

Inadvertent Parathyroidectomy during Thyroid Surgery for Papillary Thyroid Carcinoma and Postoperative Hypocalcemia

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Background and Objectives: The aim of this article is to report our experience of inadvertent parathyroidectomy during thyroid surgery and to analyze its associated factors and clinical implications. In addition, we attempted to determine causative factors that result in permanent hypocalcemia after thyroid surgery. **Materials and Methods:** We performed a retrospective review of 500 patients who underwent thyroid surgery for the treatment of papillary thyroid carcinoma from 2004 to 2008. **Results:** Inadvertent parathyroidectomy was identified in 7.4% of patients and only 1 parathyroid gland was inadvertently removed in most cases. The incidence of inadvertent parathyroidectomy was not associated with gender, age, type of surgical procedure, tumor size, coexisting Hashimoto's thyroiditis (HT), extra-thyroidal extension (ETE), lymph node (LN) metastasis, and surgeon's experience. Nor was inadvertent parathyroidectomy associated with permanent postoperative hypocalcemia. Although operating time >120 min, ETE, and total thyroidectomy (TT) with central neck dissection (CND) were found to be related to permanent hypocalcemia on univariate analysis, tumor size ≥ 1 cm and surgeon's experience ≤ 5 years was statistically associated with permanent hypocalcemia on both univariate and multivariate analyses. **Conclusion:** Although inadvertent parathyroidectomy is not an uncommon complication of thyroid surgery, it appears to have only modest clinical implications. Permanent hypocalcemia was significantly associated with tumor size ≥ 1 cm and short surgical experience of surgeons, especially in the case of TT with CND. Therefore, we suggest that more accurate risk stratification should be made for routine CND, when it is performed by young surgeons.

Key Words: Thyroidectomy, Parathyroidectomy, Hypocalcemia

Introduction

Because thyroid cancer is the most common head and neck malignancy worldwide, thyroidectomy is the most frequent surgical procedure performed by head and neck surgeons.^{1,2)} It is relatively safe and many studies have reported a major complication rate around 1%.^{3,4)} However, despite careful surgical technique, postthyroidectomy hypoparathyroidism has been reported in up to 25% of patients.^{5,6)} This may

be due to a variety of factors, such as injury, devascularization of the parathyroid glands, and accidental resection of parathyroid parenchyma. Incidental parathyroidectomy during thyroid surgery is a potential complication; its occurrence varies widely among centers and among surgeons and is dependent on regional and individual experience. Anecdotally, incidental removal of parathyroid gland is often identified in histological reports of thyroid specimens from some patients, even after meticulous thyroidectomy without signs or symptoms of clinical hypocal-

emia. However, the incidence of this complication and its clinical impact on hypocalcemia remain obscure. Although the removal of 1 or 2 parathyroid glands may not have any clinical relevance, it has been noted as a risk factor for postthyroidectomy hypocalcemia by some authors.^{2,7)} Thus, in order to reduce the incidence of unintentional resection of parathyroid glands and of postthyroidectomy hypocalcemia, it is important for thyroid surgeons to identify factors that could potentially increase the risk of inadvertent parathyroidectomy during thyroid surgery and to understand its possible association with hypocalcemia. The aim of this article is to report our experience of inadvertent parathyroidectomy during thyroid surgery, and to analyze its associated factors and clinical implications. In addition, we attempted to determine causative factors related to the incidence of permanent hypocalcemia after thyroid surgery.

Materials and Methods

Patients

A database of patients with thyroid cancer was established in 1997 at the authors' institution. Analysis of data from these patients identified 1634 patients who underwent thyroid surgery at our institution during the 5-year period from January 2004 to December 2008. Of these patients, 500 who received initial treatment including thyroid lobectomy with isthmusectomy, total thyroidectomy (TT), and TT with central neck dissection (CND) for papillary thyroid carcinoma (PTC) at our institution and had medical records accessible for review were included in the study. The remaining patients were excluded due to inaccessible or incomplete medical charts, inappropriate pathologic slides for review of the previous diagnosis, revision surgery for recurrence, or other types of thyroid cancer including follicular, medullary, and anaplastic thyroid cancer. Patients who underwent comprehensive neck dissection, such as radical neck dissection, modified radical neck dissection, and selective neck dissection level II to V, were also excluded for uniform design of the present study. The cohort of 500 patients enrolled in our present study consisted of 59

men and 441 women, with a mean age of 48.1 years at the time of surgery. Thyroid lobectomy including isthmusectomy was performed in 102 patients (20.4%), and TT without neck dissection was performed in 318 patients (63.6%). TT with CND but without lateral neck dissection was performed in 80 (16.0%).

