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Correlation between preoperative calcium and parathormone levels with parathyroid gland volume

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Objective. Hyperparathyroidism is a prevalent disease with parathyroid adenomas being the most common cause. Surgical excision remains the standard treatment for parathyroid adenoma. Successful preoperative localization of the parathyroid adenoma could facilitate the decision regarding the extent of surgical exploration. The aim of the current study was to assess the correlation between the preoperative values of parathyroid hormone and ionized calcium with the adenoma weight and volume in patient with primary hyperparathyroidism caused by single-gland adenoma.

Patients and Methods. We did this retrospective review for all patients who were diagnosed with primary hyperparathyroidism due to a solitary parathyroid adenoma in our general surgery department over 4 years. SPSS software was used to get the correlation coefficient between the peak preoperative levels of calcium and parathyroid hormone with the parathyroid adenoma weight and volume.

Results. Ninety-nine patients were included into the study. The average age at surgery was 62.65±12.00 years. The correlation coefficient between the adenoma volume and weight with the preoperative ionized calcium level was weakly positive ($r=0.329$, $p<0.01$) and ($r=0.281$, $p=0.019$), respectively, while the correlation with the preoperative parathyroid hormone level was stronger ($r=0.708$, $p<0.01$) and ($r=0.650$, $p<0.01$), respectively.

Conclusions. The strong positive relationship between the preoperative parathyroid hormone and calcium levels with the parathyroid adenoma size and weight can help the surgeon to predict the volume of the involved gland and avoid an unnecessary dissection.

Key words: parathyroid adenoma, weight, volume, parathyroid hormone, calcium, correlation

The parathyroid gland (PTG) plays an important role in controlling the calcium level in human through the production of parathyroid hormone, i.e., parathormone (PTH). More than 95% of the human population have four parathyroid glands (Lappas et al. 2012). Embryologically, the inferior PTG is derived from the third pharyngeal pouch, while the superior PTG is developing from the fourth pouch (Sadler et al. 2010). The normal PTG weight is 29.5–62.4 mg (Akerstrom et al. 1984) with total weight of all parathyroid glands of 90 to 130 mg. The average dimension of the normal PGL is 3x5x7 mm (Botushanova et al. 2017).

Hyperparathyroidism can be classified as primary, secondary, or tertiary one, based on the etiology of the PTG pathology. Primary hyperparathyroidism (pHPT) is a relatively common disease with an estimated prevalence of 7 per 1000 cases in adults

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(Adami et al. 2002). It is mainly caused by excessive production of PTH. Untreated hyperparathyroidism can lead to potential complications including the musculoskeletal, renal, neurocognitive, and cardiovascular systems.

Single parathyroid adenoma accounts for up to 90% of the hyperparathyroidism cases (Clarck and Duh 1989), while multiple parathyroid adenomas have been reported in 2–4% of cases (Casas et al. 1993). Less common causes of hyperparathyroidism include parathyroid hyperplasia, multiple parathyroid adenomas or parathyroid carcinoma. Parathyroid adenoma can be treated successfully with surgical excision (Farmer and Kim 2008). To increase the chance of cure, bilateral neck exploration with excision of all parathyroid tissue was the standard approach in patients with a single parathyroid adenoma (Udelsman 2002). With re-exploration, the risks of morbidity and mortality is relatively high (Sosa et al. 1998).

The recent advances in localization techniques including ultrasonography (US), intraoperative PTH assays, scintigraphy, Technetium-99 m Sestamibi (MIBI) scan, and computed tomography (CT) have increased the involved PTG localization accuracy. However, no single test can identify parathyroid adenomas in all patients. Intraoperative PTH monitoring has also increased the success rate of minimally invasive parathyroidectomy in patients with parathyroid adenoma up to 98%, and minimized the rate of re-operation (Moretz et al. 2007). However, the intraoperative PTH monitoring is not widely used over the centers. Therefore, the ability to predict the minimum volume and weight of the gland could be of a great value when a minimal invasive surgery is applied. Many studies have examined the correlation between the volume and weight of the PTG adenoma with the preoperative biomarkers including PTH, calcium, and phosphate. Nevertheless, even the results of these studies are controversial (Dubost et al. 1978; Wagner and Rothmund 1983; Rutledge et al. 1985; Hedback et al. 1995; Bindlish et al. 2002; Randhawa et al. 2007).

