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Long-term prognosis of parathyroid function in chronic dialysis patients after PEIT—a single-centre trial

Reika Tanaka[1], Takatoshi Kakuta[1], Fumihiko Koiwa[2], Masafumi Fukagawa[3] and Akira Saito[1]

[1]Department of Internal Medicine, Tokai University School of Medicine, [2]Department of Internal Medicine, Division of Nephrology, Showa University Fujigaoka Hospital and [3]Division of Nephrology and Dialysis Center, Kobe University School of Medicine, Japan

Abstract

Background. Secondary hyperparathyroidism (SHPT) is a common complication observed in long-term dialysis patients. Percutaneous ethanol injection therapy (PEIT) of parathyroid glands (PTGs) is now established in Japan as a treatment option for SHPT. In this study, to elucidate the factors influencing efficacy in 1 year and relapse following PEIT, we analysed the long-term prognosis of parathyroid function that is known to have the greatest effect on therapeutic results.

Methods. The study design was a retrospective cohort study. We studied 104 patients with SHPT, who underwent PEIT at Tokai University Hospital between January 1993 and December 2002, and we followed them up until January 2008. The effective group reached intact parathyroid hormone of 200 pg/ml or less, corrected calcium (Ca) of 10.5 mg/dl or less and phosphate (P) of 6.0 mg/dl or less. The ineffective group failed to achieve these criteria.

Results. Among the 104 patients, 66 patients (63%) fulfilled the criteria for the effective group within the first year of PEIT. Using the multivariate logistic regression analysis, the number of PTGs before PEIT was a significant risk factor to deviate from the criteria. At the end of the surveillance period, 31 patients (30%) fulfilled the criteria, and their SHPT was controlled with PEIT. Using the multivariate logistic regression analysis, more than three PTGs at the beginning, and the increase in PTGs during the observation period were significant risk factors to deviate from the criteria. In conclusion, superior results with PEIT are obtained in terms of efficacy, remission period and risk of relapse, regardless of the size of the gland.

Keywords: haemodialysis; long-term prognosis; parathyroid gland; percutaneous ethanol injection therapy; secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism (SHPT) is one of the most widespread and important abnormalities of mineral metabolism in patients with chronic kidney disease (CKD). In addition to fractures and bone pain caused by osteitis fibrosa, this condition causes ectopic calcification associated with elevated calcium (Ca) and phosphate (P) products. In recent years, hypercalcaemia and hyperphosphataemia have also been associated with reduced life expectancy [1,2]. There are several medical therapies, including intravenous pulse infusion of calcitriol and its analogue (maxacalcitol) [3–5], but when patients become resistant to drug therapy, hypercalcaemia, hyperphosphataemia and ectopic calcification may develop [6]. For these patients, surgical removal of the enlarged parathyroid gland (PTG) (parathyroidectomy, PTx) is usually necessary to control parathyroid hormone (PTH) secretion [7–10]. In Japan, with its high proportion of long-term dialysis patients, we can anticipate an increase in the incidence of SHPT. Percutaneous ethanol injection therapy (PEIT) of parathyroid tumours under ultrasound (US) guidance was developed in Italy in 1985 as an alternative to PTx as an intervention for SHPT unresponsive to medical treatment [11]. This method grew in popularity in Japan during the 1990s as a treatment for resistant SHPT [12–18]. But there were two main reasons why dialysis centres had reservations or hesitated about performing PEIT, namely the possibility of recurrent nerve paralysis and the difficulty in confirmation of recurrent nerve paralysis in cases of PTx following PEIT, because of the presence of adhesions. These problems cause clinicians to favour PTx as the initial surgical treatment. It is important to improve the outcome for PEIT by preventing transudation of the drug outside the target PTGs and avoid unnecessary procedures. In this study, we evaluated the long-term prognosis of parathyroid function after PEIT and remission period.

