

# To identify or not to identify parathyroid glands during total thyroidectomy

Yuk Kwan Chang, Brian H. H. Lang

Department of Surgery, The University of Hong Kong, Hong Kong SAR, China

**Contributions:** (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Brian H. H. Lang, Department of Surgery, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China. Email: blang@hku.hk.

**Abstract:** Hypoparathyroidism is one of the most common complications after total thyroidectomy and may impose a significant burden to both the patient and clinician. The extent of thyroid resection, surgical techniques, concomitant central neck dissection, parathyroid gland (PG) autotransplantation and inadvertent parathyroidectomy have long been some of the risk factors for postoperative hypoparathyroidism. Although routine identification of PGs has traditionally been advocated by surgeons, recent evidence has suggested that perhaps identifying fewer number of *in situ* PGs during surgery (i.e., selective identification) may further lower the risk of hypoparathyroidism. One explanation is that visual identification may often lead to subtle damages to the nearby blood supply of the *in situ* PGs and that may increase the risk of hypoparathyroidism. However, it is worth highlighting the current literature supporting either approach (i.e., routine *vs.* selective) remains scarce and because of the significant differences in study design, inclusions, definitions and management protocol between studies, a pooled analysis on this important but controversial topic remains an impossible task. Furthermore, it is worth noting that identification of PGs does not equal safe preservation, as some studies demonstrated that it is not the number of PGs identified, but the number of PG preserved *in situ* that matters. Therefore a non-invasive, objective and reliable way to localize PGs and assess their viability intra-operatively is warranted. In this aspect, modern technology such as the indocyanine green (ICG) as near-infrared fluorescent dye for real-time *in situ* PG perfusion monitoring may have a potential role in the future.

**Keywords:** Total thyroidectomy; hypoparathyroidism; hypocalcemia; parathyroid gland identification (PG identification)

Submitted May 18, 2017. Accepted for publication Jun 08, 2017.

doi: 10.21037/gs.2017.06.13

**View this article at:** <http://dx.doi.org/10.21037/gs.2017.06.13>

## Introduction

Total thyroidectomy is a common surgical procedure and is often the treatment of choice for a number of benign and malignant conditions. However, despite being a relatively safe procedure in experienced hands, hypoparathyroidism remains one of the most common complications (1,2). Patients suffering from postoperative hypoparathyroidism generally present with a low postoperative serum calcium (Ca), a high phosphate and a low parathyroid

hormone (PTH) level. Symptomatic hypocalcemia (such as numbness, muscle spasms, confusion) may occur, although it is getting less common because of the improved postoperative Ca management (3). Regarding the etiology of postoperative hypoparathyroidism, it is generally thought that it is due to a transient reduction in blood supply of *in situ* parathyroid glands (PGs), which results in a transient reduction of parathyroid function (or hormone secretion). Although inadvertent removal of PGs (i.e., incidental parathyroidectomy) may contribute to hypoparathyroidism,

it does not happen often. As a result, provided the PG is not entirely stripped of its blood supply, normalization of parathyroid function is expected for the majority of patients. Nevertheless, this recovery phase may take several weeks to months (i.e., protracted hypoparathyroidism) (2). After normalization, patients are usually able to stop their oral Ca ± calcitriol supplements. However, a small proportion (<5%) may not have their parathyroid function normalized and they are considered as having persistent or permanent hypoparathyroidism. The reported rates of temporary and permanent hypoparathyroidism in the literature vary widely between 19% to 38% and 0% to 3% respectively, depending on the definition of hypoparathyroidism (4), casemix and type of thyroid resections.

Although postoperative hypoparathyroidism can often be managed by taking regular oral Ca ± vitamin D supplements, some patients may experience persistent hypocalcemic symptoms leading to impaired daily living and quality of life. This situation also poses challenges to clinicians and increases health costs (5-7). Long term morbidities such as renal failure, basal ganglia calcifications, neuropsychiatric derangements and infections have been reported as a result of supplementation over a prolonged period (8,9).

### **Risk factors leading to postoperative hypoparathyroidism**

The extent of resection and surgical technique are factors known to influence the subsequent risk of postoperative hypoparathyroidism (10). For instance, patients who undergo a bilateral thyroidectomy are at greater risk of hypoparathyroidism than those who undergo a unilateral thyroidectomy (10,11). Similarly, those who undergo peripheral ligation of the inferior thyroid artery at the thyroid capsule are more prone to develop hypoparathyroidism than those who undergo sub-capsular dissection (10). Parathyroid auto-transplantation, inadvertent excision of PGs and presence of PGs in the thyroid specimen have also been shown to increase the risk of post-operative hypoparathyroidism (1,11-17). This is because they all lower the number of *in situ* PGs and therefore, the residual parathyroid function is immediately compromised. Concomitant central neck dissection has also been found to be an independent risk factor, presumably because this procedure increases risk of incidental parathyroidectomy (15,16). Surgeon's experience (12) and hospital operative volume (11) have also been shown to

