Diagnostic value of clinical parameters and parathyroid scintigraphy for asymptomatic primary hyperparathyroidism

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Keywords: Primary hyperparathyroidism, - Single photon emission computed tomography, - Scintigraphy

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Received:
4 May 2020
Accepted revised:
24 June 2020

Abstract

Objective: The purpose of this study was to evaluate the diagnostic value of clinical parameters and parathyroid scintigraphy for asymptomatic primary hyperparathyroidism (aPHPT), including quantitative parameter of laboratory and semiquantitative parameters derived from technetium-99m-metoxyisobutylisonitrile (^{99m}Tc-MIBI) single photon emission computed tomography/computed tomography (SPECT/CT). **Patients and Methods:** Two hundred and fourteen patients who had been diagnosed as PHPT and underwent surgical treatment were enrolled in this study. All patients were divided into two groups: aPHPT and symptomatic PHPT (sPHPT). Dual tracer ^{99}Tc-pertechnetate/^{99m}Tc-MIBI, dual time point and tomography scintigraphy with ^{99m}Tc-MIBI SPECT/CT were performed. Clinical parameters included basic information, serum calcium (Ca), phosphorus (P), parathyroid hormone (PTH) and alkaline phosphatase (ALP) levels. Semiquantitative parameters of parathyroid scintigraphy included the average counts of early parathyroid (PT_1), late parathyroid (PT_2), early thyroid (T_1) and late thyroid (T_2), the ratio of PT_1/T_1 (R_1), the ratio of PT_2/T_2 (R_2), parathyroid washout ($PTW=(PT_1-PT_2)/PT_1$) and retention index ($RI=(R_2-R_1)/R_1$). $P<0.05$ was considered as statistically significant. **Results:** A total of 167 aPHPT patients (46 males, 121 females) were studied. One hundred and seventy four parathyroid glands were removed after operation: 146 (87.4%) lesions were adenoma, 12 (7.2%) lesions were hyperplasia and 1 (0.6%) lesion was adenocarcinoma. There were significant differences in previous history (P=0.000), echo of parathyroid (P=0.004), thyroid function (P=0.029), clinical course (Z=-3.422, P=0.001), ^{99m}Tc-pertechnetat thyroid uptake (TcTU) (Z=-2.126, P=0.033), serum Ca level (t=-2.926, P=0.004) and serum PTH level (Z=-3.028, P=0.002) between aPHPT and sPHPT. For patients with aPHPT, there were significant differences for serum Ca level (t=2.832, P=0.005), R_2 (Z=-2.597, P=0.009) and RI (Z=-2.100, P=0.036) between adenoma and hyperplasia, and serum Ca level in aPHPT patients with adenoma was significantly higher compared with patients with hyperplasia. The areas under the curve (AUC) of clinical course, TcTU, serum Ca and PTH levels were 0.662, 0.399, 0.642 and 0.645 respectively for differential diagnosis of aPHPT and sPHPT. The AUC of R_2 and RI were 0.737 and 0.692 respectively for differential diagnosis of adenoma and hyperplasia in patients with aPHPT. The sensitivity, negative predictive value (NPV) and accuracy for diagnosing aPHPT combined ^{99m}Tc-MIBI SPECT/CT with ultrasound (US) were significantly higher than dual tracer, dual time point, ^{99m}Tc-MIBI SPECT/CT and US, which were 97.5%, 95.2% and 55.6% respectively. **Conclusions:** Laboratory inspection and semi-quantitative parameters of parathyroid scintigraphy had higher value for differential diagnoses of aPHPT and sPHPT, the same for adenoma and hyperplasia in patients with aPHPT. When combined ^{99m}Tc-MIBI SPECT/CT with US, the diagnostic efficiency would be significantly improved.

Hell J Nucl Med 2020; 23(2): 148-157 *Epub ahead of print: 27 July 2020* *Published online: 24 August 2020*

Introduction

Primary hyperparathyroidism (PHPT) is a common kind of endocrine system disease that is being diagnosed based on the increased serum calcium (Ca) or parathyroid hormone (PTH) levels [1-2]. The common pathological types include adenoma, hyperplasia and carcinoma, in which adenoma is in the majority [3-5]. The clinical presentation of PHPT would change from asymptomatic PHPT (aPHPT) to severe disease with multiple organs and systems were involved in [1].

In clinical practice, about 80% of patients with PHPT were aPHPT and incidentally discovered when serum Ca and PTH levels were routinely measured [6-8]. There were few studies to evaluate the incidence or prevalence of aPHPT specifically [9]. The study of Sun B et al. (2018) showed the number of symptomatic PHPT (sPHPT) and aPHPT patients increased 1 to 2.5 times and 1.5 to 3 times respectively from 2005 to 2016 in Shanghai [10], and over time some of these patients with aPHPT would progress to sPHPT. Even the patients with aPHPT did not meet guidelines for surgery, parathyroidectomy was appropriate as long as he or she had not medical contraindications [1].