The aim of the present study was to find out if there is any relation between the volume and weight of parathyroid adenoma with the preoperative levels of PTH and ionized calcium. The occurrence of this correlation could help to predict the size of the adenoma before surgery and avoid any unnecessary dissection process.

Patients and Methods

We did a retrospective review for all patients who were diagnosed with primary hyperparathyroidism in our general surgery department during the period from January 2017 to December 2020. All patients' data were collected from the hospital recording system. Patients of any age with a single parathyroid adenoma with a surgical excision of the adenoma were included into the study. Exclusion criteria included patients with multiple adenomas, secondary and tertiary hyperparathyroidism, recurrent or persistent hyperparathyroidism, parathyroid carcinoma, and patients

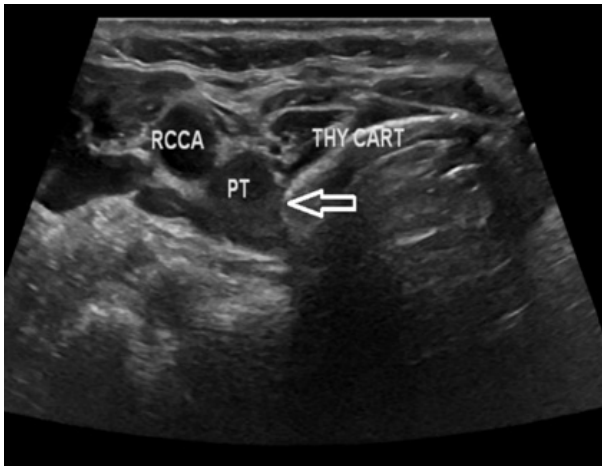


Figure 1. Neck ultrasonography scan showing a 10x7x23 mm well-defined hypoechoic vascular lesion cranially adjacent to the upper pole right thyroid consistent with a right superior parathyroid adenoma.

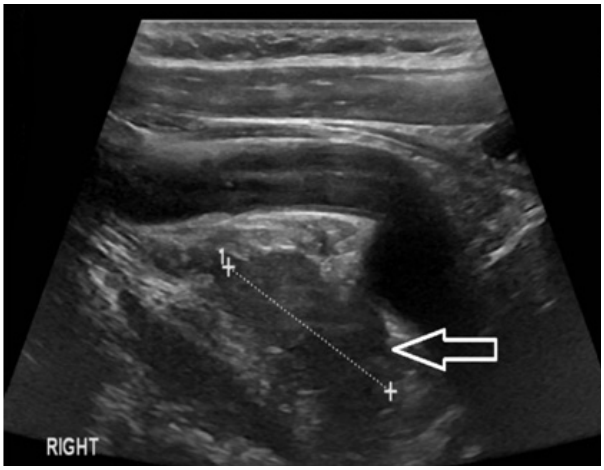


Figure 2. Neck ultrasonography scan showing a 2.7 cm lesion lying inferior to the right thyroid lobe, medial to the proximal portion of the right subclavian artery, and lateral to the tracheoesophageal groove. Appearances would be consistent with a parathyroid adenoma.

without surgical treatment. An informed consent was obtained from all patients before any surgical intervention explaining all the possible risks of surgery.

The preoperative imaging techniques used for localization of the tumor included US scan, MIBI scan and/or CT scan (Figures 1–4). Some of these patients were under calcimimetics medication (e.g., cinacalcet). Thus, the peak preoperative values of PTH and ionized calcium were obtained for more standardization of the results. Our reference value for PTH was 1.3–7.3 pmol/L and for ionized calcium 2.2–2.6 mmol/L.

All patients had surgical excision of the parathyroid adenoma through either bilateral neck exploration or minimal invasive surgery. All parathyroid adenomas were confirmed histologically. Parathyroid weight was obtained from the histology report, while the volume calculated indirectly from the tumor dimensions mentioned in the report.