be important in post-operative hypoparathyroidism. After operation, clinical symptoms and signs such as numbness and tetany, as well as serum Ca level should be monitored. Some suggested that an early postoperative decrease in serum iPTH concentrations (8,10), combining with serum Ca concentration may predict hypoparathyroidism and guide the administration of Ca or vitamin D supplements (18,19). Post-operative hypoparathyroidism results from a reduction of functioning parathyroid parenchyma, which could be secondary to intraoperative damages caused by mechanical or thermal trauma, gland devascularization, obstruction of venous outflow, and inadvertent parathyroid excision (14,15,17). Therefore, the question has been whether there are strategies or approaches a surgeon could follow intra-operatively to minimize PG injuries and hypoparathyroidism. One approach has been to see if there is a relationship between the number of PGs identified intra-operatively and post-operative hypoparathyroidism. To date, there are two schools of thought with some surgeons advocating routine identification of all PGs (i.e., the operating surgeon spending time in visualizing all or as many PGs as possible at surgery) while others advocating the opposite and would spend little to no time in visualizing PGs at surgery (i.e., selective identification).

### **Routine versus selective identification**

The term "routine identification" refers to a strategy where the surgeon would try his or her best to identify each and every PG in its orthotopic or non-orthotopic position (20-23). This has traditionally been the approach accepted by many surgeons. However, the pitfall with this strategy is that not all PGs could be found in their orthotopic or usual positions. For example, some superior PGs are located at the superior pole of the posterior thyroid gland near the cricothyroid junction and some inferior PGs may be located far away from the neck in the thymus and mediastinum (24,25). Therefore, even with the best intention, it may not be always possible to identify each and every PG at the time of total thyroidectomy. The other pitfall is that this strategy may lead to inadvertent damage to the nearby blood supply and therefore, may devitalize PGs leading hypoparathyroidism. Also, this strategy may unnecessarily prolong the operation.

On the other hand, some surgeons advocate a selective approach where the PGs are encountered rather than being actively searched for during surgery. This approach might be more time-saving as the surgeon does not need to

**Table 1** Publications supporting routine identification approach

Year	Author (reference)	No. of patients	Definition of hypoCa	Rate of hypoCa	Findings
1998	Pattou (28)	1,071	Temporary: serum calcium level under 8.0 mg/dL (2 mmol/L) on at least two consecutive measurements	3.3%	No. of PG identified <i>in situ</i> correlated with the outcome of hypoCa (P=0.01)
			Permanent: requiring Ca or vitamin D therapy or both 1 year after surgery	1.1%	No. of PGs identified <i>in situ</i> correlated with the outcome of hypoCa (P=0.01)
2002	Thomusch (10)	5,846	Temporary: calcium or vitamin D therapy required to treat clinical symptoms of tetany, regardless of calcium serum levels; within 6 months after operation	6.0–23.0%	Identification of PG less than 2 was 1.4 times more likely to develop temporary hypocalcemia (P=0.17)
			Permanent: calcium or vitamin D therapy required to treat clinical symptoms of tetany, regardless of serum calcium levels; exceeded 6 months beyond operation	0.9–9.0%	Identification of PG less than 2 was 4.1 times more likely to develop permanent hypoCa (P=0.001)
2008	Bergenfelz (21)	1,648 (bilateral)	HypoCa treated with vitamin D at first follow-up after 1–6 weeks	2.6%	No. of identified PG is protective to hypoCa (OR, 0.741; CI: 0.621–0.883)
2010	Sitges-Serra (23)	442	Temporary: iPTH <12 pg/mL at 1 month after surgery	18.1%	Identified 1–2 PG had 52% hypoCa; identified 3–4 PG had 30.5% hypoCa (P=0.018)
			Permanent: serum calcium level under 8.0 mg/dL (2 mmol/L) 1 year after operation	3.9%	Identified 1–2 PG had 32% hypoCa; identified 3 PG had 22% hypoCa; identified 4 PG had 5% hypoCa (P=0.096)
2014	Puzziello (29)	2,631	NA	27.9%	Temporary hypoCa rate in PG identified is higher than PG not identified (29.2% vs. 18.7%, P<0.01)
				0.9%	Permanent hypoCa rate in PG identified is lower than PG not identified

No., number; PG, parathyroid gland; hypoCa, hypocalcemia; PTH, parathyroid hormone; OR, odds ratio; CI, confidence interval; P, P value; NA, not applicable.

search all sites and because of the less extensive dissection, the chance of inadvertently jeopardizing the blood supply to PGs would be less. Nevertheless, in either approaches, when parathyroid blood supply is jeopardized, expeditious autografting of the affected PG should be performed, although the benefit of autografting has also been questioned (26,27).