Minimally invasive surgery has been successfully applied in aPHPT, which depend on accurately preoperative localization. Ultrasound (US), technetium-99m metoxyisobutylisonitrile (^{99m}Tc-MIBI) scintigraphy and computed tomography (CT) is commonly used [11, 12]. Technetium-99m-MIBI single photon emission computed tomography (SPECT) had been used for parathyroid scintigraphy for several years [7], which based on that ^{99m}Tc-MIBI washes out more rapidly from the thyroid gland than from hyper-functioning parathyroid glands [8]. But the sensitivity and specificity was limited because of inaccurate localization. Single photon emission computed tomography/CT as a kind of functional and anatomical examination could provide much more located information. There were few studies about semi-quantitative parameters of ^{99m}Tc-MIBI SPECT/ CT for PHPT, which showed the semi-quantitative parameters derived from ^{99m}Tc-MIBI SPECT/CT might have correlation with clinical parameters, such as serum Ca, phosphorous (P), and PTH levels [12-14].

The purpose of this study was to evaluate the diagnostic value of clinical parameters and parathyroid scintigraphy for aPHPT. The semi-quantitative parameters derived from ^{99m}Tc-MIBI SPECT/CT would be involved in. The outcomes of this study could provide clinical evidence for the rational application of clinical parameters and ^{99m}Tc-MIBI SPECT/CT.

Patients and Methods

Patients

Following institutional ethics committee approval, this study performed a retrospective review for the hospital information system about the patients diagnosed as PHPT in Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University from September 2013 to November 2019. The inclusion criteria were as follows: diagnosed as PHPT, with US and parathyroid scintigraphy within one month before operation and with parathyroidectomy. Patients presented with any of the following conditions were excluded: secondary hyperparathyroidism, tertiary hyperparathyroidism and other causes of hypercalcemia such as vitamin D intoxication, malignancy, medications and other endocrine diseases, abnormal urea nitrogen and creatinine values.

Clinical parameters collected from the hospital information system included the basic information, the first symptoms, clinical course, previous history, serum Ca, P, PTH and alkaline phosphatase (ALP) levels during two weeks before operation, the outcomes of US and parathyroid scintigraphy and postoperative pathology and so on.

Parathyroid scintigraphy

All patients underwent examination of the dual tracer (^{99m}Tc-pertechnetate/^{99m}Tc-MIBI) and dual time point ^{99m}Tc-MIBI SPECT/CT during one month before operation. Technetium-99m-pertechnetat planar scintigraphy was performed in the first day. Then in the next day, early (at 5min) and delayed (at 120min) planar scintigraphy of the neck after the injection of 925 MBq ^{99m}Tc-MIBI have been performed. The tomography scintigraphy at 120min with SPECT/CT was performed with low-energy high-resolution collimators (140Kev energy peak, 20% window width, 128×128 matrix, 1.0 zoom, 30s every frame) and the function of CT (5mm slice thickness, 140Kev tube voltage and 2.5mA current). After processing by Xeleris Function Imaging Workstation: Version 4.0, the images of parathyroid scintigraphy was analyzed with qualitative and semi-quantitative analysis by two independent nuclear medicine physicians. If the patient had more than one focus, the result was recorded, respectively.

Semi-quantitative parameters have been extraced from ^{99m}Tc-MIBI planar scintigraphy, which included the average counts of early parathyroid (PT_1) and late parathyroid (PT_2), early thyroid (T_1) and late thyroid (T_2), the ratio of PT_1/T1 (R_1), the ratio of PT_2/ T_2 (R_2), parathyroid washout (PTW=(PT_1-PT_2)/PT_2) and retention index (RI=(R_2-R_1)/R_1) were recorded respectively (Figure 1). When the patients had ≥2 lesions, the average value of all lesions was recorded.

