Risk factors of permanent hypoparathyroidism after total thyroidectomy

Retrospective analysis of 285 consecutive patients

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AIM: *Permanent hypoparathyroidism is the most common long-term complication after total thyroidectomy. The aim of the present study was to investigate the risk factors of this complication.*
MATERIAL AND METHODS: *Patients undergoing thyroidectomy in our Unit between January 2017 and February 2018 were retrospectively analysed. They were divided into 2 groups: those with normal parathyroid function in the long term were included in Group A, those who developed permanent hypoparathyroidism in Group B.*
RESULTS: *Two hundred and eighty-five patients were included in this study: 271 in Group A and 14 in Group B. No statistically significant difference was found in terms of sex, age, extent of surgery, rate of retrosternal goiter, postoperative stay and histopathological findings between the 2 groups. On the contrary, mean operative time, rate of patients with PTH values < 6.3 pg/mL on postoperative day 1 and mean thyroid weight were significantly greater in Group B than in Group A ($P = 0.049$, $P < 0.001$, $P = 0.014$; respectively).*
CONCLUSIONS: *Long operative times, PTH levels < 6.3 pg/mL on postoperative day 1 and high thyroid weight have proved to be strong risk factors of permanent hypoparathyroidism after total thyroidectomy. Thus, in these cases a careful follow-up is highly recommended.*

KEY WORDS: Permanent hypoparathyroidism, Risk factors, Total thyroidectomy

Introduction

Total thyroidectomy (TT) is the most widely surgical procedure performed in endocrine surgery, for both benign and malignant diseases.
Hypoparathyroidism (HPT) is a common complication after TT [1-13]. This condition is characterized by decreased values of circulating parathyroid hormone leading to hypocalcemia and slightly higher phosphate levels.
Hypocalcemia can cause symptoms ranging from numbness of the face and hands to tetany, convulsions and suffocation (caused by laryngeal and diaphragmatic spasms). Moreover, manifestations of chronic hypoparathyroidism include some severe conditions, such as kidney stones, nephrocalcinosis, chronic kidney disease, basal ganglia calcifications, myocardial dysfunction, dental abnormalities and cataracts [14-19].
In case of HPT, the main purpose of treatment is to maintain normal blood calcium levels. Medical therapy of hypocalcemia consists in the administration of calcium and vitamin D [20].
Although HPT after TT reverses spontaneously within a few months in most cases, in a few patients, it can persist for more than 1 year [8]. In this case this condition has to be considered permanent and, to avoid subtle but potentially lethal complications, long-term therapy and careful follow-up are mandatory. However, long-term calcium supplementation can also cause side effects, such as myocardial infarction, urinary calculi and gastrointestinal reactions [21].

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The incidence of transient and permanent hypoparathyroidism is 6.9–46% and 0-10%, respectively [6,9,22].
Costs to society in terms of increased postoperative stay, sick leave, medical treatments and surveillance, with periodic laboratory testing, are considerable. Moreover, permanent HPT is an important cause of medical litigation.
In order to ensure patients the best follow-up, it is very important to be aware of the risk factors of permanent HPT after total thyroidectomy. The aim of the present study was to investigate this topic.