### Supporting evidence for either approach

Given that the issue of whether to routinely identify or not identify PGs during total thyroidectomy has remained controversial, the present review aimed to look into the current literature for supporting evidence in either approach. To improve the clarity of the evidence, studies were divided into those reporting temporary (<6 months)

and those reporting persistent/permanent (≥6 months) after operation. For studies reporting both, they were included in both tables.

### The evidence for routine identification

Table 1 lists the studies which support the routine identification approach.

#### Temporary hypocalcemia

Bergenfelz *et al.* reported a multicenter retrospective audit with 3,660 patients, involving both benign and malignant thyroid diseases and various types of thyroid operations. Among these, 1,648 patients received bilateral thyroidectomy. It was found that at 6-week post-op, 10% and 8% of patients were on vitamin D and Ca supplements,

respectively; and the number of identified PGs intra-operatively was protective to hypocalcemia [odds ratio (OR), 0.74; confidence interval (CI): 0.621–0.883]. Association with hypocalcemia at 6-month post-op was not analyzed since missing data was high (4.5%) (21).

Siteges-Serra *et al.* reported the outcome of post-thyroidectomy hypocalcemia in 422 patients retrospectively, and found that 50.2% developed hypocalcemia post-operatively, which was defined as Ca less than 2.0 mmol/L (23). At one month after operation the rate of hypoparathyroidism was 18.1%; and within the group of patients who had post-operative hypocalcemia, identifying 3 or 4 PGs had less hypocalcemia than identifying 1 or 2 PGs (30.5% *vs.* 52.0%,  $P=0.018$ ). However, one fifth of their patients underwent central neck dissection for thyroid cancer and the results were not adjusted for confounding factors. The rate of hypocalcemia at 1 year after operation was not associated with the number of PGs identified.

### Permanent hypocalcemia

A German retrospective multivariate analysis by Thomusch *et al.* involving 5,846 patients underwent bilateral thyroidectomy showed that besides extent of thyroid operations and surgical technique, number of identified PGs less than 2 increased post-operative permanent hypocalcemia (OR, 4.1;  $P=0.001$ ), which was defined as requiring Ca or vitamin D supplements 6 months after operation (10). Removal of a single PG was not associated with post-operative hypoparathyroidism. Similar trend was observed for transient hypocalcemia (less than 6 months) however statistical significance was not reached (OR, 1.7;  $P=0.700$ ). Together with some other reports which showed that permanent hypoparathyroidism emerged exclusively after less than 3 PGs had been identified intra-operatively (22,30), it was suggested that at least 2 PGs should be identified and preserved *in situ* during operation (10).

This suggestion was also supported by Pattou *et al.* (28), who prospectively evaluated the incidence and predictive factors of hypocalcemia in 1,071 consecutive patients. It was found that number of PGs identified *in situ* during surgery was correlated with the outcome of hypocalcemia ( $P=0.010$ ). Patients carried a high risk for permanent hypocalcemia (Ca <2 mmol/L and symptomatic 1 year after operation) if fewer than 3 PGs were identified *in situ* during surgery. When 3 or more PGs identified and preserved during surgery, spontaneous recovery was observed in all patients except one (28).

Similar findings were reported in a recent multi-centre

prospective study by Puzziello *et al.* involving 2,631 patients, showing that identifying PGs was important to prevent permanent hypocalcemia. Interestingly, the percentage of developing transient hypocalcemia in patients with identification of PGs intra-operatively was higher than in patients with PGs not identified (29.2% *vs.* 18.7%,  $P<0.010$ ). This suggested that identifying PGs during operation may have a protective role in hypocalcemia in long-term, though in expense of a higher risk of hypocalcemia in short term (29).

### The evidence for selective identification

In contrast, some recent studies showed that patients with a greater number of PGs identified intra-operatively might be at greater risk of hypoparathyroidism. Some suggest that identification of PGs is not equivalent to preserving them; instead, may increase direct trauma or disrupt blood supply during surgical manipulation (29,31). Therefore, surgeons start to advocate “selective approach” while PGs are only sought in their orthotopic locations with no attempt to identify them elsewhere. It was hypothesized that with the adoption of extra-capsular dissection, not seeing a PG usually implies that it is being covered by vascularized tissue and therefore had a better chance of being *in situ* (31). Of course, this assumption is only valid in high quality extra-capsular dissection and experienced hands. Table 2 summarizes the evidence in support of selective identification approach.