Diagnostic criteria

The normal reference value of serum Ca, P, PTH and ALP levels were (2.11-2.52)mmol/L (equalled to (8.46-10.10)mg/dL),

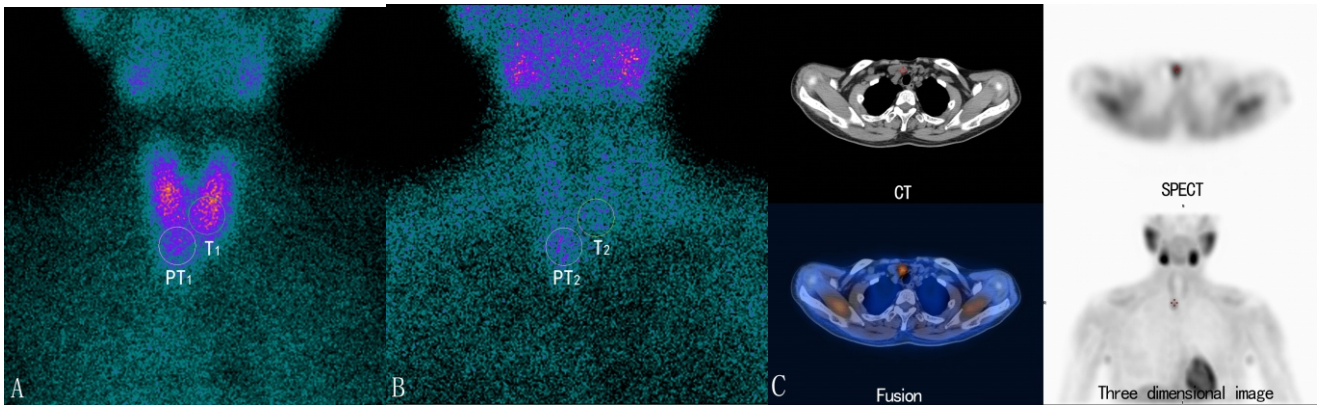

Figure 1. A 45-year-old woman with aPHPT in which a parathyroid adenoma has been confirmed. Regions of interest of equal pixel numbers were drawn around the abnormal parathyroid and the contralateral normal thyroid. Parathyroid scintigraphy (**A:** early-phase ^{99m}Tc-MIBI planar scintigraphy. **B:** delayed-phase ^{99m}Tc-MIBI planar scintigraphy. **C:** ^{99m}Tc-MIBI SPECT/CT) showed a mildly increased focal uptake below the right lower pole of the thyroid and a nodule in corresponding area on SPECT/CT (red cross).

(0.85-1.51)mmol/L, (15-65)ng/L (equalled to(15-65)pg/dL) and (35-135)U/L, respectively. Both of localization and qualitative diagnosis were correct was defined as diagnostic criteria of parathyroid scintigraphy or US for aPHPT, one of SPECT/CT or US was correct was defined as diagnostic criteria of combined SPECT/CT with US.

Statistical analysis

Standard statistical analysis was performed using SPSS 19.0. All quantitative and semi-quantitative results were expressed as mean±SD or minimum, maximum, mean and range of 25%-75%. Independent samples t test and Mann-Whitney U test were applied to assess the diagnostic value. Pearson's chi-squared test and Fisher's exact test were proceeded to evaluate the qualitative datum. If there was significant difference, the receiver operating characteristic (ROC) curve was established. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of parathyroid scintigraphy and US was analyzed. $P<0.05$ was considered as statistically significant.

Results

Basic information of PHPT and aPHPT

A total of 214 PHPT patients (65 males, 149 females, average age 54.76±12.21years) were studied. All patients were divided into two groups: 167 patients with aPHPT (46 males, 121 females, average age 55.31±11.39years) and 47 patients with "sPHPT" (19 males, 28 females, average age 52.79±14.72 years), without significant differences in gender (χ^2= 2.877, P=0.090) and age (t=1.254, P=0.211). In the group of aPHPT, 174 parathyroid glands were removed after operation: 146 (87.4%) lesions were adenoma, 12 (7.2%) lesions were hyperplasia and 1 (0.6%) lesion was adenocarcinoma. Fisher's exact test was proceeded. There were significant differences in previous history (P=0.000), echo of parathyroid (P=0.004), thyroid function (P=0.029), serum Ca level (t=-2.926, P= 0.004), serum PTH level (Z=-3.028, P= 0.002), clinical course (Z=-3.422, P=0.001) and ^{99m}Tc-pertechnetat thyroid uptake (TcTU) (Z=-2.126, P=0.033) between aPHPT and sPHPT (Tables 1-3).

