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The Preservation and Autotransplantation of the Parathyroid Glands in Total Thyroidectomy in Patients With Thyroid Cancer—A Strategy for Avoiding Permanent Hypoparathyroidism

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Hypoparathyroidism is a complication that occurs after total thyroidectomy (TT) in patients with thyroid cancer. We tried to determine a strategy for avoiding permanent hypoparathyroidism. A total of 42 patients underwent TT for thyroid cancer between April 2009 and March 2014. One or more parathyroid glands (PGs) could be macroscopically preserved in all of the patients. First, we evaluated the association between the number of PGs that were macroscopically preserved and the postoperative course in 28 patients without autotransplantation. The number of preserved PGs was not associated with postoperative tetany or the serum levels of calcium or phosphorous on postoperative day 1, or the proportion of patients who needed to take calcium supplements or a vitamin D analog. However, only the patients with a single preserved PG required calcium supplementation for longer than 1 year (33.3%, $P < 0.05$). Next, we compared the clinical course with PG autotransplantation in 16 patients in whom a single PG was preserved. Although the result was not statistically significant, only the patients without autotransplantation required calcium supplementation for longer than 1 year. To avoid permanent hypoparathyroidism after TT, it should be essential to preserve at least 2 PGs or to preserve 1 PG and perform autotransplantation.

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Hypoparathyroidism is a major complication after total thyroidectomy. The condition leads to deterioration in the quality of life due to its characteristic symptoms and the extra medical expenses associated with regular hospital visits or the calcium and/or vitamin D analog supplementation. Transient hypocalcemia and permanent hypoparathyroidism have been reported to occur in 12.5% to 27.9% and 0.3% to 1.5% of patients undergoing total thyroidectomy, respectively.[1–4]

In patients with papillary thyroid cancer (PTC), which tends to spread to the lymph nodes of the neck, central neck dissection is considered to be a risk factor for hypoparathyroidism.[5] There have been few reports on the relationship between the number of preserved parathyroid glands (PGs) and postoperative hypoparathyroidism. Song *et al*[6] analyzed the relationship between the number of microscopically preserved PGs and hypoparathyroidism and found that transient hypoparathyroidism was increased when incidental parathyroidectomy occurred and that there was no association between the number of preserved PGs and permanent hypoparathyroidism. We hypothesized that the results might not be conclusive because all the PGs that were removed incidentally could not be found in routine pathologic examinations due to their small size. We generally identify PGs intraoperatively by their characteristic yellowish features.

In the present study, we analyzed the relationship between the number of macroscopically preserved PGs and the postoperative courses, and evaluated the utility and indications of PG autotransplantation, in order to determine a strategy for avoiding permanent hypoparathyroidism after total thyroidectomy in thyroid cancer patients.

Patients and Methods

We reviewed the clinical and laboratory data of 42 consecutive thyroid cancer patients with 1 year or more of follow-up who had undergone first-time total thyroidectomy in our department between April 2009 and March 2014. This retrospective study was approved by the institutional review board of our institution, and the requirement to obtain informed consent was waived. All of the thyroidectomies were performed via conventional open surgery. Central lymph node dissection was performed if PTC was confirmed. Lateral lymph node dissection was performed if lateral node metastasis was suspected before the operation. The operating surgeons identified the number of macroscopically preserved PGs and decided whether to perform autotransplantation. After extraction, part of the presumed PG was confirmed to be a PG by a frozen section examination. Each PG was sliced into sections of 1 mm in diameter and grafts were implanted into the separated muscle pockets of the sternocleidomastoid muscle; the muscle was then closed with absorbable sutures. The number of PGs microscopically preserved was determined by subtracting the number of pathologically proven PGs in a given thyroid or lymph node specimen from 4.[6]

On postoperative day 1, we measured the serum calcium (Ca) and phosphorous (P) levels in all the patients, normal levels of which were 8.8 to 10.1 and 2.7 to 4.6 mg/dL, respectively. Calcium supplements and a vitamin D analog were given to patients with symptomatic hypocalcemia defined by below normal serum level of Ca. The patients who had to continue to receive calcium supplementation for longer than 1 year and who also had a low (below normal) serum level of intact parathyroid hormone (PTH), normal level of which was 10.3 to 65.9 pg/mL, were defined as having permanent hypoparathyroidism.