### Temporary hypocalcemia

In 2000, a small Swedish prospective cohort by Lindblom *et al.* with 38 patients undergone total or near total thyroidectomy reported that number PGs identified intra-operatively was associated with Ca reduction within 24 hours after operation via stepwise multiple linear regression ( $B=2.57$ ,  $P=0.036$ ) (32). Recently, Lang *et al.* reported a prospective study with 117 patients evaluating predictive factors of hypocalcemia after thyroidectomy and found that the more PGs identified intra-operatively, the more post-operative transient hypocalcemia ( $P=0.017$ ) (34). Later the same group conducted another prospective study with 569 patients to specifically look into the relationship between number of PGs identified intra-operatively with post-operative hypocalcemia, and confirmed that greater number of PGs identified was an independent risk factor for temporary (within 24 hours) and protracted (4–6 weeks after operation) hypocalcemia ( $P<0.001$ ,  $P=0.007$ , respectively).

**Table 2** Publications supporting selective identification approach

Year	Author (reference)	No. of patients	Definition of hypoCa	Rate of hypoCa	Findings
2000	Lindblom (32)	38	Two or more episodes of serum calcium less than 2.00 mmol/L or symptomatic within 24 hours after surgery	26.3%	Stepwise multiple linear regression analysis showed PGs identified was associated with Ca reduction (B=2.57, P=0.036)
2009	Pfleiderer (33)	162	Temporary: symptomatic patients with serum calcium <2.12 mmol/L or asymptomatic patients with serum calcium <2.0 mmol/L within 6 months post-op	42.6%	When no PG identified, 70% have normocalcemia and 30% have temporary hypoCa; when all PG identified, 90% has temporary hypoCa
			Permanent: symptomatic patients with serum calcium <2.12 mmol/L or asymptomatic patients with serum calcium <2.0 mmol/L 6 months beyond operation	5.6%	When no PG identified, 70% have normocalcemia and 0% has permanent hypoCa; when all PG identified, 10% had permanent hypoCa
2012	Lang (34)	117	Serum Ca <1.9 mmol/L or symptomatic; requiring calcium +/- vitamin D supplements upon discharge after operation	14.5%	More PG identified was associated with hypoCa (P=0.017)
2013	Sheahan (35)	126	Biochemical criteria: any post-operative serum calcium <2.00 mmol/L; clinical criteria: symptomatic hypoCa	22.2% (biochemical) and 10.3% (clinical)	Identified 0–2 PGs had lower incidence of clinical hypoCa than identified 3–4 PG (3.2% vs. 17.1%, P=0.02); difference in biochemical hypoCa was not significant (16.1% vs. 28.1%, P=0.13)
2015	Prazenica (36)	788	NA	NA	Identified 0–2 PG had lower incidence of temporary hypoCa than identified 3–4 PG in univariate analysis (P=0.015)
			NA	NA	Identified 0–2 PG had lower incidence of permanent hypoCa than identified 3–4 PG in univariate analysis (P=0.040)
2016	Lang (31)	569	Temporary: serum adjusted Ca <2.00 mol/L or need for oral calcium or vitamin D supplements to maintain normocalcemia at 24 h after operation; protracted: a subnormal PTH <1.2 pmol/L or need for oral calcium or vitamin D supplements to maintain normocalcemia at post-operative 4–6 weeks	Temporary = 22.8%; protracted = 12.1%	Greater No. of PG identified was an independent risk factor for temporary and protracted hypoCa (P<0.001, P=0.007); recovery time from protracted hypoCa for identifying <4 PGs was shorter than identifying all 4 PG (2.8 vs. 7 months, P<0.001); identifying all 4 PG has 1.8x of temporary hypoCa
			Permanent: need calcium or vitamin D supplements for more than 1 year after operation	2.6%	Identified 4 PGs had higher permanent hypoCa rate than identified 0–1 PGs (11.2% vs. 1.5%, P<0.001); but not an independent risk factor (P=0.702) in multivariate analysis

No., number; PG, parathyroid gland; hypoCa, hypocalcemia; PTH, parathyroid hormone; OR, odds ratio; P, P value; NA, not applicable.

Recovery time from protracted hypocalcemia for identifying <4 PGs was significantly shorter than identifying all 4 PGs (2.8 vs. 7 months, P<0.001). Chance of having 4 glands *in situ* decreased with greater number of PGs identified and identifying all 4 PGs has 1.8 times risk of temporary hypocalcemia (31).

Similar results were found when comparing patients

with 0–2 to 3–4 PGs seen intra-operatively. In a prospective study by Sheahan *et al.* with 126 patients underwent total thyroidectomy, 0–2 PGs identified has lower incidence of clinical hypocalcemia than 3–4 PGs found (3.2% vs. 17.1%, P=0.02). No difference was observed in inadvertent parathyroidectomy between the two groups, which might suggest routine identification of PGs may not be helpful

in preventing inadvertent parathyroidectomy (35). In a retrospective study by Prazenica *et al.* with 788 patients, higher temporary hypocalcemia ( $P=0.015$ ) was found in 3–4 PGs identified group (36). In the study of Puzziello *et al.* (29), although it suggested that number of identified PGs may increase permanent hypocalcemia, it was associated with more transient hypocalcemia.