Table 1. *Qualitative parameters of PHPT patients.*

Qualitative parameters		PHPT (n=214)	aPHPT (n=167, 78.0%)	sPHPT (n=47, 22.0%)
Previous history	No	74(34.6%)	57(34.1%)	17(36.2%)
	Stone	35(16.4%)	20(12.0%)	15(31.9%)
	Fracture	5(2.3%)	1(0.6%)	4(8.5%)
	Operation	80(37.4%)	75(44.9%)	5(10.6%)
Pathology	Adenoma	185(86.7%)	146(87.4%)	40(85.1%)
	Hyperplasia	18(8.4%)	12(7.2%)	6(12.8%)
	Adenocarcinoma	1(0.5%)	1(0.6%)	0(0.0%)
Location	Upper-left	27(12.6%)	20(12.0%)	7(14.9%)
	Lower-left	76(35.5%)	62(37.1%)	14(29.8%)
	Upper-right	26(12.1%)	21(12.6%)	5(10.6%)
	Lower-right	75(35.0%)	57(34.1%)	18(38.3%)
	≥2 lesions	10(4.7%)	7(4.2%)	3(6.4%)

(continued)

Echo of parathyroid	Hypoecho	172(80.4%)	142(85.0%)	30(63.8%)
	Hyperechoic	8(3.7%)	5(3.0%)	3(6.4%)
	Mixed echo	9(4.2%)	4(2.4%)	5(10.6%)
	Isoechoic	9(4.2%)	4(2.4%)	5(10.6%)
	Negative	16(7.5%)	12(7.2%)	4(8.5%)
US of thyroid	Negative	66(30.8%)	50(29.9%)	16(5.1%)
	Nodular goiter	119(55.6%)	94(56.3%)	25(53.2%)
	Thyroiditis	28(13.1%)	22(13.2%)	6(12.8%)
	Thyroid cancer	1(0.5%)	1(0.6%)	0(0.0%)
Thyroid function	Normal	185(86.4%)	150(89.8%)	35(74.5%)
	Hypothyroidism	6(2.8%)	4(2.4%)	2(4.3%)
	Hyperthyroidism	6(2.8%)	4(2.4%)	2(4.3%)
	Contradictory	1(0.5%)	1(0.6%)	0(0.0%)

Table2. *The result of independent samples t test of parameters for patients with PHPT.*

	PHPT (n=214)		**aPHPT (n=167)**		**sPHPT (n=47)**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**t**
PT_1	16.49	6.69	16.50	6.29	16.47	5.33	0.028
R_1	1.26	0.49	1.24	0.50	1.31	0.43	-0.778
Ca(mmol/L)	2.90	0.31	2.87	0.31	3.02	0.31	-2.926*
P(mmol/L)	0.83	0.19	0.83	0.18	0.80	0.22	1.114

** meant significant difference*

Table 3. *Mann-Whitney U test of quantitative and semiquantitative parameters for patients with PHPT.*

	PHPT （n=214）				aPHPT(n=167)				sPHPT(n=47)			
	Mean (SD)	**Maxi -mum**	**Mini -mum**	**Median (range)**	**Mean (SD)**	**Maxi -mum**	**Mini -mum**	**Median (range)**	**Mean (SD)**	**Maxi -mum**	**Mini -mum**	**Median (range)**
Clinical course (m)	17.07 (38.13)	360.00	0.00	2.00 (1.00-12.00)	11.55 (33.33)	360.00	0.00	2.00 (1.00-7.00)	36.66 (47.63)	192.00	0.20	12.00 (1.00-60.00)
Maximum diameter (cm)	1.93 (0.93)	9.00	0.50	1.91 (1.50-2.20)	1.92 (1.00)	9.00	0.50	1.80 (1.30-2.10)	1.96 (0.94)	3.80	0.50	2.00 (1.50-2.30)
Thyroid weight (g)	32.51 (12.46)	101.65	10.85	30.41 (26.27-37.21)	32.68 (13.00)	101.65	10.85	30.54 (25.42-37.21)	31.91 (10.45)	61.23	17.62	29.75 (25.03-37.06)
TcTU (%)	1.30 (1.03)	6.20	0.00	1.10 (0.60-1.70)	1.37 (1.04)	6.20	0.00	1.20 (0.70-1.70)	1.07 (0.97)	5.90	0.00	0.80 (0.50-1.40)
ALP (U/L)	143.13 (145.41)	1806.00	4.80	113.00 (84.50-159.50)	128.70 (77.56)	498.00	4.80	105 (82.00-156.00)	195.50 (271.76)	1806.00	53.00	118.50 (94.50-179.50)
PTH (ng/L)	251.30 (280.18)	2043.00	22.99	159.60 (113.80-242.70)	216.27 (202.59)	1385.00	22.99	150.00 (106.90-227.70)	375.77 (441.70)	2043.00	74.06	206.5 (136.90-409.30)
T_1	14.09 (8.17)	106.88	2.71	13.40 (10.54-15.89)	14.31 (8.11)	106.88	5.80	13.44 (10.66-15.92)	13.18 (4.60)	25.94	2.71	13.10 (10.44-15.68)
PT_2	8.41 (4.44)	26.74	0.33	7.63 (5.23-10.22)	8.57 (4.29)	21.75	0.33	7.88 (5.30-10.60)	7.81 (4.98)	26.74	2.29	5.88(4.57-9.93)
T_2	5.40 (2.59)	18.72	0.87	5.18 (3.67-7.00)	5.56 (2.65)	18.72	0.87	5.30 (3.80-7.06)	4.81 (2.29)	10.19	1.71	4.41 (3.04-6.26)
R_2	1.66 (0.79)	4.99	0.38	1.39 (1.14-1.96)	1.66 (0.82)	4.99	0.38	1.39 (1.14-1.93)	1.66 (0.63)	3.09	0.9	1.51 (1.15-2.05)
PTW	3.83 (1.55)	48.79	-0.76	0.96 (0.46-1.75)	1.56 (4.22)	48.79	-0.76	0.94 (0.44-1.58)	1.52 (1.47)	7.41	0.06	1.12 (0.66-2.07)
RI	0.48 (1.46)	17.55	-0.61	0.26 (0.06-0.53)	0.52 (1.62)	17.55	-0.61	0.26 (0.07-0.53)	0.33 (0.46)	1.54	-0.33	0.25 (-0.03-0.46)