The correlations between the volume and weight of the parathyroid adenoma with the blood levels of PTH and calcium were calculated using SPSS Software (Statistical Package for the Social Sciences) version 25.

Results

Ninety-nine patients were included in our study after applying the inclusion and exclusion criteria. Thirty patients (30.3%) were males and 69 females (69.7%). The average age at the time of surgery was 62.65±12.00 years.

The calculated volume of the adenoma was ranged from 0.027 to 25.39 cm^3 with an average of 2.11±3.50 cm^3. The weight of the tumor was ranged from 0.14 g to 1.87 g, with an average of 1.93±4.1 g. The calcium levels ranged from 2.61 to 3.66 mmol/L with an average value of 2.908±0.226 mmol/L. The PTH levels ranged from 8.6 to 101 pmol/L with an average of 19.73±15.40 pmol/L.

The correlation coefficient between the volume of the adenoma and the preoperative ionized calcium level was relatively strong ($r=0.329$, $p<0.01$), while the correlation with the preoperative PTH level was stronger ($r=0.708$, $p<0.01$). The correlation between the adenoma weight and the preoperative ionized calcium level was weakly positive ($r=0.281$, $p=0.019$), while with the preoperative PTH level more significant ($r=0.650$, $p<0.01$) (Figures 5–8).

Discussion

The PTG contains a population of cells called chief cells, which are responsible for synthesizing the PTH, which helps to maintain calcium homeostasis by enhancing the osteoclast activity, increasing the bone breakdown, and the release of calcium and phosphate (Summers and Macnab 2017). Excessive secretion of PTH from the PTG is known as hyperparathyroidism, with primary parathyroid adenoma accounting for more than 90% of the cases (Clarck and Duh 1989). People in the sixth decade of life are more commonly affected, whereas female to male ratio takes about 3:1 (Rosen et al. 2005).

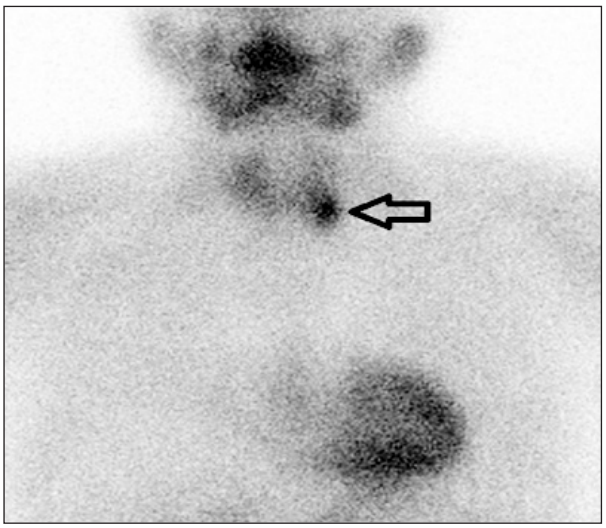


Figure 3. Technetium-99 m Sestamibi (MIBI) scan showing focal retained activity in relation to the lower pole of the left thyroid lobe. Appearance is suggestive of a parathyroid adenoma.

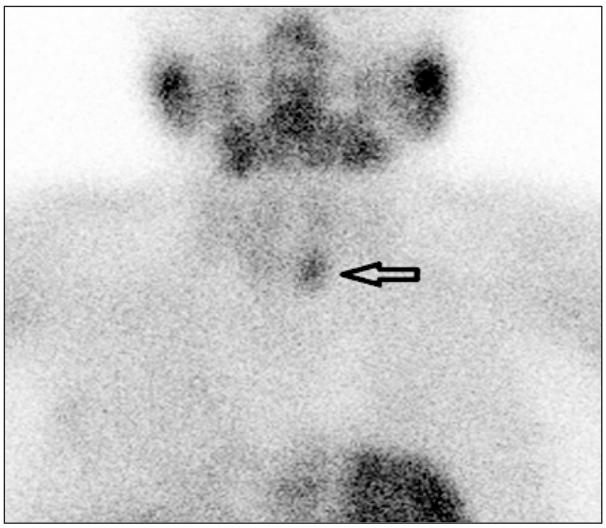


Figure 4. Technetium-99 m Sestamibi (MIBI) scan showing focal retained activity at the lower pole of the left thyroid lobe consistent with a parathyroid adenoma.