Methods

Subjects

One hundred and four CKD patients with SHPT underwent PEIT at Tokai University Hospital between January 1993

Correspondence and offprint requests to: Reika Tanaka, Department of Internal Medicine, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-1193, Japan. Tel: +81-463-93-1121 (Ext. 2350); Fax: +81-463-91-3350; E-mail: kakuta@is.icc.u-tokai.ac.jp

and December 2002, and we were able to follow them up until January 2008. Each patient's follow-up time began with the date of the first PEIT and continued until the PTx, renal transplant, death or until 31 January 2008, whichever came first. The study design was a retrospective cohort study. Prior to the publication of the Japanese PEIT Guidelines in 2000 [19], PEIT was performed in accordance with the following indications. The indications for PEIT of the PTGs were (i) intact parathyroid hormone (iPTH) of 400 pg/ml or more; (ii) the presence of hyperplastic PTGs detectable by ultrasonography (no limit on the number of affected glands); (iii) serum corrected Ca 10.5 mg/dl or more; (iv) SHPT resistant to medical treatment; (v) the use of activated vitamin D formulations as adjuvant therapy (no specification as to type or dosage), (vi) the presence of high-turnover bone disease according to the measurement of bone metabolism markers or plain X-ray and (vii) informed consent given to undergo PEIT.

After the year 2000, PEIT was performed in accordance with the guidelines for PEIT of the PTG in chronic dialysis patients, published by the Japanese Working Group of PEIT of the Parathyroid [19]. In summary, these are as follows: (i) iPTH of 400 pg/ml or more; (ii) verification of osteitis fibrosa or high bone turnover (confirmed radiologically or by bone metabolism markers); (iii) estimated volume of enlarged PTGs of 0.5 cm^3 or more detectable by ultrasonography, or suspected nodular hyperplasia because of the increased intraglandular vascularity, and judged to be treatable even if 0.5 cm^3 or less; (iv) resistance to medical treatment and (v) informed consent given to undergo PEIT.

Definitions

Resistance to medical treatment is defined as the PTH level above the target range despite administration of vitamin D or analogues, and uncontrollable serum Ca and P levels. Patients with hypercalcaemia were excluded when it was determined that the hypercalcaemia was drug induced. PEIT procedures performed at an interval of up to 6 months were regarded as one cycle of treatment. Activated vitamin D preparations were administered immediately after each PEIT procedure. No limitation on the type or dosage of medications was given for the purpose of this study. The dose of ethanol injected depended on the volume of the gland but never exceeded 80% of the estimated volume ($\pi/6 \times a \times b \times c$; the diameters of the gland's three dimensions).

Post-PEIT management

Activated vitamin D preparations were administered immediately after each PEIT procedure. No limitation on the type or dosage of medications was set for the purpose of this study. The efficacy of PEIT was determined at 2–4 weeks later by measuring the serum corrected Ca, P and iPTH. If these factors do not reach to the target range, PEIT should be repeated at a PTG with blood flow. Every 1–3 months, serum Ca, P and iPTH were measured. If these levels increase again, ultrasonographic examination should be repeated and additional PEIT should be planned. The effective group reached iPTH of 200 pg/ml or less, corrected Ca of 10.5 mg/dl or less and P of 6.0 mg/dl or less. The ineffective group failed to achieve these criteria.

Measurements

Serum iPTH was measured using the two-site immunoradiometric method (Nichols Institute, San Juan Capistrano, CA, USA). US examinations were performed using an Aloka SSD-5000 unit (Aloka Co. Ltd, Tokyo, Japan) with 7.5 MHz transducers.

Statistical analyses

To investigate the significant factors influencing efficacy of PEIT, we used the univariate logistic regression model, and then analysed it using the multivariate logistic regression model. We used the following factors for analysis: serum corrected Ca, P, iPTH (the median value for category), number of PTGs, number of PTGs with an estimated volume of 0.5 cm^3 or more, and increase in PTGs. The level of significance was defined as $P < 0.05$.

Results

There were 104 patients (67 males and 37 females) who were observed for more than 5 years after PEIT. Their average age was 53.6 ± 10.9 years and their average dialysis period was 168.2 ± 69.8 months. None of the patients had diabetes mellitus as a primary disease (Table 1).

The average conservative duration with PEIT for the all 104 patients until the end of the follow-up period was 78.7 ± 34.7 months. After that, 18 patients died, 23 patients underwent PTx and 2 patients received renal transplantation. Causes of death for the 18 patients were cardiac disease in 6 patients, cerebrovascular disease in 7 patients and others in the remaining 5 patients. There was no direct relationship between the PEIT and the cause of death in all institutions.

Effectiveness of PEIT

Among the 104 patients, 66 patients (63%) fulfilled the three criteria for the effective group (i.e. Ca of 10.5 mg/dl or less, P of 6 mg/dl or less and iPTH of 200 pg/ml or less), within the first year of PEIT. The remaining 38 patients (37%) did not fulfil at least one criterion and they were designated as the ineffective group (Table 2). However, seven more patients fulfilled the three criteria after the second year onwards.