Surgical technique

All surgeries were performed by 6 head and neck surgeons including 2 senior surgeons (surgical experience >5 years) and 4 junior surgeons (surgical experience ≤5 years). Thyroidectomy was performed under general anesthesia via a transverse cervical incision. The procedure was performed in a similar fashion by all surgeons by using careful subcapsular dissection technique and attempting to identify and preserve the parathyroid glands and recurrent laryngeal nerves. A particular effort was made to avoid injury to and devascularization of the parathyroid glands. All resected thyroid specimens were carefully examined intraoperatively to identify the presence of parathyroid tissue. Incidentally removed parathyroid glands were autotransplanted immediately and these cases were not included in the present study. At the time this evaluation, novel hemostatic devices such as Harmonic Scalpels and LigaSure, which replaced the classical clamp-and-tie technique after 2009, were not used.

Evaluation of clinical and biochemical hypocalcemia

Data relating to postoperative biochemical and clinical hypocalcemia were thoroughly evaluated. Serum calcium levels were measured preoperatively, before surgery on the day of surgery, and on every postoperative day until discharge. Biochemical hypocalcemia was defined as the lowest serum calcium concentration of less than 8 mg/dl in serial postoperative calcium levels, regardless of signs or symptoms of hypocalcemia. Transient hypocalcemia was defined as clinical hypocalcemia requiring treatment and was associated with a serum calcium level lower than 8.0 mg/dl after surgery that resolved completely within 6 months. Permanent hypocalcemia was defined as a case of oral calcium supplement-

tation for more than 6 months following surgery regardless of calcium level.

Review of histopathological parameters

Histopathological parameters of each patient were blindly determined by 1 co-author specializing in thyroid and parathyroid pathology. All pathologic slides were reviewed for the presence, number, and location (extrathyroidal, intrathyroidal, or intracapsular) of inadvertently removed parathyroid glands within the submitted thyroid specimen. Histopathological features of the removed parathyroid glands were also evaluated. Moreover, in terms of thyroid histopathology, primary tumor size, the status of the extra-thyroidal extension (ETE) and subtype of each primary PTC and the presence of cervical lymph node (LN) metastasis and coexisting Hashimoto's thyroiditis (HT) were carefully reviewed.

Statistical analysis

SPSS for Windows (version 12.0; SPSS, Chicago, IL, USA) was used to analyze the data. Continuous data are represented as mean \pm standard deviation. To compare continuous variables, mean age and mean operating time were tested using an independent t-test. We separated the surgeon's experience variable into 2 categories as senior surgeon (surgical experience >5 years) and junior surgeon (surgical experience ≤ 5 years) to evaluate impact on occurrence of permanent hypocalcemia. The associations between inadvertent parathyroidectomy or permanent hypocalcemia and various clinicopathological parameters such as gender, age ≥ 45 years old, tumor size ≥ 1 cm, operating time >120 min, ETE, coexisting HT, LN metastasis, surgical procedures, and surgeon's experience were assessed using a Chi-square test or Fisher's exact test. Variables with $p < 0.1$ on univariate analysis were included in a multivariate analysis. Multivariate analysis was performed by binary logistic regression. With regard to the results, p -values were 2-sided throughout, and statistical significance was defined as a p value of <0.05 .

Results

Characteristics of inadvertently removed parathyroid glands

Table 1 shows the characteristics of inadvertently resected parathyroid glands. Inadvertent parathyroidectomy was identified in 37 patients (7.4%). One and 2 parathyroids were accidentally removed in 35 (94.6%) and 2 (5.4%) patients, respectively. In most of the patients (30 patients, 81.1%), the excised parathyroid was normal; however, in 5 patients (13.5%), direct PTC invasion was found in the excised gland, and in 2 other patients (5.4%), parathyroid adenoma was found. In total, unnecessary excision of normal parathyroid glands were identified in 30 patients (6.0%). Examination of the location of the parathyroid tissue within the thyroid specimen showed that of the inadvertently removed parathyroid glands, 21 (56.8%) were found in an extrathyroid location, 5 (13.5%) in an intracapsular location, and 11 (29.7%) were located in an intrathyroidal position.