Comparison between adenoma and hyperplasia in patients with aPHPT

In patients with aPHPT, there were 146 patients diagnosed as adenoma (41 males, 105 females, average age 55.31± 11.35years) and 12 patients diagnosed as hyperplasia (4 males, 8 females, average age 53.75±12.72years), without significant differences in gender (continuity correction χ^2= 0.003, P=0.956) and age (t=0.375, P=0.708). There were significant differences for serum Ca level (t=2.832, P=0.005), R_2 (Z=-2.597, P=0.009) and RI (Z=-2.100, P=0.036), and serum Ca level in patients with adenoma was significantly higher than patients with hyperplasia (Tables 4 and 5). The outcomes of Spearman's rank correlation showed there were no correlation between serum Ca level and RI (r=0.082, P= 0.336), and serum Ca level and R_2 (r=0.029, P=0.746).

Table 4. *The results of Independent samples t test of parameters for patients with aPHPT.*

	Adenoma (n=146)		Hyperplasia (n=12)		t
	mean	SD	mean	SD	
PT_1	16.576	6.437	15.821	4.352	0.381
R_1	1.260	0.510	1.100	0.237	1.027
Ca(mmol/L)	2.893	0.287	2.639	0.425	2.832*
P(mmol/L)	0.826	0.178	0.902	0.190	-1.521

** meant significant difference*

ROC curve

Because parts of parameters were significant differences, ROC curves were delineated to evaluate the diagnostic values (Figures 2 and 3). The areas under the curve (AUC) of clinical course, TcTU, serum Ca level, serum PTH level were 0.662 (P=0.001), 0.399 (P=0.034), 0.642 (P=0.003) and 0.645 (P=0.002), respectively for differential diagnosis of aPHPT and sPHPT. Best clinical course, TcTU, serum Ca level, serum PTH level were 21.00m, 0.85%, 2.78mmol/L and 125.85ng/L, respectively. The AUC of R_2 and RI were 0.737 (P=0.009) and 0.692 (P=0.036) respectively and the AUC of serum Ca level was 0.676 (P=0.054) for differential diagnosis of adenoma and hyperplasia in patients with aPHPT. Best R_2 and RI were 1.25 and -0.0015, respectively.

Diagnostic efficacy of parathyroid scintigraphy

The sensitivity, accuracy and NPV of combined ^{99m}Tc-MIBI SPECT/CT with US for diagnosing aPHPT were significantly higher than dual tracer, dual time point, ^{99m}Tc-MIBI SPECT/CT and US, which were 97.5%, 95.2% and 55.6%, respectively (Table 6).

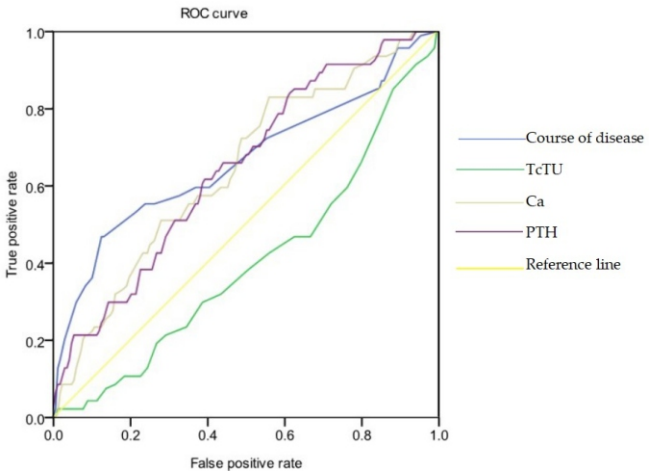

Figure 2. The ROC curves of clinical course, TcTU, serum Ca level, serum PTH level for differential diagnosis of aPHPT and sPHPT. The AUC of clinical course and serum Ca and PTH levels were between 0.6-0.7, with significant differences (all P<0.05).