### Permanent hypocalcemia

Pflederer *et al.* reported a prospective cohort involving 162 patients who underwent total or completion thyroidectomy (33). Association test between number of PGs identified and the development of hypocalcemia produced a significant result in post-operative 6 months ( $\text{Chi} = 11.4$ ,  $P=0.022$ ). When no PGs were seen, 70% had normo-calcemia and 30% has temporary hypocalcemia. For those with all PGs identified, 90% developed temporary hypocalcemia and 10% with permanent hypocalcemia, which required exogenous Ca and vitamin D beyond 6 months after operation (33).

Similarly, a recently published prospective study by Lang *et al.* with 569 patients who underwent total thyroidectomy for benign disease reported that permanent hypocalcemia, which was defined as requiring exogenous Ca or vitamin D one year after operation, was significantly higher in patient with 4 PGs identified than in patients with 0–1 PGs identified (11.2% *vs.* 1.5%,  $P<0.001$ ). Although the number of PGs identified was not an independent risk factor ( $P=0.702$ ) in multivariate analysis, this might be due to small number of permanent hypocalcemia in the study ( $n=15$ , 2.6%) (31). Similarly, Prazenica *et al.* also found that identifying 4 PGs intra-operatively had higher permanent hypocalcemia rate than identifying 0–1 PGs in univariate analysis ( $P=0.040$ ) (36).

### Shortcomings with the literature

It is worth noting that majority of the studies were retrospective in design, for instance, multi-institutional observational studies and audits, thus only the association but not the causative relationship can be determined. Moreover, the low incidence of permanent hypoparathyroidism, which was reported to be 0–3.6% (1), leads to lack of statistical significance in the association test between number of identified PGs and permanent hypocalcemia. Although multi-institutional studies provide large sample size, they involved a heterogeneous population with different inclusion and exclusion criteria, various extents of thyroid resections (total or subtotal thyroidectomy, bilateral

lobectomy, completion thyroidectomy, central neck dissection, etc.), different definition of hypoparathyroidism, drug prescription and follow-up protocol. These may miss out certain confounding factors that give rise to postsurgical hypoparathyroidism (1,17). On the other hand, single-institutional studies provide clearer definition and better quality data. However, they were frequently under power due to small sample size and the results may not be applicable in other institutions due to different volume of operations and surgeon's experience.

A systemic review and meta-analysis focusing on reducing post-thyroidectomy hypocalcemia found that no measures, including intra-operative PG identification, were significantly associated with reduction of hypocalcemia, given the majority of trials were of low quality due to a lack of blinding and also wide variability in study design and definitions (37). So far there is no meta-analysis specifically summarizes the relationship of intra-operative identifications of PGs with post-operative hypoparathyroidism; understandably it would be difficult because of the very heterogeneous studies. Moreover, an inevitable limitation for all studies is that PGs were “identified” *in situ* solely based on operative surgeon's assessment without any histological proof; understandably biopsy of the identified PG may actually inflict more damage and thus lead to more iatrogenic hypoparathyroidism. In addition, the current available studies only focus on the relationship between number of identified PGs and hypocalcemia, which may not truly reflect on the comparison between routine and selective identification approach. A lot of time PGs were encountered during dissection without surgeon's intention to look for them. Thus, a high number of PGs identified is not necessarily equivalent to adopting a routine identification approach. It is also difficult to have carried out prospective study or randomized controlled trial to compare these two approaches, since a large number of patients would be required to ensure adequate power.

### Relationship between number of identified PGs and parathyroid function

Despite the conflicting data in the literature, one thing is clear: to reduce the risk of postoperative hypoparathyroidism, the ability of leaving as many “vascularized” PGs *in situ* is very important. In a prospective study of 657 patients who underwent first-time total thyroidectomy, the prevalence of hypocalcemia

and of protracted and permanent hypoparathyroidism were inversely related to the PGs remaining *in situ* score (i.e., 4 minus “auto-transplanted PGs” minus “PGs in specimen”). By logistic regression, this score turned out to be one of the most significant variables influencing acute and chronic parathyroid failures. On the other hand, the number of PGs identified intraoperatively did not appear to have any impact on transient, protracted or permanent hypocalcemia (38).

