

## Can we Avoid Inadvertent Parathyroidectomy during Thyroid Surgery?

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**Abstract.** *Objectives.* To identify risk factors of inadvertent parathyroidectomy (IP) during thyroid surgery with the aim of decreasing the incidence of this unpleasant complication and to evaluate the impact on temporary and permanent hypocalcaemia following bilateral thyroidectomy. *Patients and Methods:* All consecutive thyroid surgical procedures performed at the Special Surgical Pathology Department of Padova General Hospital and Padova University during one year (January-December 2005) were retrospectively reviewed. Demographic data as well as data on diagnosis, operative reports, pathology findings, and postoperative serum calcium values were collected. A total of 882 patients (F=685 M=197) were included in the study. The patients were divided into 2 groups: those with IP and those without IP, and their data were compared to find factors affecting the occurrence of IP. The impact of IP on residual early and late postoperative parathyroid function was assessed. Hypercalcaemic (calcium level below 2.10 mMol/L) patients were followed from 1 week to 3 years. *Results:* Seventy of 882 patients (7.9%) were found to have IP. In 11 cases (16% of IP cases and 1.2 % of entire series) the parathyroid glands

were completely intrathyroidal. The results of bivariate analysis showed young age ( $p=0.037$ ), malignant disease ( $p<0.0001$ ), total thyroidectomy with lymph node dissection ( $p<0.0001$ ), low weight of thyroid specimen ( $p<0.0001$ ), and non-visualisation of any parathyroid gland at operation ( $p<0.0001$ ) as predictive factors for IP. Multivariate analysis revealed significant correlation between IP and malignant disease ( $p=0.004$ ), and between lymph node dissection and permanent postoperative hypocalcaemia ( $p=0.018$ ). The incidence rate of transient and permanent hypocalcaemia was higher in IP than in those without. The mean diameter of excised parathyroid glands was 3.2 mm, suggesting more extended or difficult surgical procedures. *Conclusion:* IP is not uncommon during thyroidectomy and is associated with a higher, though not statistically significant, incidence of transient and permanent postoperative hypocalcaemia. Malignant disease, lymph node dissection, non-visualization of any parathyroid gland at operation and younger age seem to be risk factors and should be considered by the surgeon. Further efforts must be taken to reduce the incidence beginning by avoiding parathyroid fragmentation.

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Incidental excision of one or more parathyroid glands during thyroid surgery is not a rare occurrence even with a skilled endocrine surgeon and could become a cause of concern to both clinicians and patients. Several factors that may relate to this inadvertent parathyroidectomy (IP) have been investigated in an effort to reduce the risk. Although IP represents a minor complication of thyroid resection compared to recurrent laryngeal nerve injury and permanent hypoparathyroidism (1-3), it has been reported in 3.7 to 21.6% of specimens of patients undergoing surgical thyroid procedures, with incidentally excised parathyroid glands ranging from 1 to 4. The clinical relevance of IP is debatable (2, 4), due to non-homogeneity of thyroid pathology,

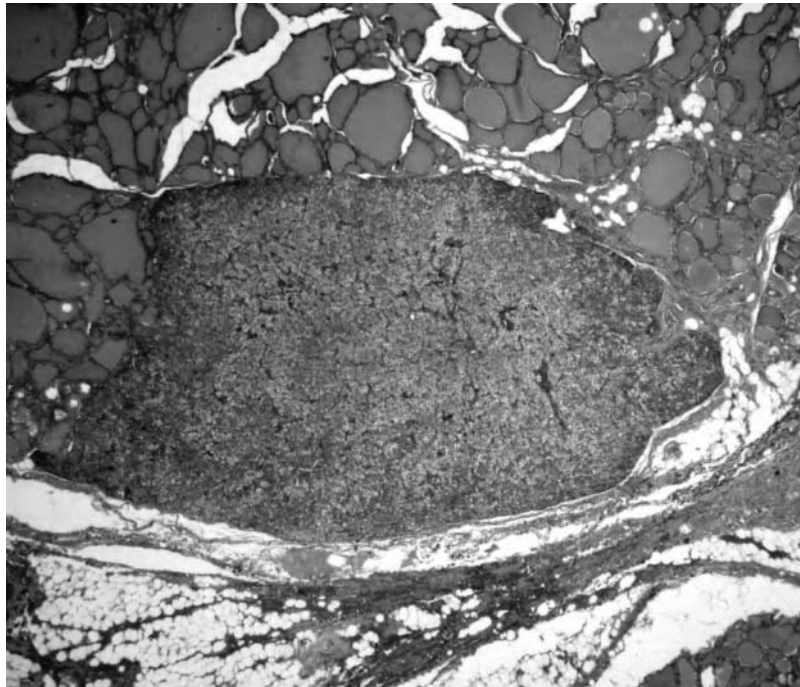


Figure 1. Photomicrograph of an intrathyroidal parathyroid gland (hematoxylin-eosin stain).