Table 1. Baseline characteristics of the patients

Variable	($n = 104$)
Male/female	67/37
Age (years)	53.6 ± 10.9
Duration of haemodialysis (months)	168.2 ± 69.8
Duration of following PEIT (months)	78.7 ± 34.7
Primary cause of CKD	
Glomerulonephritis	83
Other	21
Diabetes mellitus	0

Table 2. Clinical and laboratory backgrounds of the patients on the effectiveness of PEIT within 1 year

Variable	Effective	Ineffective	*P*
Subjects *n* (%)	66 (63.4%)	38 (36.6%)	
Male/female	45/21	22/16	
Age (years)	53.4 ± 11.4	54.0 ± 9.9	N.s
Duration of hemodialysis (months)	165.3 ± 70.3	173.2 ± 69.5	N.s
Calcium corrected (mg/dl)	10.78 ± 0.92	10.77 ± 0.86	N.s
Phosphorus (mg/dl)	6.00 ± 1.27	5.82 ± 1.03	N.s
Mean ± SD	622.0 ± 245.6	811.0 ± 423.0	0.013
Median	548	686	
Number of parathyroid glands (PTG)	2.18 ± 0.99	2.81 ± 0.87	0.001
	No. of patients	No. of patients	
1	18	2	
2	27	12	
3	12	15	
4	9	9	
No. of PTGs with ≥ 0.5 cm^3	0.96 ± 0.77	1.29 ± 0.93	0.058
	No. of patients	No. of patients	
0	19	9	
1	33	12	
2	12	14	
3	2	3	

Mann–Whitney U test.

Table 3. Univariate analysis of the effectiveness of PEIT within 1 year

Factor	*P*–value	OR	95% CI
Age (every 1 year)	0.760	1.006	0.969–1.044
Duration of haemodialysis (every 1 month)	0.577	1.002	0.996–1.007
Calcium corrected (every 1 mg/dl)	0.974	0.993	0.635–1.551
Phosphorus (every 1 mg/dl)	0.390	0.869	0.631–1.197
Intact PTH (every 1 pg/ml)	0.010	1.002	1.000–1.003
Intact PTH (⩾600 pg/ml)	0.061	2.187	0.964–4.961
No. of PTGs (every 1 gland)	0.002	1.992	1.278–3.105
No. of PTGs (3 or 4/1 or 2)	0.002	3.673	1.589–8.459
No. of PTGs with ≥0.5 cm^3 (every 1 gland)	0.054	1.681	0.992–2.640
No. of PTGs with ≥0.5 cm^3 (2, 3 or 4/0 or 1)	0.026	2.701	1.128–6.470

Univariate logistic regression model.

To evaluate the effectiveness of PEIT within 1 year, univariate logistic regression analysis of significant factors was performed. There was no significant difference of age, dialysis period and serum corrected Ca and P concentrations between the two groups. However, significant difference was observed in iPTH ($P < 0.01$) and the number of hyperplastic PTGs before PEIT ($P < 0.002$).

The OR of 3.673 (CI 1.589–8.459) was observed for the three PTGs in comparison with up to two PTGs before PEIT. The OR became 2.701 (CI 1.128–6.47) for more than two PTGs of 0.5 cm^3 or more, in comparison with zero or one PTG of 0.5 cm^3 or more (Table 3). These factors were analysed using the multivariate logistic regression model and it was observed that the number of more than three PTGs before PEIT, in comparison with up to two PTGs, was the significant factor with the OR 2.902 (CI 1.189–7.082) (Table 4).

Table 4. Multivariate analysis of the effectiveness of PEIT within 1 year

Variable	*P*-value	OR	95% CI
No. of PTGs (3 or 4/1 or 2)	0.019	2.902	1.189–7.082
Intact PTH (⩾600 pg/ml)	0.102	2.059	0.866–4.894
No. of PTGs with ≥0.5 cm^3 (2, 3 or 4/0 or 1)	0.177	1.926	0.744–4.986

Multivariate logistic regression model.

Effectiveness at the end of the surveillance period

1. At the end of the surveillance period, 31 patients (30%) fulfilled the three criteria and SHPT was controlled with PEIT.
2. Although not all the three criteria were fulfilled, 50 patients (48%) were maintained with PEIT.
3. Twenty-three patients (22%) underwent PTx (Table 5).