Material and Methods

This is a retrospective study on patients who underwent total thyroidectomy in our Unit of General and Endocrine Surgery (University of Cagliari) between January 2017 and February 2018.
Patients simultaneously submitted to lateral and/or central neck dissection were included in this study, while those who simultaneously underwent parathyroidectomy or parathyroid autotransplantation were excluded.
Patients were divided into 2 groups: those with normal parathyroid function in the long term were included in Group A, those who developed permanent HPT in Group B.
Demographic data (sex, age), information on surgical procedure (extent of surgery, operative time, rate of retrosternal goiter), histopathological findings, surgical outcomes (PTH value on postoperative day 1, postoperative stay) and complications (recurrent laryngeal nerve injury, hypoparathyroidism, postsurgical cervical haematoma, wound infection) were recorded.
All operations were performed under general anaesthesia. Lateral and/or central neck dissection was performed in patients with preoperative diagnosis or intraoperative suspicion of lymph node metastases. Recurrent laryngeal nerves and parathyroid glands were systematically searched and identified. Intraoperative nerve monitoring (IONM) was often used in order to facilitate nerve identification and to confirm its functional integrity. Haemostasis was mainly achieved by means of energy-based devices. One or two closed suction drains were placed below the strap muscles. The cervical linea alba and platysma were sutured with absorbable sutures and skin was closed by a continuous intradermal suture. The duration of the surgical procedure was estimated in minutes from skin incision to skin closure.
Retrosternal goiter was defined as a thyroid in which any part of the gland extended below the thoracic inlet with the patient in the surgical position.
Serum calcium and PTH levels were assayed preoperatively and on the first and second postoperative days. Postsurgical HPT was defined as PTH < 10 pg/mL following the operation (normal range = 10-65 pg/mL). All patients with postsurgical HPT, even if asymptomatic, received treatment with calcium carbonate (1–3 g/day) and calcitriol (0.5–1.5 μg/day). In case of severe hypocalcemia, intravenous calcium gluconate was used.
Permanent HPT was defined as PTH concentrations below the normal range for more than 12 months.
Parathyroid hormone was measured with ADVIA Centaur XPT Immunoassay Systems (Siemens Healthcare Diagnostics, Inc.). The detection threshold of the PTH test used is equal to 6.3 pg/mL (PTH levels < 6.3 pg/mL are undetectable).
In case of suspected recurrent laryngeal nerve injury, a fibrolaryngoscopy was performed to assess vocal cord mobility.
Statistical analyses were performed with MedCalc® 18.0.2. Fisher exact test or Chi-squared test were used for categorical variables and t-test for continuous variables. *P* values < 0.05 were considered statistically significant.

Results

A total of 285 patients were included in this study.
Demographic data, information on surgical procedure and histopathological findings of the entire sample are shown in Table I.
There were 90 (31.58%) males and 195 (68.42%) females, with a mean age of 52.34 ± 14.97 years old. Two hundred and sixty-five (92.98%) patients underwent total thyroidectomy, 10 (3.51%) total thyroidectomy with ipsilateral central neck dissection, 4 (1.40%)

Table I - *Demographic data, information on surgical procedure and histopathological findings.*

	Total (n = 285)
Sex	
- Male	90 (31.58%)
- Female	195 (68.42%)
Age (mean ± SD)	52.34 ± 14.97
Extent of surgery	
- TT	265 (92.98%)
- TT + ICND	10 (3.51%)
- TT + CND	4 (1.40%)
- TT + CND + LND	6 (2.11%)
Retrosternal goiter	63 (22.11%)
Operative time (mean ± SD)	97.75 ± 31.76
Thyroid weight (mean ± SD)	55.06 ± 65.11
Histological diagnosis	
- Graves' disease	43 (15.09%)
- Autoimmune thyroiditis	80 (20.07%)
- Malignancy	115 (40.35%)

TT: total thyroidectomy; ICND: ipsilateral central neck dissection; CND: central neck dissection; LND: lateral neck dissection.

Table II - *Surgical outcomes and complications.*

	Total (n = 285)
PTH < 6.3 pg/mL on POD 1	64 (22.46%)
Postoperative stay (mean ± SD)	2.86 ± 0.96
Unilateral recurrent nerve injury	13 (4.56%)
Bilateral recurrent nerve injury	0
Cervical haematoma	2 (0.70%)
Transient hypoparathyroidism	61 (21.40%)
Permanent hypoparathyroidism	14 (4.91%)
Wound infection	1 (0.35%)

POD 1: postoperative day 1.

total thyroidectomy with central neck dissection and 6 (2.11%) total thyroidectomy with central and lateral neck dissection. Sixty-three (22.11%) patients had a retrosternal goiter. The mean operative time was 97.75 ± 31.76 minutes. The mean thyroid weight was 55.06 ± 65.11 g. Histopathological diagnosis was Graves' disease in 43 (15.09%) patients, autoimmune thyroiditis in 80 (20.07%) and malignancy in 115 (40.35%).

Surgical outcomes and complications of the entire sample are reported in Table II.