histologic evaluation and referral patterns (clinical or biochemical) of hypocalcaemia. Temporary and permanent hypocalcaemia may be missing if unilateral lobectomy was performed and this may add to the heterogeneity of the data.

Despite improvement in the technique of thyroidectomy, the risk of excision of intra-thyroidal parathyroid glands that contributes to up to 50 % of IP (5, 6) cannot be eliminated (Figure 1). However, is it possible at least to decrease the unintentional fragmentation-resection of the extra- thyroïdal parathyroid by identifying and eliminating any possible risk factor.

## Patients and Methods

All consecutive thyroid procedures (total and near total thyroidectomy, completion thyroidectomy, lobectomy) performed at the Special Surgical Pathology Department, Padova General Hospital and Padova University, during 2005 were retrospectively reviewed. The procedures were performed by seven surgeons in a similar fashion, with careful dissection along the thyroid capsule, attempting to identify and preserve the parathyroid glands and their vascular supply, as well as the recurrent laryngeal nerves.

The patients' demographics, preoperative diagnosis, operative procedure, final pathology, and preoperative and postoperative serum calcium levels were all collected. The number of parathyroid glands that were macroscopically found and preserved during the operating time was carefully recorded. When it was impossible to

preserve them with satisfactory vascularization, the parathyroid glands were immediately transplanted in the sternocleidomastoid muscle. All incidental parathyroid tissues were found during microscopic rather than macroscopic examination of the thyroid specimens. All pathology reports were reviewed and for all the specimens in which incidental parathyroid tissue was found, the slides were reviewed to identify the number, size, localization and histopathological features of the parathyroid tissue. The weight of the thyroid gland specimens was also recorded.

On the basis of the occurrence of IP, patients were divided into 2 groups: those with IP and those without IP. The collected data were compared between the 2 groups in order to evaluate the factors that could have influenced the occurrence of IP. Serum calcium levels were also recorded both preoperatively and postoperatively on days 1 and 2. The normal reference of our laboratory was 2.10-2.55 mMol/L using a colorimetric test with O-cresolntalein reaction in MODULAR DP Roche analyzer. Patients who developed postoperative hypocalcaemia, even if asymptomatic, underwent replacement therapy and further serum calcium measurements performed to separate transient from permanent hypoparathyroidism. All patients with temporary postoperative hypocalcaemia were followed up from one to a maximum of three years. Hypocalcaemia was considered permanent when requiring calcium-vitamin D replacement therapy more than one year after the operation. The postoperative transient and permanent hypocalcaemia rates were compared between IP and non-IP to evaluate the consequences of IP during thyroidectomy. Data analysis and statistical evaluation were carried out by an independent statistical specialist. Comparisons were made for unintentional parathyroidectomy and postoperative

Table I. Patients demographics, diagnosis, operative procedures, pathological findings, postoperative hypocalcemia.

Variable	No. (%) of patients (No.=882)
Gender	
Male	197 (22.3)
Female	685 (77.7)
Age, y	
Mean±STD	50±14
Median	50
Range	12.6-86.6
Preoperative diagnosis	
Benign	712 (80.7)
Malignant	170 (19.3)
Procedure	
Total thyroidectomy (TT)	516 (58.5)
Lobectomy (L)	161 (18.3)
Completion thyroidectomy (CT)	36 (4.1)
TT+lymph node dissection	158 (17.9)
L+lymph node dissection	9 (1)
CT+lymph node dissection	2 (0.2)
Parathyroid glands seen at the operation time	
No one	84 (9.5)
Almost one	798 (90.5)
Parathyroids implantation	
No	843 (95.6)
Yes	39 (4.4)
Thyroid weight, g	
Mean±STD	58.1±60.4
Median	38.0
Range	2.00-530.00
Final thyroid pathology	
Benign	642 (72.8)
Malignant	240 (27.2)
Incidental parathyroidectomy	
No	812 (92.1)
Yes	70 (7.9)
Temporary postoperative hypocalcemia	
No	348 (48.9)
Yes	364 (51.1)
Permanent postoperative hypocalcemia	
No	643 (90.3)
Yes	39 (5.5)
Missing	30 (4.2)

hypocalcaemia and predictors of both outcome measures were assessed by univariate and multivariate analyses. Univariate analysis was performed using a *t*-test; categorical values were determined using the  $\chi^2$  test. Stepwise multivariate analysis was performed using logistic regression. The level of  $p < 0.05$  was considered statistically significant.