Similarly, in a retrospective review of 454 patients who underwent total thyroidectomy for papillary thyroid carcinoma, the number of PGs preserved was obtained by subtracting the number of PGs in a given specimen from 4. It was found that the incidence of transient hypoparathyroidism increased when there were three or fewer preserved PGs than when all four PGs were preserved ( $P=0.004$ ), but did not affect permanent hypoparathyroidism. During total thyroidectomy, preserving at least one PG with an intact blood supply appeared to be sufficient to prevent permanent hypoparathyroidism when auto-transplant was not performed (39). Lang *et al.* also showed that the number of PG *in situ* was inversely proportional to post-thyroidectomy temporary, protracted and permanent hypoparathyroidism (31). In a study about multi-factorial scoring system to predict post thyroidectomy hypocalcemia so as to enable safe discharge within 24 hours of surgery with 145 patients, lesser number of PG preserved at surgery was one of the significant predictive factors ( $P=0.001$ ) (40).

Identifying PG is not a safeguard for protecting its function, because how we adequately assess the viability of the PG after finding it out based on macroscopic appearance is questionable due to subjective assessment and inter-observant variation. Moreover, function of discolored glands was not necessarily impaired and may recover within a short time after surgery (41). On the other hand, absence of discoloration was not a reliable way to suggest intact PG blood supply (42). Selective auto-transplantation was advocated for de-vascularized or inadvertent removed PGs. However, for PGs that were identified *in situ*, an intact vascular pedicle seemed cannot guarantee adequate function of PGs, because protracted and permanent hypoparathyroidism were also seen in patients with PGs that seemingly had adequate blood supply (43). Occasionally a PG can look normal even though its vascular pedicle seemed to be unsafe, and some surgeons evaluated blood supply for controversial PG by making a small incision in it with a cold knife (44). Yet it was also found that surgeons differ substantially in the ability of predicting risk of

hypoparathyroidism during thyroid surgery (45). Thus, an objective and less invasive assessment is warranted.

### Assessing viability of *in situ* PGs

So now the question continued on how we could assess parathyroid viability in real-time, and whether it is possible to identify and preserve PGs *in situ* without trying to dissect and expose them out, limiting the risk of vascular injury. Studies have been going on for locating and predicting function of PGs with indocyanine green (ICG) fluorescent imaging in both thyroid and parathyroid surgery (46-52). ICG is a water-soluble molecule that binds to plasma protein and confined to intravascular compartment. It will emit fluorescent light when being excited by near-infrared light (NIR); thus, the combination of ICG and NIR may provide real-time assessment on tissue perfusion within a focused area reflected by the fluorescent light intensity. ICG fluorescent imaging potentially helps locate PGs and thus prevent inadvertent parathyroidectomy or damaging them (48). Moreover, ICG angiography may provide quantitative evaluation of *in situ* PG perfusion after total thyroidectomy, and could be a good predictor for post-operative hypoparathyroidism (46,47,50,51). Although currently these reported studies were mainly concerning feasibility with a relative small sample size, ICG fluorescent angiography could potentially be a less invasive option for identifying PGs during thyroidectomy and provide more accurate prediction of parathyroid function.

### Conclusions

It remains controversial on how the number of PGs identified during total thyroidectomy may affect iatrogenic hypoparathyroidism. More PGs identified during surgery appear to be associated with a greater risk of temporary hypoparathyroidism. Regarding to permanent hypoparathyroidism, conclusion remains unclear because of the low incidence and heterogeneity of studies. Moreover, one should realize that studying the association between numbers of PGs identified intra-operatively and post-thyroidectomy hypoparathyroidism did not directly address on the issue of whether or not the surgeon should actively seek all PGs regardless of their location. To better answer this question, to identify or not identify the PGs during total thyroidectomy, a prospective comparative study or even a randomized control trial might be required, although this would be difficult due to requirement of large sample

size. In order to prevent iatrogenic hypocalcemia, the traditional teaching of leaving at least one vascularized pedicle attached to an *in situ* PG still remains true. With the new advancement in ICG fluorescent angiographic technology, whether to identify or not identify PGs also depends on the method to localize and assess its function in a non-invasive manner.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