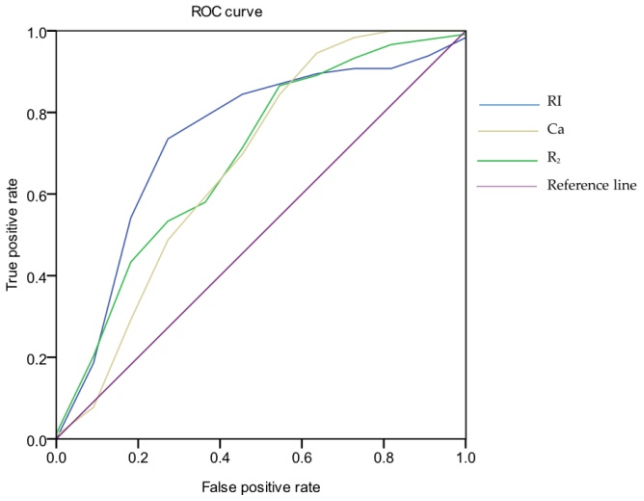

Figure 3. The ROC curves of R_2, RI and serum Ca level for differential diagnosis of adenoma and hyperplasia in patients with aPHPT. The AUC of R_2 was 0.737 (P= 0.009), with much more value.

Discussion

As a milder presentation of PHPT [9], the patients with aPHPT would have no typical symptoms [1]. Along with the introduction of the multichannel serum autoanalyzer in the 1970s, much more patients with PHPT were diagnosed. The study of Heath H 3rd et al. (1980) showed the increase in incidence was associated with a significant change in clinical spectrum, as the proportion of patients diagnosed as aPHPT rose from 18% to 51% during 1965 to 1976 in Rochester of Unite State [15]. The proportion of aPHPT patients rose from 10%-20% to approximately 45% of PHPT patients in 1990-1995 in Japan [16]. The prevalence rate of aPHPT was 0.2% in 2154 elderly subjects in Beijing in 2007 [17]. The prevalence rate of aPHPT in PHPT had increased from <21% in 2000-2006 to 42.4% to

Table 5. *Mann-Whitney U test of quantitative and semiquantitative parameters for patients with aPHPT.*

	Adenoma(n=146)				Hyperplasia(n=12)			
	Mean (SD)	Maxi -mum	Mini -mum	Median (range)	Mean (SD)	Maxi -mum	Mini -mum	Median (range)
Clinical course (m)	12.11 (34.58)	360.00	0.00	2.00 (1.00-8.00)	4.50 (4.21)	12.00	1.00	2.00 (1.00-7.00)
Maximum diameter (cm)	1.94 (0.99)	9.00	0.50	1.80 (1.48-2.18)	1.67 (0.63)	3.00	0.93	1.55 (1.13-2.00)
Thyroid weight (g)	32.71 (12.99)	101.65	10.85	30.59 (25.62-37.21)	28.52 (10.47)	45.38	13.96	28.10 (20.81-39.29)
TcTU (%)	1.39 (1.08)	6.20	0.00	1.20 (0.70-1.80)	1.18 (0.78)	2.80	0.30	1.00 (0.63-1.38)
ALP (U/L)	129.88 (78.40)	498.00	4.80	109.50 (82.00-157.50)	124.17 (89.01)	390.00	61.00	101.00 (77.25-131.75)
PTH (ng/L)	212.23 (193.31)	1385.00	22.99	151.35 (106.98-227.70)	263.97 (298.25)	1129.00	57.84	158.25 (100.21-291.23)
T_1	14.22 (9.31)	106.88	5.80	13.42 (10.67-15.76)	14.91 (4.83)	22.11	8.31	14.88 (10.84-20.35)
PT_2	8.74 (4.34)	21.75	0.33	8.14 (5.32-11.58)	7.88 (4.20)	19.85	4.26	7.06 (6.14-8.30)
T_2	5.54 (2.74)	18.72	0.87	5.22 (3.78-6.98)	6.10 (1.65)	8.87	3.56	5.96(4.83-7.42)
R_2	1.68 (0.78)	4.87	0.38	1.47 (1.19-2.01)	1.44 (1.20)	4.99	0.82	1.03 (0.94-1.22)
PTW	1.58 (4.53)	48.79	-0.76	0.87 (0.41-1.53)	1.27 (0.81)	2.42	-0.12	1.35 (0.66-1.93)
RI	0.55 (6.44)	17.55	-0.61	0.28 (0.08-0.54)	0.25 (0.70)	2.26	-0.23	-0.01 (-0.14-0.30)