Univariate analysis of association between inadvertent parathyroidectomy and various clinicopathological parameters

The results of univariate analysis of patient variables as a function of the presence (group 1) or absence (group 2) of inadvertent parathyroidectomy are

Table 1. Characteristics of inadvertently resected parathyroid glands

	Number of patients (n=500)
Inadvertent parathyroidectomy	37 (7.4%)
Histological characteristics of removed parathyroid glands	
Normal	30 (81.1%)
Papillary thyroid carcinoma invasion	5 (13.5%)
Adenoma	2 (5.4%)
Number of removed parathyroid glands	
One gland	35 (94.6%)
Two glands	2 (5.4%)
Location of the removed parathyroid gland	
Intrathyroidal	11 (29.7%)
Intracapsular	5 (13.5%)
Extrathyroidal	21 (56.8%)

Table 2. Univariate analysis of the association between inadvertent parathyroidectomy and various clinicopathological parameters

	Inadvertent parathyroidectomy (n=37)	No inadvertent parathyroidectomy (n=463)	p
Gender			
Male	4 (10.8%)	55 (11.9%)	1.000
Female	33 (89.2%)	408 (88.1%)	
Age			
≥45 years	24 (64.9%)	280 (60.5%)	0.599
<45 years	13 (35.1%)	183 (39.5%)	
Surgical procedure			
Lobectomy with isthmusectomy	8 (21.6%)	94 (20.3%)	0.848
TT alone	23 (62.2%)	295 (63.7%)	
TT with CND	6 (16.2%)	74 (16.0%)	
Tumor size			
≥1 cm	25 (67.6%)	268 (57.9%)	0.250
<1 cm	12 (33.4%)	195 (42.1%)	
Coexisting HT			
Present	6 (16.2%)	121 (26.1%)	0.182
Absent	31 (83.8%)	342 (73.9%)	
ETE			
Present	22 (59.5%)	250 (54.0%)	0.521
Absent	15 (40.5%)	213 (46.0%)	
LN metastasis			
Present	3 (8.1%)	50 (10.8%)	0.785
Absent	34 (91.9%)	413 (89.2%)	
Surgeon's experience			
>5 years	20 (54.1%)	259 (55.9%)	0.824
≤5 years	17 (45.9%)	204 (44.1%)	
Clinical hypocalcemia			
Transient	3 (8.1%)	30 (6.5%)	0.727
Permanent	1 (2.7%)	21 (4.5%)	
Lowest postoperative calcium level			
≥8 mg/dl	11 (29.7%)	227 (49.0%)	0.024*
<8 mg/dl	26 (70.3%)	236 (51.0%)	

C-ND: comprehensive neck dissection, CND: central neck dissection, ETE: extra-thyroidal extension, HT: Hashimoto's thyroiditis, LN: lymph node, TT: total thyroidectomy. *Statistically significant

summarized in Table 2. There was no statistical difference in most parameters including female gender (89.2% vs. 88.1%, $p=1.000$), age ≥ 45 years (64.9% vs. 60.5%, $p=0.599$), 3 types of surgical procedures (21.6% vs. 20.3%, $p=0.848$, for lobectomy; 62.6% vs. 63.7%, $p=0.850$, for TT alone; 16.2% vs. 16.0%, $p=0.970$, for TT with CND), tumor size ≥ 1 cm (67.6% vs. 57.9%, $p=0.250$), coexisting HT (16.2% vs. 26.1%, $p=0.182$), ETE (59.5% vs. 54.0%, $p=0.521$), LN metastasis (8.1% vs. 10.8%, $p=0.785$), and surgeons' experience ≤ 5 years (45.9% vs. 44.1%, $p=0.824$) between group 1 and group 2. The overall incidence of postoperative permanent hypocalcemia was 2.7%

(1/37) in group 1 and 4.5% (21/463) in group 2, and this difference was not statistically significant ($p=1.000$). However, the incidence of biochemical hypocalcemia, defined as a serum calcium level < 8 mg/dl, was significantly high in group 1 (26/37, 70.3%) when compared with in group 2 (236/463, 51.0%) ($p=0.024$). The incidence of inadvertent parathyroidectomy based on the extent of surgery was 7.8% (8/102), 7.2% (23/318), and 7.5% (6/80) for lobectomy, TT alone, and TT with CND, respectively, with no statistical difference identified among the surgical procedures ($p=0.979$).