The data are presented as the median (range). The Mann-Whitney's *U* test was used for comparisons of continuous variables between 2 groups. The 1-way ANOVA was used for continuous variables among 3 groups, and if a *P* value is <0.05, Tukey-Kramer test was applied for multiple comparisons. Values of $P < 0.05$ were considered to indicate statistical significance in all of the statistical analyses. The agreement of the number of macroscopically and microscopically preserved PGs was tested using the kappa test. All of the statistical analyses were performed using a commercial software program (StatMate III for Macintosh; ATMS Co., Ltd., Tokyo, Japan).

Results

The number of PGs that were judged to have been macroscopically preserved were as follows 4 PGs (n = 3; 7.1%); 3 PGs (n = 11; 26.2%); 2 PGs (n = 12; 28.6%); and 1 PG (n = 16; 38.1%). PG autotransplan-

Table 1. Association between number of parathyroid glands macroscopically preserved and postoperative courses in the cases without autotransplantation of PGs (n = 28)[a]

	Macroscopically preserved parathyroid glands, n				
	4 (n = 3)	3 (n = 11)	2 (n = 8)	1 (n = 6)	*P*
Postoperative tetany, n (%)	0 (0.0%)	5 (45.5%)	1 (12.5%)	4 (66.7%)	NS
Serum Ca on postoperative day 1, mg/dL (range) [b]	8.1 (7.8–8.2)	8.5 (7.0–9.4)	8.1 (5.9–9.5)	7.7 (7.2–8.5)	NS
Serum P on postoperative day 1, mg/dL (range)[b]	2.7 (2.3–3.8)	3.3 (2.3–5.1)	3.7 (2.7–7.1)	3.8 (3.3–6.5)	NS
Ca supplement intake, n (%)[b]	0 (0.0)	5 (45.5)	2 (25.0)	4 (66.7%)	NS
Ca supplement intake longer than 1 year, n (%)[b]	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3%)	<0.05
Vitamin D intake, n (%)	0 (0.0)	5 (45.5)	3 (37.5)	4 (66.7%)	NS
Vitamin D intake longer than 1 year, n (%)	0 (0.0)	0 (0.0)	3 (37.5)	2 (33.3%)	NS

[a]Data are presented as median (range), unless otherwise indicated.

[b]Normal levels of Ca and P were 8.8 to 10.1 and 2.7 to 4.6 mg/dL, respectively.

tation was only performed in 14 cases in which 1 to 2 PGs were preserved. We preserved a total of 85 PGs, 62 of which were upper glands (72.9%).

Table 1 shows association between the number of macroscopically preserved PGs and the postoperative courses in the patients who did not undergo PG autotransplantation. There was no association between the number of preserved PGs and postoperative tetany, the serum Ca or P at 1 day after surgery. Although the proportion of the patients needed to take calcium supplements and/or a vitamin D analog was not associated with the number of preserved PGs, only the patients with a single-preserved PG required calcium supplementation for longer than 1 year ($P < 0.05$).

The concordance rate of the number of macroscopically and microscopically preserved PGs was only 42.9% (kappa value = 0.23; Table 2). There were no significant associations between the number of microscopically preserved PGs and the postoperative courses, including tetany, the serum Ca or P levels at 1 day after surgery, the proportion of the patients who needed to take calcium supplements and/or a vitamin D analog, and those who required calcium supplements and/or a vitamin D analog for longer than 1 year (data were not shown).

Table 3 shows the efficacy of PG autotransplantation among the patients with only 1 macroscopically preserved PG. Although autotransplantation did not have a statistically significant effect on the postoperative course, no patients who received autotransplantation required calcium supplementation for longer than 1 year.

Discussion

In the present retrospective analysis, we showed that the patients with 2 or more macroscopically preserved PGs or with single PG preserved together with PG autotransplantation did not require calcium supplementation for longer than 1 year. There have been some reports, regarding the relationship between the number of microscopically preserved PGs and postoperative hypoparathyroidism. Song *et al*[6] reported that there was no relationship between the number of preserved PGs and permanent hypoparathyroidism. On the other hand, Lorente-Poch *et al*[7] reported that there was a significant correlation—noting that a lower number of preserved PGs resulted in a higher rate of postoperative hypocalcemia, and protracted and permanent hypoparathyroidism. However, both of the reports identified the number of PGs that were preserved by subtracting the number of PGs in a given specimen from 4. We therefore wondered whether all of the incidentally removed PGs could be identified in the surgical samples using this type of method because of their small size. In our study, the concordance rate between the number of macroscopically and microscopically identified PGs was only 42.9% (kappa value = 0.23). Furthermore, the number of microscopically preserved PGs did not affect the postoperative course.