### References

1. Edafe O, Antakia R, Laskar N, et al. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. *Br J Surg* 2014;101:307-20.
2. Lorente-Poch L, Sancho JJ, Munoz-Nova JL, et al. Defining the syndromes of parathyroid failure after total thyroidectomy. *Gland Surg* 2015;4:82-90.
3. Kakava K, Tournis S, Papadakis G, et al. Postsurgical Hypoparathyroidism: A Systematic Review. *In Vivo* 2016;30:171-9.
4. Mehanna HM, Jain A, Randeve H, et al. Postoperative hypocalcemia--the difference a definition makes. *Head Neck* 2010;32:279-83.
5. Cho NL, Moalem J, Chen L, et al. Surgeons and patients disagree on the potential consequences from hypoparathyroidism. *Endocr Pract* 2014;20:427-46.
6. Hadker N, Egan J, Sanders J, et al. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract* 2014;20:671-9.
7. Wang TS, Cheung K, Roman SA, et al. To supplement or not to supplement: a cost-utility analysis of calcium and vitamin D repletion in patients after thyroidectomy. *Ann Surg Oncol* 2011;18:1293-9.
8. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab* 2012;97:4507-14.
9. Underbjerg L, Sikjaer T, Mosekilde L, et al. Postsurgical hypoparathyroidism--risk of fractures, psychiatric diseases, cancer, cataract, and infections. *J Bone Miner Res* 2014;29:2504-10.
10. Thomusch O, Machens A, Sekulla C, et al. The impact of surgical technique on postoperative hypoparathyroidism in bilateral thyroid surgery: a multivariate analysis of 5846 consecutive patients. *Surgery* 2003;133:180-5.
11. Abboud B, Sargi Z, Akkam M, et al. Risk factors for postthyroidectomy hypocalcemia. *J Am Coll Surg* 2002;195:456-61.
12. Paek SH, Lee YM, Min SY, et al. Risk factors of hypoparathyroidism following total thyroidectomy for thyroid cancer. *World J Surg* 2013;37:94-101.
13. McLeod IK, Arciero C, Noordzij JP, et al. The use of rapid parathyroid hormone assay in predicting postoperative hypocalcemia after total or completion thyroidectomy. *Thyroid* 2006;16:259-65.
14. Sitges-Serra A, Gallego-Otaegui L, Suarez S, et al. Inadvertent parathyroidectomy during total thyroidectomy and central neck dissection for papillary thyroid carcinoma. *Surgery* 2017;161:712-9.
15. Zhou HY, He JC, McHenry CR. Inadvertent parathyroidectomy: incidence, risk factors, and outcomes. *J Surg Res* 2016;205:70-5.
16. Chisholm EJ, Kulinskaya E, Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. *Laryngoscope* 2009;119:1135-9.
17. Cho JN, Park WS, Min SY. Predictors and risk factors of hypoparathyroidism after total thyroidectomy. *Int J Surg* 2016;34:47-52.
18. Vanderlei FA, Vieira JG, Hojaij FC, et al. Parathyroid hormone: an early predictor of symptomatic hypocalcemia after total thyroidectomy. *Arq Bras Endocrinol Metabol* 2012;56:168-72.
19. Lecerf P, Orry D, Perrodeau E, et al. Parathyroid hormone decline 4 hours after total thyroidectomy accurately predicts hypocalcemia. *Surgery* 2012;152:863-8.
20. Dabholkar JP, Chirmade S, Chhapola S. Safe thyroidectomy: Our view point. *Indian J Otolaryngol Head Neck Surg* 2006;58:222-4.
21. Bergenfelz A, Jansson S, Kristoffersson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbecks Arch Surg* 2008;393:667-73.
22. Thomusch O, Machens A, Sekulla C, et al. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. *World J Surg* 2000;24:1335-41.
23. Sitges-Serra A, Ruiz S, Girvent M, et al. Outcome of