PTH levels < 6.3 pg/mL on postoperative day 1 were observed in 64 (22.46%) patients. The mean postoperative stay was 2.86 ± 0.96 days. There were 2 (0.70%) cervical haematomas, 13 (4.56%) unilateral recurrent laryngeal nerve lesions, 1 (0.35%) wound infection, 61 (21.40%) cases of transient HPT and 14 (4.91%) cases of permanent HPT. No bilateral recurrent laryngeal nerve injury was observed.

Of the 285 patients, 271 were included in Group A and 14 in Group B.

The comparison between the 2 groups is shown in Table III. In Group A, there were 88 (32.47%) males and 183 (67.53%) females, with a mean age of 52.38 ± 14.75 years old. Two hundred and fifty-two (92.99%) patients underwent total thyroidectomy, 10 (3.69%) total thyroidectomy with ipsilateral central neck dissection, 3 (1.11%) total thyroidectomy with central neck dissection and 6 (2.21%) total thyroidectomy with central and lateral neck dissection. Fifty-seven (21.03%) patients had a retrosternal goiter. The mean operative time was 96.91 ± 30.83 minutes. PTH concentrations < 6.3 pg/mL on postoperative day 1 were observed in 50 (18.45%) patients. The mean postoperative stay was 2.86 ± 0.98 days. The mean thyroid weight was 52.92 ± 62.43 g. Histopathological diagnosis was Graves' disease in 39 (14.39%) patients, autoimmune thyroiditis in 76 (28.04%) and malignancy in 111 (40.96%).

In Group B, there were 2 (14.29%) males and 12 (85.71%) females, with a mean age of 51.64 ± 19.40 years old. Thirteen (92.86%) patients underwent total thyroidectomy and 1 (7.14%) total thyroidectomy with central neck dissection. Six (42.86%) patients had a ret-

Table III - *Comparison between the 2 groups.*

	Group A (n = 271)	Group B (n = 14)	P value
Sex			
- Male	88 (32.47%)	2 (14.29%)	0.238
- Female	183 (67.53%)	12 (85.71%)	
Age (mean ± SD)	52.38 ± 14.75	51.64 ± 19.40	0.858
Extent of surgery			
- TT	252 (92.99%)	13 (92.86%)	1.000
- TT + ICND	10 (3.69%)	0	1.000
- TT + CND	3 (1.11%)	1 (7.14%)	0.183
- TT + CND + LND	6 (2.21%)	0	1.000
Retrosternal goiter	57 (21.03%)	6 (42.86%)	0.090
Operative time (mean ± SD)	96.91 ± 30.83	114.07 ± 44.73	0.049
PTH < 6.3 pg/mL on POD 1	50 (18.45%)	14 (100%)	< 0.001
Postoperative stay (mean ± SD)	2.86 ± 0.98	2.86 ± 0.66	0.981
Thyroid weight (mean ± SD)	52.92 ± 62.43	96.57 ± 98.61	0.014
Histological diagnosis			
- Graves' disease	39 (14.39%)	4 (28.57%)	0.239
- Autoimmune thyroiditis	76 (28.04%)	4 (28.57%)	1.000
- Malignancy	111 (40.96%)	4 (28.57%)	0.357

TT: total thyroidectomy; ICND: ipsilateral central neck dissection; CND: central neck dissection; LND: lateral neck dissection; POD 1: postoperative day 1.

rosternal goiter. The mean operative time was 114.07 ± 44.73 minutes. PTH concentrations < 6.3 pg/mL on postoperative day 1 were observed in 14 (100%) patients. The mean postoperative stay was 2.86 ± 0.66 days. The mean thyroid weight was 96.57 ± 98.61 g.
Histopathological diagnosis was Graves' disease in 4 (28.57%) patients, autoimmune thyroiditis in 4 (28.57%) and malignancy in 4 (28.57%).
No statistically significant difference was found in terms of sex, age, extent of surgery, rate of retrosternal goiter, postoperative stay and histopathological findings between the 2 groups.
On the contrary, mean operative time, rate of patients with PTH values < 6.3 pg/mL on postoperative day 1 and mean thyroid weight were significantly greater in Group B than in Group A ($P = 0.049$, $P < 0.001$, $P = 0.014$; respectively).