## Results

During the study period, 882 consecutive patients, 685 females (77.7%) and 197 males (22.3%), aged between 12.6-86.6 years (mean 50.1) underwent thyroid procedures. The descriptive analysis of the entire series is reported in Table I.

Table II. Incidentally removed parathyroid glands: incidence, number, diameter, location.

Parameter	Value (%)
Incidental parathyroid glands (total no.)	70 (7.9)
Number of incidentally removed parathyroid glands	
1	64 (91.4)
2	5 (7.2)
4	1 (1.4)
Diameter of incidental parathyroid glands (mm)	
Mean±STD	3.2±1.8
Median	3.0
Range	1.0-8.0
Location of the removed parathyroid glands	
Extrathyroidal	59 (84.3)
Intrathyroidal	11 (15.7)
Histological pattern	All normal

Indication for surgery was malignant thyroid disease in 170 cases (19.3%), benign disease in 712 cases (80.7%), multinodular goiter in 321 (36.4%), toxic goiter in 158 (17.9%), Plummer adenoma in 22 (2.5%), follicular lesion in 121 (14%), solitary node in 62 (7%) and recurrent goiter in 28 (3%).

The operation was total thyroidectomy in 516 cases (58.5%), total thyroidectomy with lymph node dissection in 158 cases (17.9%), thyroid lobectomy in 161 cases (18.3%), thyroid lobectomy with lymph node dissection in 9 cases (1%), completion thyroidectomy in 36 cases (4.1%) and completion thyroidectomy with lymph node dissection in 2 cases (0.2%). In 84 cases (9.5%) none of the parathyroid glands was identified during the operation, whereas at least one gland was identified in 798 (90.5%). When none of the parathyroid glands was seen at the operating time, the IP incidence was twice as high as when at least one parathyroid gland was seen; the difference was statistically significant ( $p < 0.0001$ ). Four parathyroid glands were identified in 377 cases (42.7%). Thirty-nine patients (4.4%) underwent re-implantation of a removed or devascularized parathyroid gland into the sternocleidomastoid muscles. The median weight of the thyroid specimens was 58 g (range 2-530 g). Definitive pathology examination reported benign diagnosis in 642 cases (72.8%) and malignant in 240 cases (27.2%).

Of the 882 patients, 70 (7.9%) were found to have inadvertent removal of parathyroid tissue. Table II shows the features of the parathyroid removed: the number of glands removed was one in 64 cases (91.4%), two in 5 (7.2%) and four in one patients (who developed only temporary hypocalcaemia) (1.4%). The mean diameter of the inadvertently excised parathyroid glands was 3.2 mm (range 1.0-8.0 mm) and in 11 cases (16%) the glands were completely intrathyroidal (1.2% of the entire series). The parathyroid tissue was normal in all patients.

Table IIIa. Univariate analysis of temporary postoperative hypocalcemia (TPH).

Variable	No. (%) without TPH	N° (%) with TPH	p
Incidental parathyroidectomy			
No	320 (49.7)	324 (50.3)	0.197
Yes	28 (40.9)	40 (59.1)	
Total cases	348 (48.9)	364 (51.1)	

Table IIIb. Univariate analysis of permanent postoperative hypocalcemia-PPH (dependent variable: definitive postoperative hypocalcemia).

Variable	PPH	Mean (CL Mean), mMol/L (v.n. 2.10-2.55)	p
Preoperative calcium levels	No	2.45 (2.44-2.46)	0.007
	Yes	2.39 (2.35-2.43)	
Postoperative calcium levels			
At first day	No	2.14 (2.13-2.15)	<0.0001
	Yes	1.99 (1.94-2.04)	
At second day	No	2.11 (2.10-2.12)	<0.0001
	Yes	1.91 (1.87-1.95)	

Within the 39 patients who underwent reimplantation, four had IP.

Indication for surgery was malignant disease in 32 patients with IP (18.8% of patients with malignant disease) whereas presumably benign disease in 38 (5.4% of patients with benign disease); at definitive pathology 33 patients had benign disease (5.1%) whereas 37 had malignant tumour (15.4%).

