Original Article

Predictors of accidental parathyroidectomy and hypoparathyroidism in thyroid surgery

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Background: Accidental parathyroidectomy in thyroid surgery refers to inadvertent resection of parathyroid tissue during thyroidectomy and is associated with temporary hypoparathyroidism and permanent hypoparathyroidism. This cohort study set out to identify the incidence and risk factors for accidental parathyroidectomy and hypoparathyroidism in patients undergoing total thyroidectomy with the aim of developing a risk stratification to aid clinical practice by predicting which patients are at risk of post-operative hypoparathyroidism.

Methods: A retrospective analysis of patients from three Australian tertiary referral hospitals from 2010 to 2020 who underwent total thyroidectomy was performed using the Sydney Head and Neck Cancer Institute database. Chi-square and Fisher's exact tests were used to determine the significance of associations between variables. Logistic regression was used to determine predictors for the risk stratification tables and were constructed using the predicted probabilities of significant variables.

Results: A total of 295 patients were included in this study. Accidental parathyroidectomy was reported in 78/295 (26%) of cases and was associated with temporary hypoparathyroidism [P<0.001; odds ratio (OR) =3.1; 95% confidence interval (CI): 1.81–5.31] and permanent hypoparathyroidism (P=0.04; OR =17.75; 95% CI: 2.1–149.94). Significant risk factors identified for accidental parathyroidectomy were malignancy (P=0.015; OR =1.91; 95% CI: 1.13–3.26) and central lymph node dissection (P<0.001; OR =4.94; 95% CI: 2.44–10.2). Temporary hypoparathyroidism was also associated with malignancy (P=0.044; OR =1.63; 95% CI: 1.01–2.65), central lymph node dissection (P<0.001; OR =4.74; 95% CI: 2.32–10.2) and auto-transplantation of parathyroid glands (P<0.001; OR =3.03; 95% CI: 1.85–5.00). Permanent hypoparathyroidism was associated with malignancy (P=0.006; OR =16.82; 95% CI: 0.95–297.19). Risk stratification tables were generated providing predicted probability for hypoparathyroidism and accidental parathyroidectomy providing probability values for each event occurring for a given set of pre-operative parameters. Maximal risk for temporary hypoparathyroidism of 74.1% occurred with thyroidectomy for malignant disease, neck dissection and parathyroid auto-transplantation and maximal risk for accidental parathyroidectomy was 59.5% and occurred with a thyroidectomy was performed for malignant disease and required a neck dissection. Whenever a central neck dissection was performed, the risk of temporary

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hypoparathyroidism was greater than 50% and auto-transplantation of parathyroid resulted in risks greater than 40%.

Conclusions: Accidental parathyroidectomy occurs commonly and is associated with malignancy and central neck dissection. Hypoparathyroidism is strongly associated with malignancy, central lymph node dissection, and auto-transplantation. The reported risk stratification tables can assist in the post-operative management of patients by identifying patients most at risk of requiring post-operative calcium and vitamin D supplementation.

Keywords: Thyroidectomy; hypoparathyroidism; parathyroid

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Introduction

Accidental parathyroidectomy is the inadvertent removal of parathyroid glands during thyroid surgery (1). Previous published studies have demonstrated that accidental parathyroidectomy is associated with factors such as diagnosis of malignancy, concurrent central neck dissection and intercurrent thyroiditis (2,3). Accidental parathyroidectomy is a risk factor for temporary hypoparathyroidism, permanent hypoparathyroidism and clinically significant hypocalcaemia necessitating calcium and vitamin D replacement (4).

The aim of this study is to identify predictors of accidental parathyroidectomy and hypoparathyroidism following total thyroidectomy and stratify these predictors according to their clinical importance. This can assist surgeons in deciding when to commence prophylactic calcium supplementation.