Discussion

Despite progress in surgical technique and even in the most experienced hands, postsurgical HPT remains a challenging problem. Permanent HPT is the most common long-term complication after TT [1-13].
During surgery parathyroid glands can be damaged due to various mechanisms: thermal or mechanical stress, vascular injury (interrupted blood flow or impaired venous efflux) and involuntary removal [11,23-26].
To prevent inadvertent injury of the parathyroid glands, it is important to have a detailed anatomical understanding of these organs and their vasculature.
Identification of these glands during surgery may be difficult even with a careful dissection technique due to their variable location. It is usual for the superior parathyroid glands to be posterior to the superior poles of the thyroid, close to the cricothyroid junction. The inferior parathyroid glands, instead, are mostly located at the inferior poles of the thyroid gland, but they are sometimes in a different location.
Most authors, including us, claim that systematic research and identification of the parathyroid glands during thyroid surgery helps to reduce the incidence of inadvertent parathyroid injury.
According to the literature, after thyroidectomy, the rate of presence of parathyroid tissue on histopathological examination varies from 5.2% up to 21.6% [2].
Incidentally removed parathyroid glands were reported in intrathyroidal location, in subcapsular location and in extracapsular location. In some studies the rate of intrathyroidal localization was quite high. On the basis of this finding, complete avoidance of incidental parathyroidectomy during thyroid surgery appears to be virtually impossible [2,27]. However, many authors advise to carefully inspect the surgical specimen surface for the presence of inadvertent removed parathyroid glands and, if present, they recommend to autotransplant them into the sternocleidomastoid muscle. Autotransplantation can also be performed in case of detection of accidentally devascularized parathyroid glands [33].
Some factors have been associated with an increased risk of developing permanent HPT: female gender, long duration of thyroid disease before surgery, autoimmune thyroiditis, Graves' disease, thyroid cancer, high thyroid weight, low postoperative PTH and calcium levels, long duration of surgery, low surgeon experience and central neck dissection [1,23-44]. Another important risk factor, not investigated in this study, is represented by reoperations for recurrent goiter. These operations are complicated due to the presence of scar tissue that causes a distortion of the surgical field; making accurate identification of the anatomical structures quite difficult [27,45].
Among the factors we analysed, mean operative time, mean thyroid weight and rate of patients with PTH concentrations < 6.3 pg/mL on postoperative day 1 were significantly greater in patients who developed permanent HPT. As already explained, the cut-off value of 6.3 pg/mL was established on the basis of the detection threshold of the PTH test used. About the thyroid weight, it appears quite obvious that heavier, and therefore larger, glands entail longer and more difficult operations, thus with greater risk of complications. In this regard, it is important to note that although the difference between the 2 groups in terms of rate of retrosternal goiter was not statistically significant, the P value was only slightly above the threshold for the declaration of statistical significance.
Differently from other studies, no statistically significant difference was found in terms of sex, extent of surgery and histopathological findings between the 2 groups.
The main limit of this study consists in the limited number of patients analysed. Thus, further larger, possibly multicenter and prospective, studies are needed to better investigate this topic.

Conclusions

Long operative times, PTH levels < 6.3 pg/mL on postoperative day 1 and high thyroid weight have proved to be strong risk factors of permanent hypoparathyroidism after total thyroidectomy. Thus, in these cases, but also in the presence of risk factors identified in other studies, a careful follow-up is highly recommended.

Riassunto

L'ipoparatiroidismo permanente è la più comune complicanza a lungo termine della tiroidectomia totale. Lo scopo del presente studio è stato di analizzare i fattori di rischio di questa complicanza.
Sono stati analizzati retrospettivamente i pazienti sottoposti a tiroidectomia totale nella nostra U.O.C. di