At the end of the surveillance period, the following factors were evaluated between the effective group of 31 patients and the ineffective group of 73 patients. In addition to the Ca, P, iPTH, number of hyperplastic PTGs and number of PTGs of 0.5 cm^3 or more at the start of surveillance, the presence or absence of the increased PTG was evaluated, because the number of PTGs might have changed during the surveillance period (Table 6).

Using the univariate logistic regression analysis, there was no significant difference in the starting age, dialysis period and starting serum corrected Ca and iPTH concentrations between the two groups. However, the starting number of PTGs, number of PTGs of 0.5 cm^3 or more, P concentration and the presence or absence of increased PTGs were significant factors. When one hyperplastic PTG before PEIT was designated as 1, the OR for two hyperplastic PTGs was 4.350 (CI 1.381–13.705), for three hyperplastic PTGs was 5.250 (1.468–18.772) and for four hyperplastic PTGs was 7.500 (1.626–34.591). When zero or one of the PTGs of 0.5 cm^3 or more was designated as 1, the OR for two PTGs or more was 5.478 (CI 1.520–19.742). The OR became 4.571 (CI 1.262–16.556) when the number of PTGs increased during the surveillance period (Table 6).

The multivariate logistic regression analysis was done using the factors that had showed significance in the univariate logistic regression analysis. More than three PTGs at the beginning, and the increase in PTGs during the observation period were significant risks to deviate from three criteria. Concerning the risk of deviation during the long-term surveillance after PEIT, when up to two PTGs at the beginning were designated as 1, the OR was 3.027 (CI 1.042 to 8.795) for three PTGs or more. When a new PTG was observed during the period, the OR became 6.816 (CI 1.697–27.386) (Table 7).

Changes in number and size of PTGs detected by ultrasonography

Compared with the beginning of PEIT in 104 patients, 27 patients (26%) showed increased PTGs and 13 patients (13%) showed decreased PTGs on ultrasonography. Nineteen patients (18%) showed increased PTGs of 0.5 cm^3 or

Table 5. Backgrounds of the patients on the effectiveness of PEIT at the end of surveillance ($n = 104$)

Variables	Effective	Ineffective			Effective	Ineffective		
	PEIT($n = 31$) Baseline	PEIT($n = 50$) Baseline	PTx ($n = 23$) Baseline	*P*	PEIT($n = 31$) Final	PEIT($n = 50$) Final	PTx ($n = 23$) Final	*P*
Male/female	17/14	37/13	10/13					
Age (years)	55.1 ± 11.7	53.7 ± 10.2	51.4 ± 113	N.s.				
Duration of HD (months)	185.7 ± 79.6	158.8 ± 63.0	165.2 ± 68.3	N.s.				
Duration of following PEIT (months)					84.8 ± 28.1	86.0 ± 36.7	54.3 ± 27.8	0.003
Calcium corrected (mg/dl)	10.75 ± 1.09	10.74 ± 0.80	10.90 ± 0.83	N.s.	10.01 ± 0.28	10.17 ± 0.48	10.99 ± 0.79	0.001
Phosphorus (mg/dl)	6.36 ± 1.44	5.92 ± 1.18	5.55 ± 1.15	N.s.	5.20 ± 0.58	5.70 ±1.33	6.16 ± 1.21	0.013
Intact PTH (pg/ml)	685.8 ± 290.1	667.1 ± 273.8	751.0 ± 481.0	N.s.	130.9 ± 55.7	343.3 ± 186.3	878.6 ± 307.7	0.001
Median	632.1	585.5	605.1		142.3	292.5	860.3	
No. of PTGs	2.00 ± 1.00	2.46 ± 0.97	2.87 ± 0.81	0.005	2.06 ± 1.09	2.64 ± 0.98	3.43 ± 0.66	0.001
	No. of patients	No. of patients	No. of patients		No. of patients	No. of patients	No. of patients	
1	12	8	0		13	8	0	
2	10	20	9		7	12	2	
3	6	13	8		7	20	9	
4	3	9	6		4	10	12	
No. of PTGs with ≥ 0.5 cm^3	0.80 ± 0.60	1.14 ± 0.90	1.30 ± 0.93	N.s.	0.45 ± 0.50	0.62 ± 0.70	1.35 ± 0.93	0.001
	No. of patients	No. of patients	No. of patients		No. of patients	No. of patients	No. of patients	
0	9	14	5		17	24	4	
1	19	18	8		14	22	10	
2	3	15	8		0	3	6	
3	0	3	2		0	1	3	
No. of patients with increased PTGs					3	15	9	
No. of patients with increased PTGs ≥ 0.5 cm^3					2	8	9	
No. of patients with undetective PTGs					0	1	8	
No. of additional PEIT					No. of patients	No. of patients	No. of patients	
0					23	19	3	
1					4	20	16	
2					3	8	4	
>3					1	3	0	

Kruskal–Wallis H test.