Methods

A retrospective cohort study was conducted using the Sydney Head and Neck Cancer Institute database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Sydney Local Health District Ethics and Review Committee (protocol X16-0367). Because of the retrospective nature of the research, the requirement for informed consent was waived. Inclusion criteria were patients having a total thyroidectomy with or without central neck dissection. Patients who underwent parathyroidectomy at the same time as thyroid surgery and those undergoing partial thyroidectomy or completion thyroidectomy were excluded. The study is reported according to the STROBE reporting guidelines (available at https://www.theajo.com/article/view/10.21037/ajo-24-32/rc).

Post-operative calcium and parathyroid hormone (PTH) levels were measured either on the day of surgery or on the day following surgery (if surgery was performed late in the day). Temporary hypoparathyroidism was defined as PTH levels <1.6 pmol/L with a normal reference range of 1.6 to 6.9 pmol/L. Patients were considered to have permanent hypoparathyroidism if their PTH levels remained below 1.6 pmol/L at 6 months post-procedure. Hypocalcaemia was defined as serum levels of <2.1 mmol/L with a normal reference range of 2.1 to 2.6 mmol/L.

Pre-operative information was obtained from the medical record which included patient's age, sex and indication for surgery. Operation reports were accessed to determine whether a neck dissection was performed, the number of parathyroids identified intraoperatively, and the number of parathyroids auto-transplanted. Histopathology reports were used to determine the presence and number of parathyroid glands inadvertently removed, thyroid weight and whether thyroiditis was present. Auto-transplantation was performed by mincing the parathyroid gland and either placing it directly into the sternocleidomastoid muscle or mixing with buffered salt solution and injecting into the sternocleidomastoid muscle.

Statistical analysis

Statistical analysis was performed using software R version 4.3.1 (5). Three quantitative variables used in the analysis where categorised. These include identification of parathyroids intraoperatively and the number of parathyroids present in the histopathological specimen which were grouped into 0, 1, or >1 parathyroids. Thyroid

Table 1 Demographic profile of patients undergoing total thyroidectomy (n=295)

Characteristics	N [%]
Gender	
Male	75 [25]
Female	220 [75]
Age (years)	
17 to 25	14 [5]
26 to 50	125 [42]
51 to 75	141 [48]
76 to 89	15 [5]
Malignant disease	
Yes	144 [49]
No	151 [51]
Neck dissection	
Yes	37 [13]
No	258 [87]
Parathyroid auto-transplantation	
Yes	123 [42]
No	172 [58]
Thyroid weight (g)	
<20	65 [22]
20–100	173 [59]
>100	37 [13]
Unknown	20 [7]
Thyroiditis	
Yes	71 [24]
No	224 [76]
Goitre	
Yes	116 [39]
No	179 [61]
Accidental parathyroidectomy	
Yes	78 [26]
No	216 [73]
Unknown	1 [0]
Number of parathyroids removed	
One	56 [19]
Two or more	15 [5]
Parathyroids removed, number unspecified	7 [2]
Temporary hypoparathyroidism	
Yes	107 [36]
No	186 [63]
Unknown	2 [1]
Permanent hypoparathyroidism	
Yes	7 [2]
No	287 [97]
Unknown	8 [3]

weight was grouped into three groups which were <20, 20 to 100, and >100 g. Associations between categorical variables were performed using the Chi-square test and Fisher's exact test. Univariate logistic regression analyses were performed for accidental parathyroidectomy and temporary hypoparathyroidism with insufficient patients to generate a model for permanent hypoparathyroidism. Predicted probabilities for accidental parathyroidectomy and temporary hypoparathyroidism were generated based on the logistic regression models, producing risk stratification tables. A significance level of 5% ($P<0.05$) was used throughout.