Table 6. *The results of Pearson's chi-squared test (P_1) and Fisher's exact test (P_2) for diagnostic efficacy.*

	Dual tracer	Dual time point	^{99m}Tc-MIBI SPECT/CT	US	^{99m}Tc-MIBI SPECT/CT with US	χ^2	P_1	P_2
Sensitivity(%)	82.3	47.5	89.2	84.2	97.5	145.995*	0.000*	
Specificity(%)	33.3	66.7	22.2	44.4	55.6			0.432
Accuracy(%)	79.6	48.5	85.6	82.0	95.2	121.801*	0.000*	
PPV(%)	95.6	96.2	95.3	98.5	97.5			0.863
NPV(%)	9.7	6.7	10.5	13.8	55.6			0.005*

**meant significant difference.*

52.5% in 2007-2010 in China [18]. In 2012, several scholars proposed the concept of "aPHPT", which was introduced to describe patients who lack obvious signs and symptoms referable to either excess Ca or PTH [19]. Clarke BL (2019) proposed the prevalence estimated at 1:1,000 in men and 2-3: 1,000 in women in 2019 [9]. The outcomes of our study showed 78% PHPT patients were diagnosed as aPHPT and females were 2.5 times as many as males, similar with the above studies. The changes in the nutritional status of vitamin D in China might have reduced the racial disparity.

There were a few studies to distinguish the risk factors for patients with aPHPT. The study of Tay YD et al. (2018) showed mean serum Ca level was 10.5±0.5mg/dL (range:9.9-11.8mg/dl) and that of PTH was 86.9±42ng/L (range:26-290ng/L) in New York for aPHPT [20]. There were other studied proposed scrum of Ca and PTH was generally within 1mg/dL of the upper limit of the normal range [12,16] and within 1.5-2 times above the upper limit of normal respectively for aPHPT [21]. One study (2013) in China was to describe the changing clinical patterns of PHPT in Chinese patients from 2000 to 2010 [18]. In this study, 38.6% were aPHPT. The outcomes showed the sPHPT patients had significantly higher serum Ca, PTH and ALP levels and lower serum P level compared with aPHPT patients, which also could be used to differential pathological type for aPHPT patients [18], the same with the study of Bae JH et al. (2012) [22]. The ROC analysis revealed serum Ca and PTH levels were greater than 2.77mmol/L and 316.3pg/dL, respectively had excellent capacity to differentiate the sPHPT patients from aPHPT patients [18]. The patients with aPHPT could have higher ALP level (114±48)U/L and lower serum P level (2.7±0.4)mg/dL [23]. Our study showed serum Ca and PTH levels were (2.87± 0.31)mmol/L and 150.00(106.90-227.70)ng/L in aPHPT and serum Ca level in patients with adenoma was significantly higher compared with patients with hyperplasia (AUC= 0.676, P=0.054). When the concentrations of Ca and PTH were greater than 2.78mmol/L (AUC=0.642, P=0.003) and 125. 85ng/L (AUC=0.645, P=0.002), respectively could be used to differentiate the sPHPT from aPHPT, with poor performance. The reason for the low diagnostic value might be due to the widespread of general health examination and the improvement of the nutritional condition, most of the patients with aPHPT were diagnosed in the early stages with low serum Ca and PTH levels. Other parameters, such as maximum diameter, location and ALP and so on were similar between aPHPT and sPHPT, which was similar with above studies.

In addition, our study also showed there was significant difference in previous history and the clinical course. More than 40% of aPHPT patients had a history of surgery, such as caesarean, trauma and malignant tumor. The mean and median of the clinical course for aPHPT were shorter than sPHPT. Other study (2007) showed causal relationships between clinic course or hypercalcemia and malignancy seems unlikely, given that the risk of breast cancer remains unchanged at least 15 years after parathyroid adenomectomy [24]. Our study had excluded malignant tumors that could cause hypercalcemia. We speculated that after operation the patient would be remind to review regularly, which was helpful for the diagnosis of aPHPT more early, but the outcome showed the clinical course had poor performance. Between aPHPT and sPHPT, there were significant differences in thyroid function and TcTU. The study of Sloan DA et al. (2015) showed 31% of PHPT had thyroid disease (hypothyroidism most commonly), and 22% of patients had palpable thyroid abnormalities unrecognized in 67% of cases by the referring physicians [25]. Our study showed the US of thyroid had no significant difference between aPHPT and sPHPT. But thyroid function and TcTU were significant differences between the two groups, but most parameters of TcTU were in the normal range and without performance. The possible reason might be the abnormal serum levels of PTH, vitamin D and Ca would affected the levels of angiogenic growth factors [26], which might play a vital role in various thyroid diseases through prompting angiogenesis. The echo of parathyroid also was different between the two groups. Because the interference of artificial factors, the difference had no clinical significance and would not be discussed here.