There was no significant difference in the incidence of IP between different surgeons. The results of bivariate analysis of IP are reported in Table III.

Tracheo-esophageal groove node dissection was carried out in 169 patients (19.2% of entire series). Incidence of IP was 16.6% (28 cases) in dissected patients and 5.9% (42 cases) in non-dissected patients.

Thirty-eight patients had repeat operation for recurrent disease. Completion thyroidectomy was not a risk factor for IP. Thyroid specimen's weight was significantly related to IP ( $p < 0.0001$ ): the mean weight was lower in IP (mean 46.1; range 37.8-54.5) than non-IP (mean 66.5; range 61.3-71.6).

Patients with postoperative calcemia values less than 2.10 mMol/L were discharged with replacement therapy and considered hypercalcaemic.

In the entire series, temporary postoperative hypocalcaemia occurred in 364 (51.1%) patients (Tables III and IV). The incidence of transient hypocalcaemia was higher in IP (59.1%) than in non-IP (50.3%), NS ( $p = 0.20$ ). Permanent postoperative hypocalcaemia involved 39 patients (5.5% of

Table IV. Univariate analysis of permanent postoperative hypocalcemia (PPH).

Variable	No. (%) without PPH	No. (%) with PPH	p
Incidental parathyroidectomy			
No	584 (94.8)	32 (5.2)	0.089
Yes	59 (89.4)	7 (10.6)	
Total cases	643 (94.3)	39 (5.7)	
Missing	30		

Table V. Univariate analysis of incidental parathyroidectomy.

Variable	No. (%) without IP	No. (%) with IP	p
Gender			
Male	183 (92.9)	14 (7.1)	0.625
Female	629 (91.8)	56 (8.2)	
Age, y			
Mean (CL mean)	50.4 (49.4-51.4)	46.7 (43.0-50.45)	0.037
Preoperative diagnosis			
Benign	674 (94.6)	38 (5.4)	<0.0001
Malignant	138 (81.2)	32 (18.8)	
Procedure			
Total thyroidectomy (TT)	479 (92.8)	37 (7.2)	<0.0001
Lobectomy (L)	157 (97.5)	4 (2.5)	
Completion thyroidectomy (CT)	35 (97.2)	1 (2.8)	
TT+lymph node dissection	131 (82.9)	27 (17.1)	
L+lymph node dissection	9 (100)	0 (0)	
CT+lymph node dissection	1 (50)	1 (50)	
Lymph node dissection			
No	671 (94.1)	42 (5.9)	
Yes	141 (83.4)	28 (16.6)	
Parathyroid glands seen at the operation time			
No one	72 (85.7)	12 (14.3)	<0.0001
Almost one	740 (92.7)	58 (7.3)	
Parathyroid gland transplantation	35 (89.7)	4 (10.3)	0.583
Specimen's weight, g	66.5 (61.3-71.6)	46.1 (37.8-54.5)	<0.0001
Final thyroid pathology			
Benign	609 (94.9)	33 (5.1)	<0.0001
Malignant	203 (84.6)	37 (15.4)	

entire series). The incidence of permanent hypocalcaemia in IP was twice as high as in non-IP: 10.6% vs. 5.2% respectively, NS ( $p = 0.089$ ).

It was observed that the preoperative and postoperative values of serum calcium levels in all patients with permanent hypocalcaemia were lower than in patients without permanent hypocalcaemia: 2.39 mMol/L (range 2.35-2.43) vs. 2.45



Table VI. *Multivariate analyses.*

A) Multivariate model: Dependent variable: incidental parathyroid Probability modeled is the incidental parathyroid='Yes'.				
Covariate	Logit			
	OR	95% CI		P
Malignant thyroid histology	2.457	1.345	4.489	0.0035
Lympho-adenectomy	1.841	0.986	3.435	0.055
Testing Global Null Hypothesis: BETA=0 (Test Likelihood Ratio) <i>p</i> -value=<.0001. c=0.652				
B) Multivariate model: Dependent variable: permanent hypocalcemia Probability modeled is hypocalcemia_def='Si'.				
Covariate	Logit			
	OR	95% CI		P
Limpho-adenectomy	2.246	1.147	4.396	0.0183
Testing Global Null Hypothesis: BETA=0 (Test Likelihood Ratio) <i>p</i> -value=0.0183. c=0.583				
C) Multivariate model: Dependent variable: definitive hypocalcemia Probability modelled is permanent hypocalcemia='Yes'.				
Covariate	Logit			
	OR	95% CI		P
Lympho-adenectomy	2.251	1.127	4.497	0.0215
Hypocalcemia in the first post-operative day	6.929	3.125	15.364	<0.0001
Testing Global Null Hypothesis: BETA=0 (Test Likelihood Ratio) <i>p</i> -value=<0.0001. c=0.747.				