In the current study, 30 patients (30.3%) were males and 69 females (69.7%). The average age at the time of surgery was 62.65±12.00 years. It has been reported that the normal PTG has a mean maximum diameter of 6 mm and a mean weight of 60 mg. The average volume of the adenoma in our study was 2.11±3.50 cm^3 and the mean weight 1.93±4.10 g.

Primary hyperparathyroidism (pHPT) is characterized by an elevated serum-ionized calcium level in the setting of inappropriate elevation in the PTH level with or without clinical symptoms (Baloch and LiVolsi 2013). Clinical symptoms may include renal calculi, osteopenia, osteoporosis, constipation, and other mental side effects. Surgery is considered as a gold standard for treating patients with pHPT (Farmer and Kim 2008). The traditional operation for treating parathyroid adenoma was bilateral neck exploration, which was associated with multiple complications. The advances in localization techniques including neck US scan, neck CT scan, neck magnetic resonance imaging (MRI), and MIBI parathyroid scintigraphy have allowed for minimal invasive surgery (Figures 1–4). Minimal invasive surgery is associated with a reduced operative time, a lower rate of complications, and an improved cosmetic appearance. However, no single survey has been proved to reliably detect parathyroid adenomas in all patients. Whenever, the localization methods fail to identify the abnormal PTG, neck exploration should be considered (Wheeler 1998).

There are many studies, in which correlation between the preoperative biomarker levels and the gland size or weight have been investigated. Nevertheless, the results are variable and conflicting. For example, Hamidi et al. (2006) looking for correlation between the preoperative serum calcium, phosphate, and PTH levels with parathyroid adenoma size, have revealed that PTH level is not a reliable guide for estimating the adenoma size. In addition, they did not find any significant association between the preoperative serum calcium and/or phosphate levels with the tumor size (Hamidi et al. 2006). In another study performed on 77 patients with primary hyperparathyroidism, Randhawa et al. (2007) have concluded that biochemical markers cannot accurately predict the adenoma size. Saxe et al. (1987) have also reported that the preoperative measurements of calcium and PTH are too

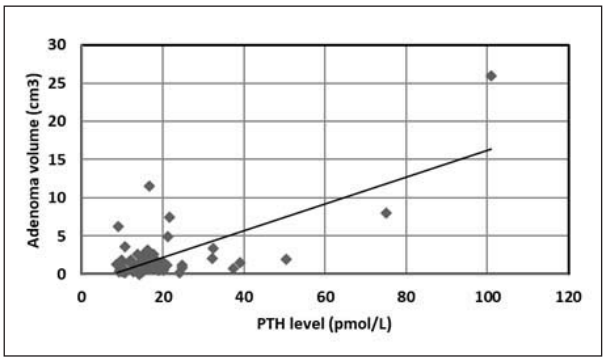


Figure 5. A simple scatter of the correlation between adenoma volume and serum parathyroid hormone (PTH) level.

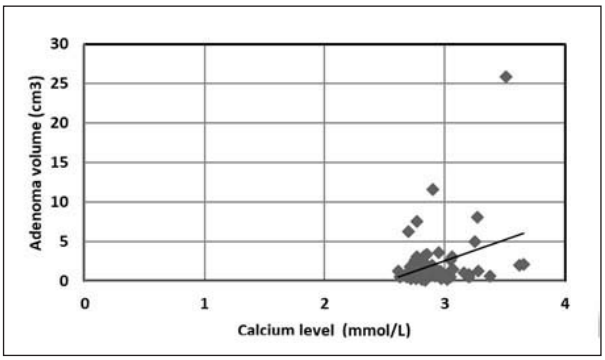


Figure 6. A simple scatter of the correlation between adenoma volume and serum calcium level.