Univariate and multivariate analysis of associations between permanent hypocalcemia and various clinicopathological parameters

There was a considerably higher percentage of female patients with permanent hypocalcemia than the percentage of female patients without permanent hypocalcemia, although the statistical significance of this finding was not verified (100% vs. 87.7%, $p=0.094$). Other parameters such as age ≥ 45 years, inadvertent parathyroidectomy, and coexisting HT were not significantly correlated with permanent hypocalcemia. Although the mean operating time was not significantly different as a function of permanent

hypocalcemia (179 ± 47.8 min vs. 167 ± 43.4 min, $p=0.231$), an operating time longer than 120 min had significantly higher incidence in patients with permanent hypocalcemia than that in patients without permanent hypocalcemia (100% vs. 82.6%, $p=0.035$). Moreover, in patients with permanent hypocalcemia, tumor size ≥ 1 cm and ETE were more frequent than in patients without permanent hypocalcemia and this difference was statistically significant (81.8% vs. 57.5%, $p=0.024$ and 77.3% vs. 53.3%, $p=0.028$, respectively). Surgeries with permanent hypocalcemia were more frequently performed by junior surgeons as compare to surgeries without permanent hypocalcemia (86.4% vs. 42.3%, $p<0.001$). With respect to

Table 3. Univariate analysis of the association between the permanent hypocalcemia and various clinicopathological parameters

	Permanent hypocalcemia (n=22)	No permanent hypocalcemia (n=478)	p
Gender			
Male	0 (0.0%)	59 (12.3%)	0.094
Female	22 (100.0%)	419 (87.7%)	
Age			
≥ 45 years	14 (63.6%)	290 (60.7%)	0.780
< 45 years	8 (36.4%)	188 (39.3%)	
Inadvertent parathyroidectomy			
Yes	1 (4.5%)	36 (7.5%)	1.000
No	21 (95.5%)	442 (92.5%)	
Operating time (min)			
Mean	179 ± 47.8	167 ± 43.4	0.231
> 120	22 (100%)	395 (82.6%)	0.035*
≤ 120	0 (0.0%)	83 (17.4%)	
Tumor size			
≥ 1 cm	18 (81.8%)	275 (57.5%)	0.024*
< 1 cm	4 (18.2%)	203 (42.5%)	
Coexisting HT			
Present	8 (36.4%)	119 (24.9%)	0.227
Absent	14 (63.6%)	359 (75.1%)	
ETE			
Present	17 (77.3%)	255 (53.3%)	0.028*
Absent	5 (22.7%)	223 (46.7%)	
LN metastasis			
Present	6 (27.3%)	47 (9.8%)	0.021*
Absent	16 (72.7%)	431 (90.2%)	
Surgical procedure			
TT with CND	8 (36.4%)	72 (15.1%)	0.014*
Other procedures [†]	14 (63.6%)	406 (84.9%)	
Surgeon's experience			
> 5 years	3 (13.6%)	276 (57.7%)	$< 0.001^*$
≤ 5 years	19 (86.4%)	202 (42.3%)	

CND: central neck dissection, ETE: extra-thyroidal extension, HT: Hashimoto's thyroiditis, LN: lymph node, TT: total thyroidectomy. *Statistically significant, [†]Includes lobectomy with isthmusectomy and total thyroidectomy alone

Table 4. Multivariate analysis of the association between the permanent hypocalcemia and various clinicopathological parameters

	Univariate	Multivariate	Odds ratio	95% CI
Female gender	0.094	0.997	0.000	—
Operating time >120 min	0.035*	0.997	7.554	—
Tumor size ≥1 cm	0.024*	0.042*	3.485	1.044–11.630
ETE	0.028*	0.354	1.690	0.557–5.125
LN metastasis	0.021*	0.259	2.507	0.508–12.382
TT with CND	0.014*	0.800	0.825	0.187–3.643
Surgeon's experience ≤5 years	<0.001*	0.001*	12.482	3.527–44.172

CI: confidence interval, CND: central neck dissection, ETE: extra-thyroidal extension, LN: lymph node, TT: total thyroidectomy.