Results

A total of 683 patients were available in the database who underwent total thyroidectomy between 2010 and 2022. Complete data was available for 295 of these patients and they were all included in the final study to limit selection bias. Out of the cohort of 295 patients, 220 (75%) were female with a median age of 53 years. There were 144 (49%) total thyroidectomies performed for malignant disease and 37 (13%) patients underwent concurrent central lymph node dissection. Parathyroids were identified in the histological specimens of 78 (26%) patients who underwent surgery with 56 (19%) patients having one gland removed and 15 (5%) patients having two or more glands removed. There were 107 (36%) patients who developed temporary hypoparathyroidism and 7 (2%) patients who developed permanent hypoparathyroidism. Demographic, clinical, pathological, and biochemical data are shown in *Table 1*. Two patients did not have sufficient

Table 2 Univariate logistic regressions for risk factors and accidental parathyroidectomy

Characteristics	N or n [%]	OR	95% CI	P value[†]
Malignant disease	295			0.015
No	152 [52]	–	–	
Yes	143 [48]	1.91	1.13, 3.26	
T-stage	82			0.234
1	48	1.29	0.6, 2.77	
2	15	0.6	0.13, 2.78	
3	15	3.39	1.14, 10.06	
4	4	1.29	0.13, 12.84	
Central lymph node dissection	295			<0.001
No	257 [87]	–	–	
Yes	38 [13]	4.94	2.44, 10.2	
Goitre	295			0.912
No	180 [61]	–	–	
Yes	115 [39]	0.97	0.567, 1.64	
Number of parathyroids identified intraoperatively	287			0.175
0	5 [1.7]	–	–	
1	36 [13]	0.333	0.040, 2.27	
2 or more	246 [86]	0.225	0.029, 1.39	
Thyroiditis	295			0.638
No	225 [76]	–	–	
Yes	70 [24]	0.862	0.454, 1.58	
Thyroid weight (g)	276			0.816
<20	65 [24]	–	–	
20–100	174 [63]	1.10	0.579, 2.17	
>100	37 [13]	0.845	0.309, 2.17	
Temporary hypoparathyroidism	291			<0.001
No	186 [64]	–	–	
Yes	105 [36]	3.1	1.81, 5.31	
Permanent hypoparathyroidism	293			0.04
No	286 [98]	–	–	
Yes	7 [2]	17.75	2.1, 149.94	

[†], logistic regression. OR, odds ratio; CI, confidence interval.

Table 3 Univariate logistic regressions for risk factors and temporary hypoparathyroidism

Characteristics	N or n [%]	OR	95% CI	P value[†]
Malignant disease	293			0.044
No	150 [51]	–	–	
Yes	143 [49]	1.63	1.01, 2.65	
T-stage	82			0.473
1	48	1.76	0.9, 3.43	
2	15	0.83	0.25, 2.72	
3	15	1.26	0.4, 3.95	
4	4	2.26	0.31, 16.55	
Central lymph node dissection	293			<0.001
No	255 [87]	–	–	
Yes	38 [13]	4.74	2.32, 10.2	
Parathyroid auto-transplantation	291			<0.001
No	169 [58]	–	–	
Yes	122 [42]	3.03	1.85, 5.00	
Number of parathyroids identified intraoperatively	285			0.963
0	5 [1.8]	–	–	
1	35 [12]	0.783	0.114, 6.56	
2 or more	245 [86]	0.841	0.137, 6.47	
Thyroiditis	293			0.109
No	223 [76]	–	–	
Yes	70 [24]	1.57	0.904, 2.71	
Accidental parathyroidectomy	292			<0.001
No	215 [74]	–	–	
Yes	77 [26]	3.12	1.83, 5.38	

Discrepancy in total number is due to missing biochemistry data for two patients. [†], logistic regression. OR, odds ratio; CI, confidence interval.

post-operative biochemistry results to assess for temporary hypoparathyroidism and eight patients did not have results to assess permanent hypoparathyroidism. These patients were excluded from the analysis in these respective sections.