- protracted hypoparathyroidism after total thyroidectomy. *Br J Surg* 2010;97:1687-95.
24. Fancy T, Gallagher D 3rd, Hornig JD. Surgical anatomy of the thyroid and parathyroid glands. *Otolaryngol Clin North Am* 2010;43:221-7, vii.
  25. Melo C, Pinheiro S, Carvalho L, et al. Identification of parathyroid glands: anatomical study and surgical implications. *Surg Radiol Anat* 2015;37:161-5.
  26. Lorente-Poch L, Sancho J, Munoz JL, et al. Failure of fragmented parathyroid gland autotransplantation to prevent permanent hypoparathyroidism after total thyroidectomy. *Langenbecks Arch Surg* 2017;402:281-7.
  27. Tartaglia F, Blasi S, Giuliani A, et al. Parathyroid autotransplantation during total thyroidectomy. Results of a retrospective study. *Int J Surg* 2016;28 Suppl 1:S79-83.
  28. Pattou F, Combemale F, Fabre S, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. *World J Surg* 1998;22:718-24.
  29. Puzziello A, Rosato L, Innaro N, et al. Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. *Endocrine* 2014;47:537-42.
  30. Olson JA Jr, DeBenedetti MK, Baumann DS, et al. Parathyroid autotransplantation during thyroidectomy. Results of long-term follow-up. *Ann Surg* 1996;223:472-8; discussion 478-80.
  31. Lang BH, Chan DT, Chow FC. Visualizing fewer parathyroid glands may be associated with lower hypoparathyroidism following total thyroidectomy. *Langenbecks Arch Surg* 2016;401:231-8.
  32. Lindblom P, Wester Dahl J, Bergenfelz A. Low parathyroid hormone levels after thyroid surgery: a feasible predictor of hypocalcemia. *Surgery* 2002;131:515-20.
  33. Pfeleiderer AG, Ahmad N, Draper MR, et al. The timing of calcium measurements in helping to predict temporary and permanent hypocalcaemia in patients having completion and total thyroidectomies. *Ann R Coll Surg Engl* 2009;91:140-6.
  34. Lang BH, Yih PC, Ng KK. A prospective evaluation of quick intraoperative parathyroid hormone assay at the time of skin closure in predicting clinically relevant hypocalcemia after thyroidectomy. *World J Surg* 2012;36:1300-6.
  35. Sheahan P, Mehanna R, Basheeth N, et al. Is systematic identification of all four parathyroid glands necessary during total thyroidectomy?: a prospective study. *Laryngoscope* 2013;123:2324-8.
  36. Praženica P, O'Keeffe L, Holy R. Dissection and identification of parathyroid glands during thyroidectomy: association with hypocalcemia. *Head Neck* 2015;37:393-9.
  37. Antakia R, Edafe O, Uttley L, et al. Effectiveness of preventative and other surgical measures on hypocalcemia following bilateral thyroid surgery: a systematic review and meta-analysis. *Thyroid* 2015;25:95-106.
  38. Lorente-Poch L, Sancho JJ, Ruiz S, et al. Importance of in situ preservation of parathyroid glands during total thyroidectomy. *Br J Surg* 2015;102:359-67.
  39. Song CM, Jung JH, Ji YB, et al. Relationship between hypoparathyroidism and the number of parathyroid glands preserved during thyroidectomy. *World J Surg Oncol* 2014;12:200.
  40. Pradeep PV, Ramalingam K, Jayashree B. Post total thyroidectomy hypocalcemia: A novel multi-factorial scoring system to enable its prediction to facilitate an early discharge. *J Postgrad Med* 2013;59:4-8.
  41. Promberger R, Ott J, Kober F, et al. Intra- and postoperative parathyroid hormone-kinetics do not advocate for autotransplantation of discolored parathyroid glands during thyroidectomy. *Thyroid* 2010;20:1371-5.
  42. Kuhel WI, Carew JF. Parathyroid biopsy to facilitate the preservation of functional parathyroid tissue during thyroidectomy. *Head Neck* 1999;21:442-6.
  43. Lang BH, Chan DT, Chow FC, et al. The Association of Discolored Parathyroid Glands and Hypoparathyroidism Following Total Thyroidectomy. *World J Surg* 2016;40:1611-7.
  44. Ji YB, Song CM, Sung ES, et al. Postoperative Hypoparathyroidism and the Viability of the Parathyroid Glands During Thyroidectomy. *Clin Exp Otorhinolaryngol* 2017;10:265-71.
  45. Promberger R, Ott J, Bures C, et al. Can a surgeon predict the risk of postoperative hypoparathyroidism during thyroid surgery? A prospective study on self-assessment by experts. *Am J Surg* 2014;208:13-20.
  46. Lang BH, Wong CK, Hung HT, et al. Indocyanine green fluorescence angiography for quantitative evaluation of in situ parathyroid gland perfusion and function after total thyroidectomy. *Surgery* 2017;161:87-95.
  47. Lavazza M, Liu X, Wu C, et al. Indocyanine green-enhanced fluorescence for assessing parathyroid perfusion during thyroidectomy. *Gland Surg* 2016;5:512-21.
  48. Yu HW, Chung JW, Yi JW, et al. Intraoperative localization of the parathyroid glands with indocyanine green and Firefly(R) technology during BABA robotic thyroidectomy. *Surg Endosc* 2017;31:3020-7.
  49. Ladurner R, Sommerey S, Arabi NA, et al. Intraoperative

- near-infrared autofluorescence imaging of parathyroid glands. *Surg Endosc* 2017;31:3140-5.
50. Zaidi N, Bucak E, Yazici P, et al. The feasibility of indocyanine green fluorescence imaging for identifying and assessing the perfusion of parathyroid glands during total thyroidectomy. *J Surg Oncol* 2016;113:775-8.
51. Vidal Fortuny J, Belfontali V, Sadowski SM, et al. Parathyroid gland angiography with indocyanine green fluorescence to predict parathyroid function after thyroid surgery. *Br J Surg* 2016;103:537-43.
52. Sound S, Okoh A, Yigitbas H, et al. Utility of Indocyanine Green Fluorescence Imaging for Intraoperative Localization in Reoperative Parathyroid Surgery. *Surg Innov* 2015. [Epub ahead of print].

**Cite this article as:** Chang YK, Lang BH. To identify or not to identify parathyroid glands during total thyroidectomy. *Gland Surg* 2017;6(Suppl 1):S20-S29. doi: 10.21037/gs.2017.06.13