mMol/L (range 2.44-2.46) respectively with statistical significance ( $p=0.007$ ), and on second postoperative day 1.91 mMol/L (range 1.87-1.95) vs. 2.11 mMol/L (range 2.10-2.12), ( $p<0.0001$ ). The analysis of ROC curve of calcium levels at first postoperative day revealed for calcium levels  $\leq 2.00$  mMol/L a sensitivity=85% and a specificity=51.3% to predict permanent hypocalcaemia, for calcium levels  $\leq 1.95$  mMol/L a sensitivity=91.9% and a specificity=43.6%.

The results of bivariate analysis (Table V) of patient variables showed young age ( $p=0.037$ ), malignant disease ( $p<0.0001$ ), total thyroidectomy with lymph node dissection ( $p<0.0001$ ), low weight of thyroid specimen ( $p<0.0001$ ), and no visualization of parathyroid gland at operation ( $p<0.0001$ ) to be risk factors for IP. Multivariate analysis revealed significant correlation between malignant

disease and IP ( $p=0.004$ ), and between lymph node dissection and permanent postoperative hypocalcaemia ( $p=0.018$ ) (Table VI).

## Discussion

Hypocalcaemia and recurrent laryngeal nerve injury are the most significant complications of thyroid surgery (1-3, 7), whereas inadvertent parathyroidectomy is often considered as a minor complication. It is commonly considered that such a risk cannot be eliminated since IP occurs even in the hands of experienced thyroid surgeons and sometimes because of intrathyroidal parathyroid location. Nevertheless, the incidence and clinical relevance of IP must not be underestimated (1-10). In fact the incidence of intrathyroidal location of parathyroid glands is approximately 0.2% according to autopsy studies, rising to between 2% and 5% for patients with primary hyperparathyroidism and up to 11% in those with persistent or recurrent hyperparathyroidism. However, intra-thyroidal location has been reported in 13.6 to 50% of cases (Table VII) of IP.

In this series, the incidence of IP was 7.9%, similar to rates reported in the literature (from 3.7 to 21.6%) (2, 4) and intra-thyroidal parathyroid glands were found in 16% of IP, that is 1.2% of the entire series.

In most cases, only 1 parathyroid gland was inadvertently resected. Sakorafas *et al.* reported a study comprising 158 cases that included 28 with IP, in which there were 4 patients with two parathyroid glands removed accidentally (3), while Lin *et al.* examining 220 cases with 20 IP reported one case with three parathyroid glands (8). Similarly, Lee *et al.* (414 cases and 45 with IP) reported three cases with three foci (7). Here 882 cases are reported (70 with IP) with one case of 4 incidentally excised parathyroid glands following which the patient developed only temporary hypocalcaemia. Although there is a great variability in parathyroid gland number, most commonly there are 4 glands of approximately 6-8 mm in diameter. In this study, the mean diameter of excised parathyroid glands was 3.2 mm, which is closer to other authors' reported mean diameter of 3.5-4.8 mm (Table VII).

Accounting for the length of the glands, it is possible that the parathyroid glands, which were found in the extra-thyroid positions, were actually small portions of preserved parathyroid glands left in the patients. It is hoped that surgeon's realization of this concept could help eliminate the risk of parathyroid tissue fragmentation.

The importance of parathyroid identification and preservation during thyroid surgery is well established. A significant association between intraoperative identification of parathyroid glands and incidental removal of the glands was found. It is feasible to achieve a reduction of IP if the surgical technique of isolation and preservation is more

Table VII. Earlier studies of inadvertent parathyroidectomy (IP).