*Statistically significant

surgical procedures, significantly higher percentage of TT with CND was found in patients with permanent hypocalcemia than that in patients without permanent hypocalcemia (36.4% vs. 15.1%, $p=0.014$) (Table 3). In 80 cases of TT with CND, only 1 out of 41 (2.4%) patients had permanent hypocalcemia after being operated on by senior surgeons while 7 out of 39 (18.5%) patients had permanent hypocalcemia after being operated on by junior surgeons ($p=0.027$).

Among these parameters, variables with $p<0.10$ on univariate analysis (gender, operating time, ETE, tumor size, LN metastasis, TT with CND, and surgeon's experience) were included in a multivariate analysis (Table 4). After adjustment for these factors, tumor size ≥ 1 cm (Odds ratio=3.485; 95% CI, 1.044–11.630; $p=0.042$) and surgeon's experience ≤ 5 years (Odds ratio=12.482; 95% CI, 3.527–44.172; $p=0.001$) were found to be significantly associated with permanent hypocalcemia. Although TT with CND was considered as an important risk factor of permanent hypocalcemia on univariate analysis, the association was not verified on multivariate analysis ($p=0.800$).

Discussion

The incidence of incidental parathyroidectomy during thyroid surgery ranges from 8% to 21.6%.^{6–9)} Taking the major complication rate of <1% thyroidectomy into account, this is not a rare complication. However, the risk factors and clinical significance of inadvertent parathyroidectomy remain obscure, and the apparent lack of concern of head and neck

surgeons for this complication contributes to ongoing ignorance of inadvertent parathyroidectomy. In our present study, we observed inadvertent parathyroidectomy in 7.4% of patients, which is comparable to the incidence reported previously. In more than 80% of reported cases, only 1 parathyroid gland was inadvertently resected (94.6% in the present study).^{2,8)} However, some studies have reported incidental resection of 2 parathyroid glands in up to 32.4% of cases.⁹⁾ As we reviewed slides which were already made, not the whole sectioned specimen, we deemed the actual incidence of inadvertent parathyroidectomy was higher than the result of our study.

The incidence of intrathyroidal parathyroid glands is approximately 0.2% according to autopsy studies, but this incidence rises to 2–5% in patients with primary hyperparathyroidism and up to 11% in those with persistent or recurrent hyperparathyroidism.^{10,11)} Inadvertently excised parathyroid glands have been reported to be intrathyroidal in up to 40–57.7% of cases.^{8,12)} In our study, 29.7% of inadvertently removed parathyroid glands were intrathyroidal, suggesting that even if a more meticulous surgical technique was introduced, the risk of inadvertent parathyroidectomy could not be eliminated completely in such cases. In contrast, in cases in which inadvertently resected parathyroid glands were in an extrathyroidal or intracapsular position, more careful dissection and examination of the thyroid specimen after thyroidectomy could possibly decrease the incidence of inadvertent parathyroidectomy.

Theoretically, the risk of inadvertent parathyroidectomy may be increased in some cases, such as in

patients who are undergoing more extensive surgical procedures, who have enlarged LNs due to metastasis or thyroiditis, who have extrathyroidal extension of a primary tumor, or who undergo reoperation for recurrent goiter.^{2,9,13,14)} Although CND and comprehensive neck dissection, such as radical neck dissection, modified radical neck dissection, have been recognized as risk factors for unintentional parathyroidectomy, there was no significant correlation between type of thyroid surgery and parathyroidectomy in our study. Furthermore, other parameters including gender, age, tumor size, coexisting HT, ETE, LN metastasis, and surgeon's experience were not associated with inadvertent parathyroidectomy.^{7,8,13)} In fact, previous studies on the risk factors for inadvertent parathyroidectomy during thyroid surgery have reported varied results for different centers and surgeons. Sakorafas et al.⁶⁾ reported that female gender and benign thyroid pathology were associated with incidental parathyroidectomy, while Abboud et al.²⁾ reported that only the presence of HT was found to be a significant risk factor for incidental parathyroidectomy. A recent prospective study showed that reoperation for recurrent goiter and concomitant CND may increase the risk of incidental parathyroidectomy.¹³⁾ In a study involving 220 patients undergoing thyroidectomy, completion thyroidectomy or reoperations were correlated with an increased risk of unintentional parathyroidectomy, probably resulting from the formation of scar tissue and fibrosis, which may cause operative difficulties.⁹⁾ In the present study, however, patients who underwent reoperation for recurrent or persistent thyroid disease or benign thyroid disease were excluded. Therefore, it is difficult to determine that which parameter is definitely associated with incidental parathyroidectomy.