Chirurgia Generale ed Endocrina (A.O.U. Cagliari) tra Gennaio 2017 e Febbraio 2018. I pazienti sono stati divisi in 2 gruppi: quelli con funzione paratiroidea normale a lungo termine sono stati inclusi nel Gruppo A, quelli che hanno sviluppato ipoparatiroidismo permanente nel Gruppo B.
Un totale di 285 pazienti sono stati inclusi in questo studio: 271 nel Gruppo A e 14 nel Gruppo B. Nessuna differenza statisticamente significativa è stata rilevata tra i 2 gruppi in termini di sesso, età, estensione dell'intervento chirurgico, tasso di gozzo retrosternale, degenza post-operatoria e reperti istopatologici. Al contrario, il tempo operatorio medio, il tasso di pazienti con valori di PTH < 6.3 pg/mL in prima giornata post-operatoria e il peso medio della tiroide sono risultati significativamente maggiori nel Gruppo B rispetto al Gruppo A (P = 0.049, P < 0.001, P = 0.014; rispettivamente).
Tempi operatori lunghi, livelli di PTH < 6.3 pg/mL in prima giornata post-operatoria e peso elevato della tiroide hanno dimostrato di essere importanti fattori di rischio di ipoparatiroidismo permanente dopo tiroidectomia totale. In questi casi è pertanto altamente raccomandato un attento follow-up.

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References

1. Puzziello A, Rosato L, Innaro N, Orlando G, Avenia N, Perigli G, Calò PG, De Palma M: *Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients*. Endocrine, 2014; 47:537-42.

2. Zheng J, Song H, Cai S, Wang Y, Han X, Wu H, Gao Z, Qiu F: *Evaluation of clinical significance and risk factors of incidental parathyroidectomy due to thyroidectomy: A single-center retrospective clinical study.* Medicine (Baltimore), 2017; 96:e8175.

3. Coimbra C, Monteiro F, Oliveira P, Ribeiro L, de Almeida MG, Condé A: *Hypoparathyroidism following thyroidectomy: Predictive factors*. Acta Otorrinolaringol Esp, 2017; 68:106-11.

4. Kakava K, Tournis S, Papadakis G, Karelas I, Stampouloglou P, Kassi E, Triantafillopoulos I, Villiotou V, Karatzas T: *Postsurgical Hypoparathyroidism: A Systematic Review*. In Vivo, 2016; 30:171-79.

5. C, Niederle B: *Hypoparathyroidism after total thyroidectomy: A prospective study*. Arch Surg, 2008; 143:132-37.

6. Villarroya-Marquina I, Sancho J, Lorente-Poch L, Galle, Park WS, Min SY: *Predictors and risk factors of hypoparathyroidism after total thyroidectomy*. Int J Surg, 2016; 34:47-52.

7. Bilezikian JP, Khan A, Potts JT Jr, Brandi ML, Clarke BL, Shoback D, Jüppner H, D'Amour P, Fox J, Rejnmark L, Mosekilde L, Rubin MR, Dempster D, Gafni R, Collins MT, Sliney J, Sanders J: *Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research*. J Bone Miner Res, 2011; 26:2317-37.

8. Asari R, Passler C, Kaczirek K, Scheuba go-Otaegui L, Sitges-Serra A: *Time to parathyroid function recovery in patients with protracted hypoparathyroidism after total thyroidectomy*. Eur J Endocrinol, 2018; 178:105-13.

9. Pattou F, Combemale F, Fabre S, Carnaille B, Decoulx M, Wemeau JL, Racadot A, Proye C: *Hypocalcemia following thyroid surgery: incidence and prediction of outcome*. World J Surg, 1998; 22:718-24.

10. Calò PG, Pisano G, Medas F, Tatti A, Tuveri M, Nicolosi A: *Risk factors in reoperative thyroid surgery for recurrent goitre: Our experience.* G Chir, 2012; 33:335-38.

11. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A: *Importance of in situ preservation of parathyroid glands during total thyroidectomy*. Br J Surg, 2015; 102:359-67.

12. Calò PG, Medas F, Conzo G, Podda F, Canu GL, Gambardella C, Pisano G, Erdas E, Nicolosi A: *Intraoperative neuromonitoring in thyroid surgery: Is the two-staged thyroidectomy justified?* Int J Surg, 2017; 41(Suppl 1):13-20.