Table 2. An analysis of the concordance between the number of macroscopically and microscopically preserved PGs without autotransplantation of PGs

Microscopically preserved PGs, n	Macroscopically preserved PGs, n				
	4	3	2	1	Total
4	2 (66.7%)	3	3	2	10
3	1	7 (63.6%)	2	2	12
2	0	0	2 (25.0%)	1	3
1	0	1	1	1 (16.7%)	3
Total	3	11	8	6	28

Percentages in parentheses indicate the degree of concordance.

Table 3. The impacts of the autotransplantation of PGs on the postoperative courses (n = 16)[a]

	Transplantation (n = 10)	Nontransplantation (n = 6)	*P*
Postoperative tetany, n (%)	8 (80.0)	4 (66.7)	NS
Serum Ca 1 day after surgery, mg/dL (range)[b]	7.9 (7.2–8.6)	7.7 (7.2–8.5)	NS
Serum P 1 day after surgery, mg/dL (range)[b]	3.5 (2.6–4.1)	3.8 (3.3–6.5)	NS
Ca intake, n (%)[b]	8 (80.0)	4 (66.7)	NS
Ca intake longer than 1 year, n (%)[b]	0 (0.0)	2 (33.3)	NS
Vitamin D intake, n (%)	8 (80.0)	4 (66.7)	NS
Vitamin D intake longer than 1 year, n (%)	6 (60.0)	2 (33.3)	NS

[a]Data are presented as median (range), unless otherwise indicated.

[b]Normal levels of Ca and P were 8.8 to 10.1 and 2.7 to 4.6 mg/dL, respectively.

Although our study showed that identifying the number of macroscopically preserved PGs could be useful for predicting permanent postoperative hypoparathyroidism, the present study was associated with some limitations. First, our study was conducted with small number of patients. Second, although we defined permanent hypoparathyroidism based on the need for calcium supplementation with a serum intact PTH level that was below normal for longer than year after surgery, we did not routinely measure the intact PTH level throughout the time course after surgery. Indeed, the criteria for the diagnosis of permanent hypoparathyroidism have not been standardized.[8,9] Some reports have defined permanent hypoparathyroidism based on the presence of low PTH levels[10]; however, permanent hypocalcemia may develop with normal PTH values after thyroid surgery, likely due to an intraoperative injury to the PGs or their vascularization.[8] Finally, in the present study, we did not evaluate vascularity of the PGs because it was retrospective in nature and we did not record the information necessary to evaluate the vascularity of the PGs in all cases. In cases in which 4 PGs were observed to have been preserved after thyroidectomy, discolored devascularized PGs were reported to induce transient, but not permanent, hypoparathyroidism.[11] However, it was unclear whether PGs with poor vascularity could prevent permanent hypoparathyroidism in the cases with 2 to 3 preserved PGs (like our cases). The color of the preserved PGs and changes in the levels of intact PTH over the pre- and postoperative time course should be evaluated in a further study because there are currently no other reliable measures of PG function.

The preservation of parathyroid vascularity or the autotransplantation of devascularized PGs might reduce the incidence of postoperative hypoparathyroidism in PTC cases involving macroscopic nodal metastasis where aggressive neck dissection is required.[12] On the other hand, autotransplantation was reported to increase postoperative hypoparathyroidism in comparison to leaving PGs in situ.[7,13] It is inevitable that the lower parathyroid glands will be accidentally removed with the lymph nodes in most cases in which total thyroidectomy and central neck dissection are performed for PTC. The macroscopic preservation of the 2 upper PGs (with vascularity) is therefore likely to be critical for preventing permanent hypoparathyroidism, and parathyroids removed accidentally should be transplanted in cases in which less than 2 parathyroid glands can be preserved in situ.

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