In univariate logistic regression analyses for accidental parathyroidectomy, significant predictors were total thyroidectomy for malignant disease [P=0.015; odds ratio (OR) =1.91; 95% confidence interval (CI): 1.13–3.26] and concurrent central lymph node dissection (P<0.001; OR =4.94; 95% CI: 2.44–10.2) as shown in *Table 2*. There was no correlation between the number of parathyroids identified intraoperatively and accidental parathyroidectomy, regardless if whether 1 or more than 1 parathyroid was identified (P=0.175; OR =0.333; 95% CI: 0.040–2.27; and OR =0.225; 95% CI: 0.029–1.39; respectively).

In univariate logistic regression analyses for temporary hypoparathyroidism, significant predictors were concurrent central lymph node dissection (P<0.001; OR =4.74; 95% CI: 2.32–10.2), auto-transplantation of parathyroids (P<0.001; OR =3.03; 95% CI: 1.85–5.00), accidental parathyroidectomy (P<0.001; OR =3.12; 95% CI: 1.83–5.38), and total thyroidectomy for malignant disease

Table 4 Risk factors for permanent hypoparathyroidism in patients undergoing total thyroidectomy

Factors	Overall (n=287)	No (n=280)	Yes (n=7)	OR	95% CI	P value[†]
Parathyroid auto-transplantation						0.7
No	166 [58]	161 [58]	5 [71]	–	–	
Yes	119 [42]	117 [42]	2 [29]	0.55	0.11, 2.89	
Unknown	2	2	0			
Malignant disease						0.006
No	148 [52]	148 [53]	0 [0]	–	–	
Yes	139 [48]	132 [47]	7 [100]	16.82	0.95, 297.19	
Central lymph node dissection						0.2
No	252 [88]	247 [88]	5 [71]	–	–	
Yes	35 [12]	33 [12]	2 [29]	2.99	0.56, 16.06	
Number of parathyroids identified intraoperatively						0.3
0	5 [1.8]	5 [1.8]	0 [0]	–	–	
1	33 [12]	31 [11]	2 [29]	0.87	0.04, 20.76	
2 or more	241 [86]	236 [87]	5 [71]	0.26	0.01, 5.22	
Unknown	8	8	0			
Thyroid weight (g)						0.6
<20	64 [24]	63 [24]	1 [14]	–	–	
20–100	167 [62]	161 [62]	6 [86]	2.34	0.27, 19.89	
>100	37 [14]	37 [14]	0 [0]	15.32	1.86, 125.83	
Unknown	19	19	0			
Thyroiditis						>0.9
No	218 [76]	212 [76]	6 [86]	–	–	
Yes	69 [24]	68 [24]	1 [14]	0.52	0.06, 4.39	
Goitre						>0.9
No	172 [60]	168 [60]	4 [57]	–	–	
Yes	115 [40]	112 [40]	3 [43]	1.13	0.25, 5.12	
Accidental parathyroidectomy						0.001
No	212 [74]	211 [76]	1 [14]	–	–	
Yes	74 [26]	68 [24]	6 [86]	18.61	2.20, 157.39	
Unknown	1	1	0			

Data are presented as n [%] or n. Discrepancy in total number is due to missing biochemistry data for eight patients. [†], Fisher's exact test. OR, odds ratio; CI, confidence interval.

(P=0.044; OR =1.63; 95% CI: 1.01–2.65) as shown in *Table 3*. As seen in *Table 4*, total thyroidectomy for malignant disease and accidental parathyroidectomy were associated with permanent hypoparathyroidism (P=0.006; OR =16.82; 95% CI: 0.95–297.19; and P=0.001; OR =18.61; 95% CI: 2.20–157.39; respectively).

Intraoperative identification of parathyroid glands, intercurrent thyroiditis, goitre, and thyroid weight were not

associated with accidental parathyroidectomy, temporary hypoparathyroidism, or permanent hypoparathyroidism. T-staging was available for 82 of the 143 patients with malignant disease and was found to not be a significant factor for accidental parathyroidectomy nor temporary hypoparathyroidism.