13. Conzo G, Avenia N, Ansaldo GL, Calò P, De Palma M, Dobrinja C, Docimo G, Gambardella C, Grasso M, Lombardi CP, Pelizzo MR, Pezzolla A, Pezzullo L, Piccoli M, Rosato L, Siciliano G, Spiezia S, Tartaglia E, Tartaglia F, Testini M, Troncone G, Signoriello G: *Surgical treatment of thyroid follicular neoplasms: results of a retrospective analysis of a large clinical series*. Endocrine, 2017; 55:530-38.

14. Lorente-Poch L, Sancho JJ, Muñoz-Nova JL, Sánchez-Velázquez P, Sitges-Serra A: *Defining the syndromes of parathyroid failure after total thyroidectomy*. Gland Surg, 2015; 4:82-90.

15. Lorente-Poch L, Sancho JJ, Carballo L, Sitges-Serra A: *Clinical profile and long-term follow-up of 32 patients with postoperative permanent hypoparathyroidism*. Gland Surg, 2017; 6(Suppl 1):3-10.

16. Mitchell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Becker CB, Burnett-Bowie SA, Mannstadt M: *Long-term follow-up of patients with hypoparathyroidism*. J Clin Endocrinol Metab, 2012; 97:4507-14.

17. Rastogi R, Beauchamp NJ, Ladenson PW: *Calcification of the basal ganglia in chronic hypoparathyroidism*. J Clin Endocrinol Metab, 2003; 88:1476-77.

18. Kinirons MJ, Glasgow JF: *The chronology of dentinal defects related to medical findings in hypoparathyroidism*. J Dent, 1985; 13:346-49.

19. Sitges-Serra A, Ruiz S, Girvent M, Manjón H, Dueñas JP, Sancho JJ: *Outcome of protracted hypoparathyroidism after total thyroidectomy*. Br J Surg, 2010; 97:1687–95.

20. Khan MI, Waguespack SG, Hu MI: *Medical management of postsurgical hypoparathyroidism*. Endocr Pract, 2011; 17(Suppl 1):18-25.

21. Reid IR, Bristow SM, Bolland MJ: *Calcium supplements: Benefits and risks*. J Intern Med, 2015; 278:354-68.

22. Costanzo M, Marziani A, Condorelli F, Migliore M, Cannizzaro MA: *Post-thyroidectomy hypocalcemic syndrome: predictive value of early PTH. Preliminary results*. Ann Ital Chir, 2010; 81:301-05.

23. Imga NN, Atas H, Torgutalp M, Daglar G, Berker D: *Stratifying the risk factors for hypoparathyroidism after total thyroidectomy. A single Center study*. Ann Ital Chir, 2019; 90:21-30.

24. Qasaimeh GR, Al Nemri S, Al Omari AK: *Incidental extirpation of the parathyroid glands at thyroid surgery: Risk factors and postoperative hypocalcemia*. Eur Arch Otorhinolaryngol, 2011; 268:1047-51.

25. Spiliotis J, Vaxevanidou A, Sergouniotis F, Tsiveriotis K, Datsis A, Rogdakis A, Kekelos S: *Risk factors and consequences of incidental parathyroidectomy during thyroidectomy*. Am Surg, 2010; 76:436–41.

26. Sitges-Serra A, Gallego-Otaegui L, Suárez S, Lorente-Poch L, Munné A, Sancho JJ: *Inadvertent parathyroidectomy during total thyroidectomy and central neck dissection for papillary thyroid carcinoma*. Surgery, 2017; 161:712-19.

27. Youssef T, Gaballah G, Abd-Elaal E, El-Dosoky E: *Assessment of risk factors of incidental parathyroidectomy during thyroid surgery: A prospective study*. Int J Surg, 2010; 8:207-11.

28. Sitges-Serra A, Gómez J, Barczynski M, Lorente-Poch L, Iacobone M, Sancho J: *A nomogram to predict the likelihood of permanent hypoparathyroidism after total thyroidectomy based on delayed serum calcium and iPTH measurements*. Gland Surg, 2017; 6(Suppl 1):11-19.

29. Yetkin G, Citgez B, Yazici P, Mihmanli M, Sit E, Uludag M: *Early prediction of post-thyroidectomy hypocalcemia by early parathyroid hormone measurement*. Ann Ital Chir, 2016; 87:417-21.