Table 6. Univariate analysis of the effectiveness of PEIT at the end of surveillance

Variable	*P*-value	OR	95% CI
Age (every 1 year)	0.350	0.981	0.943–1.021
Duration of HD (every 1 month)	0.099	0.995	0.989–1.001
Calcium corrected (every 1 mg/dl)	0.855	1.045	0.653–1.671
Phosphorus (every 1 mg/dl)	0.046	0.710	0.507–0.995
Intact PTH (every 1 pg/ml)	0.913	1.000	0.999–1.001
Intact PTH ($\gtrless$600 pg/ml)	0.931	0.964	0.416–2.233
No. of PTGS (every 1 gland)	0.018		
1		1.000	
2	0.012	4.350	1.381–13.705
3	0.011	5.250	1.468–18.772
4	0.010	7.500	1.626–34.591
No. of PTG with ≥ 0.5 cm^3 (2, 3 or 4/0 or 1)	0.009	5.478	1.520–19.742
Increased PTGs	0.021	4.571	1.262–16.556
Increased PTGs with ≥ 0.5 cm^3	0.036	1.800	1.040–3.116
Efficacy of PEIT during 1 year (ineffective/effective)	0.058	2.531	0.968–6.618

Univariate logistic regression model.

Table 7. Multivariate analysis of the effectiveness of PEIT at the end of surveillance

Variable	*P*-value	OR	95% CI
No. of PTGS (3 or 4/1 or 2)	0.042	3.027	1.042–8.795
Increased PTGs	0.007	6.816	1.697–27.386
No. of PTGs with ≥ 0.5 cm^3 (2, 3 or 4/0 or 1)	0.115	3.007	0.759–12.468

Multivariate logistic regression model.

more and 41 patients (39%) showed a decrease. Moreover, PTGs were confirmed in a position difficult to be detected by ultrasonography in nine patients. Eight patients out of these nine patients underwent PTx.

Complications

Two patients among 104 patients had hypodermal bleedings after PEIT and 6 patients had transitory roughness of voice. Both were slight in intensity and had recovered within 1 month of the outpatient follow-up surveillance.

Discussion

SHPT is a common complication observed in long-term dialysis patients. PEIT is now established in Japan as a treatment option for SHPT and its cost is covered by the National Health Insurance (NHI) System. When selective PEIT, the standard procedure in Japan, is performed, hyperplastic PTGs that are resistant to medical treatment are destroyed, and then an adjuvant vitamin D preparation is

administered to treat remaining glands that are responsive to therapy [12–19].

We have reported that selective PEIT was an appropriate treatment for the remaining PTGs after PTx [15]. During 3 years of surveillance, maintenance therapy with PEIT was possible even for multiple PTGs of 0.5 cm^3 or more [17]. PEIT deviation risk was higher in patients with two or more PTGs of 0.5 cm^3 or more [18]. In this study, the long-term prognosis after PEIT was evaluated in 104 patients, who were able to receive surveillance of 5 years or more by our hospital up to the end of January 2008. The standard for effectiveness was set at serum corrected Ca <10.5 mg/dl, P <6 mg/dl and iPTH <200 pg/ml. Patients who were not able to meet all these three criteria were in the ineffective group. In this study, 63% of the 104 patients were in the effective group and 37% of the patients were in the ineffective group within the first year after PEIT. Conditions to maintain good parathyroid function within 1 year after PEIT were (1) presence of up to two hyperplastic PTGs at the beginning ($P = 0.019$) and (2) iPTH <600 pg/ml at the time of PEIT ($P = 0.102$). Although there was a tendency towards effectiveness, a significant difference was not observed ($P = 0.177$) between the group with up to one PTG of 0.5 cm^3 or more and the group with two or more PTGs of 0.5 cm^3 or more using the multivariate logistic regression model. However, when the OR of the former group was designated as 1, the OR of the latter group was 1.926. We assumed that it did not contradict our previous report [18]. We previously assumed that the existence of the responsive gland of 0.5 cm^3 or more was the major cause that deterred the effectiveness of PEIT. It was thought that the PTG of 0.5 cm^3 or less became a responsive gland only when it enlarged and became 0.5 cm^3 or more. However, considering the fact that the number of all PTGs, including the glands of 0.5 cm^3 or less, influenced the effectiveness of PEIT, glands of 0.5 cm^3 or less were also the cause of the high PTH. When the effectiveness was not achieved, they were subjected to PEIT. However, the possibility of achieving the effectiveness was low when there were a lot of glands to confirm, and PTx was considered necessary.