However, with respect to the relationship between incidental parathyroidectomy and clinical hypocalcemia, various studies consistently reported that incidental parathyroidectomy does not increase the incidence of permanent hypocalcemia.^{2,9,13,15)} Because only 1 parathyroid gland is removed in most cases, the clinical impact on hypocalcemia is deemed to be modest. Although biochemical hypocalcemia was

more prevalent among patients with inadvertent parathyroidectomy in the present study, it was not correlated with clinical hypocalcemia. In fact, biochemical hypocalcemia has been reported in as many as 83% of cases after thyroidectomy, but symptomatic hypocalcemia is seen much less frequently.¹⁶⁾ In a study of 141 thyroid surgeries, preoperative diagnosis of malignant disease and total thyroidectomy were identified as being significantly associated with symptomatic postoperative hypocalcemia.⁸⁾ In our study focusing on permanent hypocalcemia, operating time >120 min, ETE, LN metastasis, and TT with CND were significantly associated with permanent hypocalcemia on univariate analysis ($p < 0.05$ each), but not on multivariate analysis. Tumor size ≥ 1 cm, which means the size of indication for TT, and surgeon's short experience (≤ 5 years) were found to be independent risk factors for permanent hypocalcemia on univariate analysis and on multivariate analysis. Interestingly, although TT with CND was not verified as an independent factor associated with permanent hypocalcemia, it was found that TT with CND could enhance risk of permanent hypocalcemia when the surgery was performed by unexperienced surgeon (2.4% for senior surgeons vs. 18.5% for junior surgeons, $p = 0.027$). Recently, 1 of the major debates relating to the surgical treatment of thyroid cancer has revolved around the benefits and risks of CND. This study showed that concurrent CND with TT performed by junior surgeons was associated with permanent hypocalcemia. However, we assumed CND itself does not bring about significant increase of the permanent hypocalcemia, if the blood supply to the parathyroid gland is preserved by experienced surgeon. Therefore, we suggest that more accurate risk stratification should be made for routine CND combined with TT, when it is performed by young surgeons.

The present study has some limitations. As this evaluation was designed to be a retrospective study, it could not be assessed the location of primary tumor and the number of intact or impaired (color-changed) parathyroid gland which introduces actual parathyroid gland function. In addition, postoperative parathyroid hormone level was not evaluated routinely in our insti-

tution, therefore, relationship between number of resected parathyroid gland and postoperative parathyroid hormone level could not be obtained. Despite these limitations, we deem that it is important to maintain good-quality databases in all high-volume thyroid centers and accumulate carefully documented retrospective analysis from different centers to solve several controversies concerning thyroid surgery.

Conclusion

Inadvertent parathyroidectomy is not an uncommon complication of thyroid surgery, occurring in approximately 7.4% of patients in this study. Only 1 parathyroid gland was inadvertently removed in most cases, and about 30% of the resected parathyroid gland was located in an intrathyroidal position, suggesting some inadvertent parathyroidectomies are unavoidable. The incidence of inadvertent parathyroidectomy was not associated with gender, age, type of surgical procedure, or with various histopathological variables such as tumor size, coexisting HT, ETE, LN metastasis, and surgeon's experience. In addition, no association between inadvertent parathyroidectomy and clinical hypocalcemia was found. Although operating time >120 min, ETE, LN metastasis, and TT with CND were found to be associated with permanent hypocalcemia on univariate analysis, tumor size ≥ 1 cm and surgeon's experience ≤ 5 years remained statistically significantly associated with permanent hypocalcemia on multivariate analysis. Therefore, careful decision making and meticulous surgical technique are required when thyroid surgery was performed by unexperienced surgeons, especially in the case requiring TT with CND.

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