30. Raffaelli M, De Crea C, Carrozza C, D'Amato G, Zuppi C, Bellantone R, Lombardi CP: *Combining early postoperative parathyroid hormone and serum calcium levels allows for an efficacious selective post-thyroidectomy supplementation treatment*. World J Surg, 2012; 36:1307-13.

31. Saba A, Podda M, Messina Campanella A, Pisanu A: *Early prediction of hypocalcemia following thyroid surgery. A prospective randomized clinical trial*. Langenbecks Arch Surg, 2017; 402:1119-25.

32. Stein DJ, Noordzij JP, Kepchar J, McLeod IK, Brietzke S, Calò PG: *Use of Parathyroid Hormone Assay after Thyroidectomy: A Survey of US and European Surgeons.* Clin Med Insights Endocrinol Diabetes, 2013; 6:39-45.

33. Almquist M, Hallgrimsson P, Nordenström E, Bergenfelz A: *Prediction of permanent hypoparathyroidism after total thyroidectomy*. World J Surg, 2014; 38:2613-20.

34. Caglià P, Puglisi S, Buffone A, Bianco SL, Okatyeva V, Veroux M, Cannizzaro MA: *Post-thyroidectomy hypoparathyroidism, what should we keep in mind?* Ann Ital Chir, 2017; 6:371-81.

35. Wang W, Xia F, Meng C, Zhang Z, Bai N, Li X: *Prediction of permanent hypoparathyroidism by parathyroid hormone and serum calcium 24 h after thyroidectomy*. Am J Otolaryngol, 2018; 39:746-50.

36. Calvo Espino P, Rivera Bautista JÁ, Artés Caselles M, Serrano González J, García Pavía A, García-Oria MJ, Caravaca-Fontán F, Lucena de la Poza JL, Sánchez Turrión V: *Serum levels of intact parathyroid hormone on the first day after total thyroidectomy as predictor of permanent hypoparathyroidism*. Endocrinol Diabetes Nutr, 2019; 66:195-201.

37. Canu GL, Medas F, Longheu A, Boi F, Docimo G, Erdas E, Calò PG: *Correlation between iPTH Levels on the first postoperative day after total thyroidectomy and permanent hypoparathyroidism: our experience*. Open Med (Wars), 2019; 14:437-42.

38. Docimo G, Ruggiero R, Casalino G, Del Genio G, Docimo L, Tolone S: *Risk factors for postoperative hypocalcemia*. Updates Surg, 2017; 69:255-60.

39. Roh JL, Kim JM, Park CI: *Central lymph node metastasis of unilateral papillary thyroid carcinoma: Patterns and factors predictive of nodal metastasis, morbidity, and recurrence*. Ann Surg Oncol, 2011; 18:2245-50.

40. Hallgrimsson P, Nordenstrom E, Bergenfelz A, Almquist M: *Hypocalcaemia after total thyroidectomy for Graves' disease and for benign atoxic multinodular goitre*. Langenbecks Arch Surg, 2012; 397:1133-7.

41. Medas F, Erdas E, Canu GL, Longheu A, Pisano G, Tuveri M, Calò PG: *Does hyperthyroidism worsen prognosis of thyroid carcinoma? A retrospective analysis on 2820 consecutive thyroidectomies*. J Otolaryngol Head Neck Surg, 2018; 47:6.

42. Calò PG, Conzo G, Raffaelli M, Medas F, Gambardella C, De Crea C, Gordini L, Patrone R, Sessa L, Erdas E, Tartaglia E, Lombardi CP: *Total thyroidectomy alone versus ipsilateral versus bilateral prophylactic central neck dissection in clinically node-negative differentiated thyroid carcinoma. A retrospective multicenter study*. Eur J Surg Oncol, 2017; 43:126-32.

43. Conzo G, Tartaglia E, Avenia N, Calò PG, de Bellis A, Esposito K, Gambardella C, Iorio S, Pasquali D, Santini L, Sinisi MA, Sinisi AA, Testini M, Polistena A, Bellastella G: *Role of prophylactic central compartment lymph node dissection in clinically N0 differentiated thyroid cancer patients: analysis of risk factors and review of modern trends*. World J Surg Oncol, 2016; 14:149.