When the multivariate analysis was done using factors that became significant by the univariate analysis, the difference was only seen between the group of up to two glands and the group of three glands or more. Although an iPTH of more than or less than 600 pg/ml was not a significant factor in the multivariate analysis, it was assumed to be a factor to forecast whether PEIT treatment would be effective within 1 year or not.

Among the 66 patients of effective group within the first year of PEIT, 24 patients met all of the three criteria until the end of the surveillance period. The remaining 42 patients deviated from one or more of the three criteria. Among them, 12 cases had an increase in the number of glands, and 4 cases had the enlargement of the confirmed glands. For the long-term maintenance with PEIT, regular image examination was necessary to detect the appearance of new PTGs during surveillance and to monitor the size and blood flow of existing glands.

On the other hand, patients who fulfilled the three criteria and whose SHPT was controlled at the end of the surveillance period were 30% of the entire cases, and 22% underwent PTx. The remaining 48% had an average iPTH level of 343.3 ± 186.3 pg/ml and an emphasis was put on the control of Ca and P (Table 5).

It was possible to maintain good parathyroid function after PEIT until the end of surveillance by using the medical treatments together [20]. The criteria were different from those for the acquisition of the effectiveness within 1 year. They did not contain the iPTH value at PEIT. They applied to cases with one or two hyperplastic PTGs or more, at the first time of PEIT. When there were three glands or more at the beginning of PEIT, the risk of deviation from effectiveness was an OR of 3.027. We have reported that it was possible to maintain the multiple hyperplastic PTGs with PEIT during 3 years of surveillance. In this study of >5 years, among the 45 patients who had three or more hyperplastic PTGs at the beginning, 9 patients met all of the three requirements at the end of the surveillance period. In these cases, the proper parathyroid function maintenance period after PEIT until the end of surveillance period was 83.8 ± 17.8 months (62.0–112.8 months). PTGs regressed during the surveillance period in these cases, and there was no case with more than two PTGs of 0.5 g or more at the end of the surveillance period. We observed eight cases in which PEIT was ineffective although there were only one or two hyperplastic PTGs at the beginning. In these cases, PTGs were situated in a position where detection and blood flow evaluation by ultrasonography was difficult; also, injection into these glands itself was difficult.

Recently, we performed PTx in cases where one to two courses of PEIT did not show clinical effectiveness. We considered whether effectiveness was achieved within the first year or not, as a factor of effectiveness at the end of the surveillance period. Statistically, although it was not significant, we assumed that the tendency of effectiveness was observed at $P = 0.058$ and OR 2.531.

For the application and long-term maintenance with PEIT, it is necessary to confirm the number of PTGs and the number of glands of 0.5 cm^3 or more at the beginning, and do additional PEIT when a new gland or enlarged gland appears in the regular image examination during surveillance. When the PEIT ineffectiveness continues in spite of these managements, existence of a gland difficult to be detected by ultrasonography should be suspected. When it exists, and when regular surveillance is impossible, it might be necessary to select PTx.

Among the 104 cases, there were 41 cases in which the number of PTGs of 0.5 cm^3 or more decreased during surveillance. Therefore, we assumed that it is possible to reduce the volume of enlarged PTG by PEIT. Afterwards, administration of vitamin D3 will be indispensable to control the SHPT that might arise from the remaining glands. However, Ca might rise easily, and being not able to administer enough vitamin D3 was one of the difficult reasons to maintain with PEIT. Although strict management of Ca and P is critical, the use of new medicines such as calcimimetics can increase the number of cases who can possibly be maintained with PEIT in the future [21].

In conclusion, superior results with PEIT are obtained in 1 year and long terms (>5 years) of efficacy, remission period and risk of relapse when it is restricted to patients with no more than two hyperplastic glands,

regardless of the PTG size. When a new PTG growth was observed during the period, the OR of ineffective treatment became 6.816.

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Conflict of interest statement. None declared.

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