Author, year	Number of cases	Incidence of IP, % (number of pts)	Incidence of intrathyroidal parathyroid glands, %	Mean diameter of the parathyroid gland, mm	Incidence of postoperative permanent hypocalcemia, %
Lee, 1999	414	11 (45)	22	6x4 and fragments	0
Sasson, 2001	141	15 (21)	50	3.5	0.7
Lin, 2002	220	9.1 (20)	15	-	0
Sakorafas, 2005	158	17.7 (28)	21	4	0.6
Gourgiotis, 2006	315	21.6 (68)	42.6	4.8	0
Rix, 2006	126	17.4 (22)	13.6	-	0
Sippel, 2007	513	6.4 (33)	-	-	4
Irkorucu, 2007	273	3.7 (10)	20	3.5	0
Abboud, 2007	307	12 (38)	24	4	0
Manouras, 2008	508	19.7 (100)	49	-	0

meticulous, particularly in avoiding fragmentation during more advanced procedures. The preservation of parathyroid glands should be attempted even when radical surgery is contemplated for malignant disease.

Completion thyroidectomy has been found in many studies to have a substantially higher complication rate compared to those without prior thyroid surgery (3, 8) since dissection during a second-visit operation is complicated by scarring, inflammation and bleeding, making accurate identification of the critical structures more difficult. In our experience, despite the difficulties of a second-visit surgery, there was no significant increase in complications, particularly in the incidence of IP.

The risk of IP may be increased in patients undergoing surgery for malignant thyroid disease in which case recurrent laryngeal nerve lymph node dissection is performed. In fact, these lymph nodes are located in the tracheo-esophageal groove on the posterior surface of the thyroid gland close to where the parathyroid glands are commonly located. The superior parathyroid glands are fairly consistently located at the superior pole of the thyroid, but the inferior parathyroid glands are more variable in location and, at times, are intrathyroidic. Lin *et al.* (8) and Sasson *et al.* (6) reported the notable association of IP with dissection of tracheo-esophageal groove lymph nodes and modified neck dissection concomitant with thyroidectomy, respectively. In the present study, malignant disease and lymph node dissection were significantly related to IP. Careful inspection of thyroid and tracheo-esophageal dissected tissue for the presence of normal parathyroid tissue is prudent without compromising the oncological indication for resection.

A correlation was found between size of the thyroid lesion in relation to the specimen weight and incidence of IP. The size of the thyroid lesion was predictive of IP: inadvertent removal of parathyroid tissue was less frequent in cases with heavier goiter. That seems in contrast with the common expectation of technical difficulties to operate large goitres

resulting in postoperative complications such as recurrent laryngeal nerve palsy and hypoparathyroidism. However, it needs to be taken into consideration that malignant pathology is more often associated with smaller thyroid specimen than benign pathology with the aim of surgery to remove as much as possible of the gland's volume.

There is no mention in the literature of a correlation between IP and clinical hypocalcaemia (1-10), as was the case in the present study. Although IP does not seem to correlate with postoperative permanent hypocalcaemia, every attempt should be made to avoid this potentially preventable complication of thyroid resection. The association between intraoperative identification of parathyroid glands and development of postoperative hypocalcaemia is variable; whereas Pattou *et al.* (11) reported a significant relationship between identification of less than three parathyroid glands and hypocalcaemia, Sasson *et al.* (6) could demonstrate no such link. In 1907, William Halsted (12) asserted as a maxim that 'Tetany is...less often due to removal of the parathyroids than interference with their circulation'. The aim should therefore be to identify and preserve the parathyroid glands and their vascular supply as a matter of routine for every patient undergoing any form of thyroidectomy for benign or malignant disease.

As most patients have at least four parathyroid glands, it seems logical that removal of one gland or its fragments should not lead to problems with calcium homeostasis. However, an increased incidence of hypocalcaemia was observed in patients with IP, although without any statistical significance. It may be that the removal of some parathyroid tissue correlates to a more aggressive or difficult surgery and that unintended removal of parathyroid tissue acts as an indicator of damage to the other glands as well. IP is not uncommon during thyroidectomy and may be considered as a minor but unpleasant complication of thyroid procedures. Most of the accidentally excised parathyroid gland tissues should be fragments of the parathyroid gland left in the

patients; therefore, it is possible to decrease the incidence of IP with more meticulous parathyroid gland isolating techniques during thyroid procedures. Young age, malignant disease, lymph node dissection, low weight of thyroid specimen and non-visualization of parathyroid glands at operation seem to be predictive risk factors for IP since the aim of surgeons is directed towards avoiding recurrent laryngeal nerve damage or bleeding and/or favouring a radical operation. Although inadvertent excision of intra-thyroidal parathyroid glands remains unavoidable, it is hoped that ample attention to these factors could play a role in reducing or eliminating the risk of parathyroid tissue fragmentation in the future.

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