44. Pesce CE, Shiue Z, Tsai HL, Umbricht CB, Tufano RP, Dackiw AP, Kowalski J, Zeiger MA: *Postoperative hypocalcemia after thyroidectomy for Graves' disease*. Thyroid, 2010; 20:1279-83.

45. Medas F, Tuveri M, Canu GL, Erdas E, Calò PG: *Complications after reoperative thyroid surgery: retrospective evaluation of 152 consecutive cases*. Updates Surg, 2019; 71:705-10.

Commento e Commentary

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Gli autori hanno condotto un interessante studio sull'ipoparatiroidismo permanente dopo interventi di tiroidectomia totale, che si configura come una delle più frequenti complicanze di questa chirurgia.
Nell'analisi retrospettiva di un campione di 285 pazienti hanno preso in considerazione quali potenziali fattori di rischio, non solo quelli ben noti e ampiamente discussi in vari reports come il sesso, la patologia neoplastica o infiammatoria, il tipo di intervento chirurgico, l'interessamento linfonodale del compartimento centrale e l'estensione della dissezione, e il basso dosaggio del PTH in prima giornata post-operatoria, ma anche altri come il tempo operatorio e il peso della ghiandola, due fattori non sempre attentamente valutati, e che ritengo degni di particolare attenzione.
La durata dell'intervento e il prolungarsi dei tempi chirurgici, associati a una ridotta concentrazione ed incaute manovre sul campo operatorio, possono essere responsabili di sofferenza vascolare delle paratiroidi accuratamente preservate con un conseguente danno parenchimale che si manifesterà nell'immediato post-operatorio o a distanza con un importante ipoparatiroidismo, che in alcuni casi può evolvere nella complicanza permanente [1,2].
Il peso della ghiandola è strettamente correlato alle sue dimensioni, e l'aumento volumetrico, come spesso si osserva nei gozzi voluminosi, può comportare un inglobamento iuxtacapsulare o intracapsulare delle paratiroidi, specie le inferiori, e non sempre, nonostante una accurata preparazione si riesce a preservarle senza importanti danni obiettivabili.
Sono pienamente d'accordo con gli autori che la loro esperienza chirurgica originale e di estremo interesse, meriti una ulteriore verifica per una ancora più significativa conferma con studi prospettici e in collaborazione con altri centri di riferimento.

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The authors evaluated, in their retrospective study, the risk factors predictive of permanent hypoparathyroidism following total thyroidectomy, one of the most frequent complication after thyroid surgery.
They enrolled 285 consecutive patients and considered both those factors as well as gender, malignant and inflammatory pathology, thyroidectomy types, the extent of lymph node dissectio in the central neck and early post-operatory PTH value, commonly considered to be proved risk factors for post thyroidectomy hypoparathyroidism, and other factors as well as the operative time and the weight of the thyroid gland, less investigated in order to affect the development of parathyroid complication.
The results of their surgical experience are extremely interesting and the two risk factors, as the operative time and the weight of the thyroid, indagated and confirmed as predictive of post-operative permanent hypoparathyroidism, deserve particular attention from Endocrinosurgery Associations.
The prolonged operative time along with reduced perioperative attention, should compromise the vascular system of the parathyroid glands just accurately preserved in the parathracheal area, and the potential ischemic damage or venous congestion may be responsible for the late permanent parathroid morbidity .1,2
The excessive weight of the thyroid stands for volumetric increase of the thyroid gland and , often, in these large goiters, the parathyroid glands, expecially the lower ones, should be incorporated in the capsular tissue and the accurate surgical procedure for their preservation, not always, results in sufficient parenchimal or vascular integrity.
As final comment, it would be interesting for the authors, in future studies, to have a larger randomizzed cohort and verify their results with those of other high- volume centers.

References

1. Ardito G, Revelli L, Polistena A, et al.: *Complications of neck dissection in papillary thyroid carcinoma: a modified procedure to reduce parathyroid morbidity.* In Vivo, 2016; 30: 303-08.

2. Ardito G. : *Complications of neck dissections in papillary thyroid carcinoma. A modified procedure to reduce parathyroid morbidity.* Leading Article. Ann. Ita. Chir. 2019; 3: 185- 190.