Risk prediction tables were constructed for accidental parathyroidectomy and temporary hypoparathyroidism, using the predicted probability of significant variables based on logistic regression analyses. Results are shown in *Tables 5,6*. The combination of malignancy with central lymph node dissection had a predicted probability of accidental parathyroidectomy of 60%, where malignancy in isolation only had a probability of accidental parathyroidectomy of 24%. The presence of all risk factors (malignant disease, central lymph node dissection, parathyroid auto-transplantation, and accidental parathyroidectomy) was associated with an 81% probability of temporary hypoparathyroidism.

Discussion

This study demonstrated that accidental parathyroidectomy was associated with temporary hypoparathyroidism and permanent hypoparathyroidism which is consistent with published studies (4,6). Risk factors for accidental parathyroidectomy, temporary hypoparathyroidism and permanent hypoparathyroidism could be derived from the data obtained. There were no protective factors identified in this study, with variables such as intraoperative parathyroid identification having no statistically significant association with outcomes. Risk prediction tables were able to be generated using established variables (*Tables 5,6*). These intend to act as a clinical aid to help identify factors associated with accidental parathyroidectomy, guide practices in monitoring post-operative PTH and calcium levels and commencement of calcitriol and calcium supplementation.

Our accidental parathyroidectomy rate of 26% is similar to results reported by Manatakis *et al.* and Gourgiotis *et al.* who reported rates of 24.9% and 21.6% with sample sizes of 315 and 281 which are similar to this study (7,8). Our study did establish a correlation between accidental parathyroidectomy and post-operative hypoparathyroidism. Studies done previously have had mixed results in regards to this relationship with a general bias to studies agreeing with the correlation (9-11). A high-volume cohort study by Applewhite *et al.* did identify correlation between accidental parathyroidectomy and temporary hypoparathyroidism, along with temporary biochemical and symptomatic hypocalcaemia (12). This is not universally appreciated as there are also studies that investigated a similar relationship and were not able to identify a statistically significant link between accidental parathyroidectomy and post-operative hypoparathyroidism and/or hypocalcaemia (2,13).

Central neck dissection and malignant disease were two significant variables associated with both accidental

Table 5 Predicted probability of accidental parathyroidectomy in patients undergoing total thyroidectomy based on risk factors

Malignant disease	Central lymph node dissection	Predicted probability of accidental parathyroidectomy[†]
No	No	0.205
Yes	No	0.236
Yes	Yes	0.595

[†], predicted probability derived from logistic regression.

Table 6 Predicted probability of temporary hypoparathyroidism in patients undergoing total thyroidectomy based on risk

Malignant disease	Central lymph node dissection	Parathyroid auto-transplantation	Predicted probability of temporary hypoparathyroidism[†]
No	No	No	0.243
No	No	Yes	0.439
Yes	No	No	0.240
Yes	No	Yes	0.435
Yes	Yes	No	0.540
Yes	Yes	Yes	0.741

[†], predicted probability derived from logistic regression.

parathyroidectomy and temporary hypoparathyroidism. This result has been mirrored by previous literature with other studies also identifying both variables as risk factors for accidental parathyroidectomy (10,12,14). With a central lymph node dissection, the inferior parathyroid glands are commonly removed and reimplanted. It can be difficult to differentiate parathyroid glands which are yellow brown from the surrounding yellow fatty tissue and in many cases parathyroids can be enveloped entirely by such fatty tissue. Enlarged central compartment lymph nodes can be difficult to differentiate from parathyroid glands. Although the surgical operation is technically the same for benign and malignant thyroid surgery, malignant disease is often associated with perithyroidal inflammation making identification of parathyroid glands challenging (3,15,16). Inspection or dissection looking for clinically suspicious central compartment lymph nodes may compromise the blood supply to parathyroid glands and influence the hypoparathyroidism rate and local invasion by malignant lesions can create adhesions with nearby tissue increasing the risk of inadvertent resection (3). While not conclusive, the lack of significance of thyroid weight and T-staging for both accidental parathyroidectomy and temporary hypoparathyroidism suggest that the mechanism by which malignancy is associated with both factors is not mass effect alone.