Although the patients with aPHPT lacked typical symptoms, it could involve multiple organs and systems along with the time [9]. In 2014 the National Institutes of Health (NIH) published the fourth edition of the guidelines for the management of aPHPT, which proposed the indications for parathyroid surgery during monitoring [12]. In a previous study (2008) that had a follow-up of 15 years, up to 37% of the previously aPHPT, non-surgery-eligible patients would meet surgery criteria during the follow-up [27]. Recent consensus indicated that aPHPT patients might have improved outcomes after curative surgery [9]. Along with the development of the minimally invasive parathyroidectomy, preoperative localization became much more important. Various diagnostic modalities were suggested to preoperative localization for PHPT [9, 12]. The study of Nafisi Moghadam R et al. (2017) was to compare parathyroid scintigraphy and US for localization of parathyroid adenoma with a systematic review and meta-analysis of the literature [28]. The outcomes showed a pooled sensitivity of 83% for parathyroid scintigraphy and 80% for US and with similar results for specificity, without significant differences between the two methods in terms of sensitivity and specificity. But in this study, subgroups of parathyroid scintigraphy including planner and tomography scintigraphy were not be analyzed. Ogo A et al. (2014) study offered a proposal that parathyroid scintigraphy should be performed whenever possible, as this modality is anticipated to play an important role in determining whether or not surgery is appropriate [29]. Other study (2018) showed parathyroid scintigraphy had better sensitivity than US in the location of parathyroid adenoma and 93% of the cases were correctly localized when located by parathyroid scintigraphy combined with US [30]. Beyond the dual tracer and dual time point ^{99m}Tc-MIBI SPECT, our study involved the tomography scintigraphy with SPECT/CT. For diagnosing aPHPT, the sensitivity and accuracy of combined ^{99m}Tc-MIBI SPECT/CT with US were significantly higher than other methods, which were greater than other studies [11, 28, 30]. But the specificity and PPV of combined ^{99m}Tc-MIBI SPECT/CT with US were unsatisfactory and would result

in false positive and false negative, which need to be promoted by the skills of the doctors in the departments of nuclear medicine and US.

The semi-quantitative parameters of parathyroid scintigraphy were analyzed in our study. All the semi-parameters could not be used for differential diagnosis of aPHPT and sPHPT. Only R_2 and RI had significant differences between adenoma and hyperplasia in patients with aPHPT and were no correlation with serum Ca level, which was significant difference between the two groups. R_2 had much more value for the diagnosis. There was a study (2018) to analyse the value of multiple semi-quantitative parameters of dual-phase ^{99m}Tc-MIBI SPECT in PHPT [13]. The outcomes showed only R_2 and was significantly higher in the group with serum Ca level of more than 11mg/dL, which might predict disease severity in PHPT [13]. The tumor to background ratios in the 10 min (TBT10) and 120min (TBT120) had a high correlation coefficient in the parathyroid adenoma and parathyroid hyperplasia groups for the patients with PHPT and only TBT10 had differential diagnosis value for different pathological types [14]. The possible reasons for the differences in the results might include: background correction for every parameter was used in some studies, the semi-quantitative parameters were from planar images by visual interpretation, the thyroid disease might change the radioactive distribution and several parathyroids were closed to thyroid with low radioactivity distribution.

In conclusion, most patients with PHPT were asymptomatic. Early diagnosis and early treatment were very important for the patients with aPHPT. Clinical parameters and laboratory inspections were the key information for the diagnosis and differential diagnosis of aPHPT and the semi-quantitative parameters of parathyroid scintigraphy should be supplemented. When combined ^{99m}Tc-MIBI SPECT/CT with US, the diagnostic efficiency would be significantly improved. There were few studies to analyze the differences in thyroid function for the patients with aPHPT. We will continue to follow up for the long term regarding, especially for aPHPT patients with thyroid disease, including cure rate, relapse rate and mortality, and expect parathyroid scintigraphy could be used for the prognostic evaluation of aPHPT patients with or without thyroid disease.

The authors declare that they have no conflicts of interest

Funding

This study was funded by Health Commission of Zhejiang Province, China (no. 2018ZD022).

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