dual phase protocol

\*\*The size of some excised lesions was not mentioned in the histopathological report

**Table 5.** Sensitivity of different parathyroid scintigraphy protocols for detection of parathyroid adenoma and hyperplasia

Protocol	Parathyroid adenoma				Parathyroid hyperplasia			
	TP*	FN**	Sensitivity	95% C.I.	TP*	FN**	Sensitivity	95% C.I.
DT	3	0	100.0%	43.8–100.0%	21	11	65.6%	48.3–79.6%
DP	5	0	100.0%	56.6–100.0%	6	3	66.7%	35.4–87.9%
DTDP	5	0	100.0%	56.6–100.0%	17	11	60.7%	42.4–76.4%
Add-on SPECT	3	0	100.0%	43.8–100.0%	9	1	90.0%	59.6–98.2%
Add-on SPECT/CT	1	0	100.0%	20.7–100.0%	7	2	77.8%	45.3–93.7%

\*TP — true positive

\*\*FN — false negative

provided better accuracy than either dual tracer or dual phase alone [25]. This could be because patients who underwent DTDP imaging were patients who initially underwent DT imaging and findings from the initial Tc-99m sestamibi and Tc-99m pertechnetate images were deemed insufficient for diagnosis by the nuclear medicine physician on duty thus prompting further delayed imaging, so patients in the DTDP group represented 'difficult' patients which findings were likely to be inconclusive to begin with. Both add-on

SPECT and SPECT/CT improved the diagnostic accuracy over planar imaging alone which concurs with previous studies [5, 16–19, 28]. However, SPECT imaging appeared to have a higher diagnostic accuracy than SPECT/CT which is unexpected and contradicts a previous study which demonstrated the superiority of SPECT/CT over SPECT alone [29]. This could be because the previous study used diagnostic quality CT as opposed to low-dose CT as was used in the current study, or could be due to chance

given the small number of patients who underwent SPECT and SPECT/CT in this study.

Regarding the effect of lesion size on detection of parathyroid lesions, overall, larger lesions were more likely to be detected than smaller lesions, a finding which is in agreement with previous studies [29–31]. All imaging protocols had perfect sensitivity for detection of parathyroid adenomas but had reduced sensitivity for parathyroid hyperplasia, a finding supported by previous studies [8, 9, 18, 20, 25] and is likely because adenomas tend to be larger and have higher degree of Tc-99m sestamibi uptake than hyperplastic glands.

Limitations of the study include the retrospective design and the relatively small sample size in each scintigraphic protocol. Comparison of diagnostic accuracy between different protocols therefore represents only trends as demonstrated by the overlapping confidence intervals among all imaging protocols. Analysis of scintigraphic results in relation to laboratory data such as parathyroid hormone level could not be done, since laboratory data could not be recovered in about one-third of cases. Comparison of scintigraphic findings could be done only in relation to lesion diameter since lesion weight was not routinely documented at the authors' center.

In conclusion, for planar scintigraphy, the dual tracer protocol seemed to provide the highest accuracy for localization of hyperfunctioning parathyroid lesions in a cohort predominated by end-stage renal disease patients. SPECT and SPECT/CT improved diagnostic accuracy although superiority of SPECT/CT over SPECT alone could not be demonstrated.

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