Thyroiditis is one of the variables that has been reported to increase the risk of accidental parathyroidectomy due to the inflammation distorting tissue appearance and hindering parathyroid identification. Studies by Khairy *et al.* and Mencio *et al.* did establish that thyroiditis increased the risk of accidental parathyroidectomy (2,16). We were unable to demonstrate a statistically significant association. Thyroid goitre similarly is another variable that has been considered as a risk for inadvertent parathyroid removal but this study, like previously established literature, found that it had no significant impact (10).

Intraoperative identification of parathyroid glands has been previously thought to be an important step to mitigate the risk of accidental parathyroidectomy (6). This has been supported by previous studies with a paper by Edafe *et al.* demonstrating that identification of two or fewer parathyroid glands was associated with an increased risk of hypoparathyroidism (17). This has led to the development of new techniques such as near-infrared autofluorescence that have demonstrated some success in improving parathyroid detection (18). We did not demonstrate a correlation between parathyroid identification and clinical outcomes of accidental parathyroidectomy or hypoparathyroidism. It is of note that not all surgeons in our unit routinely identify every parathyroid gland during thyroid surgery as dissection to identify these glands may lead to vascular compromise of the parathyroid gland.

Re-implantation of parathyroid glands was associated with temporary hypoparathyroidism but not permanent hypoparathyroidism. This is not unexpected as re-implanted parathyroid glands usually take greater than 1 month to restore function and re-implanting compromised parathyroid glands is protective for preventing permanent hypoparathyroidism (19,20). The limited number of patients with permanent hypoparathyroidism limits full exploration of this.

The primary finding of the risk tables was that a central lymph node dissection was the most influential parameter in determining the risk of either accidental parathyroidectomy or clinical hypoparathyroidism with associated groups all demonstrating a predicted probability greater than 50%. The highest risk group for temporary hypoparathyroidism occurred when all three risk factors were combined including malignant disease, central neck dissection and auto-transplantation resulting in predicted risk of 74.1%. Auto-transplantation in itself carries a risk of temporary hypoparathyroidism >40% and may be associated with prolonged requirement for calcium and vitamin D supplementation although this was not investigated in our study. Thus, in patients most at risk of developing hypoparathyroidism (malignancy, central neck dissection and auto-transplantation) prophylactic calcium supplementation is advisable to mitigate symptomatic hypocalcaemia and prolonged hospital admission.

The distinguishing feature of this study is the risk predictions tables generated which provides an easily interpretable tool to help assist in clinical practice. Accidental parathyroidectomy has a 59.5% risk of occurring in the setting of malignancy and central lymph node dissection and we have shown that accidental parathyroidectomy is significantly associated with both temporary hypoparathyroidism and permanent hypoparathyroidism. It is in this group that surgeons must be extra vigilant to carefully examine the removed thyroid gland and lymphatic tissue to look for inadvertently removed parathyroid glands.

The primary limitation of this study arises from its limited ability to comment on the occurrence and risk of permanent hypoparathyroidism due to its low incidence

rate. A much larger cohort may have been able to identify other risk factors and is required to generate a risk prediction table for permanent hypoparathyroidism.

Conclusions

The main risk factors identified in this study for accidental parathyroidectomy were central lymph node dissection and malignant disease and the risk factors for temporary hypoparathyroidism were central lymph node dissection, malignant disease and auto-transplantation. Using the data available, risk prediction tables were able to be generated, and can be used to guide clinical practice by identifying patients with high risk of accidental parathyroidectomy and temporary hypoparathyroidism.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://www.theajo.com/article/view/10.21037/10.21037/ajo-24-32/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Sydney Local Health District Ethics and Review Committee (protocol X16-0367). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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