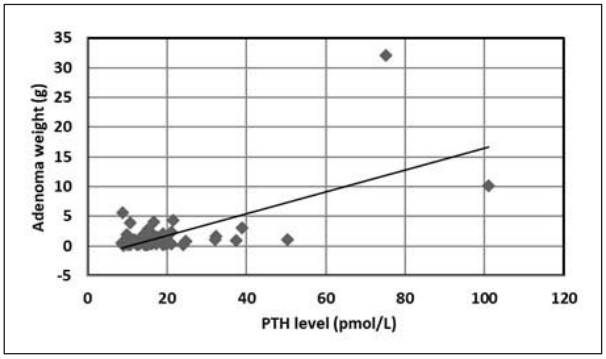


Figure 7. A simple scatter of the correlation between adenoma weight and serum parathyroid hormone (PTH) level.

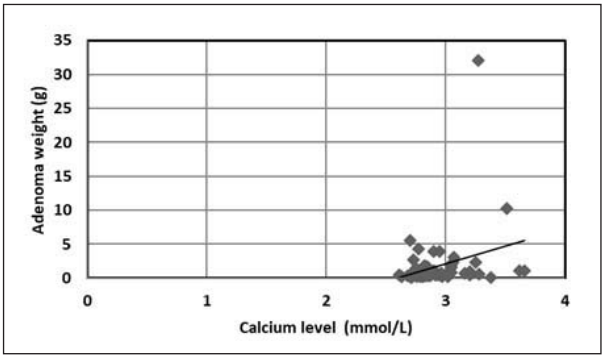


Figure 8. A simple scatter of the correlation between adenoma weight and serum calcium level.

inconsistent to rely for determining the extent of PTG resection.

Bindlish et al. (2002) in a study with 63 patients bearing a single parathyroid adenoma, have concluded a positive association between the preoperative serum calcium and PTH levels with the adenoma weight and volume. Rutledge et al. (1985) have reviewed 92 patients and found a weak positive correlation between the serum calcium level and size of enlarged parathyroid glands. In another study made on 69 patients (Kamani et al. 2013), a positive correlation between PTG weight and the preoperative PTH and calcium levels have been demonstrated. Moreover, in a large study including 371 patients (Stern et al. 2017), a significant correlation between the preoperative levels of PTH and calcium with the parathyroid weight and volume has been found. Mozes et al. (2002) have also found that with PTH levels lower than 6 pmol/L the adenoma weight was lower than 400 mg, while in patients with PTH levels higher than 18 pmol/L, the abnormal gland or glands weighed more than 800 mg.

There are many factors that may contribute to the variability of the results between these studies. The weight of the PTG could be affected by many factors such as fibrosis, calcification, hemorrhage, and cystic degeneration (LiVolsi 2001). The variability in the proportion of the functional cells is another factor to account for the variably in the adenoma weight for a given PTH level (Stern et al. 2017). Another factor that may contribute to the variability in the adenoma weight is the vitamin D deficiency. Vitamin D is known to increase the weight of the parathyroid adenoma (Kirkby-Bott et al. 2010).

In the current study, we analyzed the data of 99 patients and we found a strong positive relation between the preoperative levels of PTH with the parathyroid adenoma volume ($r=0.708$, $p<0.01$) and weight ($r=0.650$, $p<0.01$). The relations between the preoperative ionized calcium level and the adenoma volume ($r=0.329$, $p<0.01$) and weight ($r=0.281$, $p=0.019$) were less distinct (Figures 5–8). Our results are consistent with the data of other studies (Rutledge et al. 1985; Bindlish et al. 2002; Kamani et al. 2013; Stern et al. 2017).

Revealing a significant correlation between the preoperative values of PTH and calcium with the parathyroid adenoma weight and volume may have an important practical value, especially in patients with a small PTG, on preoperative localization techniques. However, the biochemical markers suggest a larger adenoma. In this condition, additional localization studies should be performed either preoperatively or intraoperatively to exclude another larger lesion. This could avoid unnecessary re-operation with increased risks of morbidity and mortality.

The study limitations. As it was designed retrospectively, the sample size was relatively low, some of our patients were under calcium chelating agent's medication before the operation. In addition, some of the patients had vitamin D deficiency, which might partially contribute to the variably in the adenomas weight. In order to overcome these limitations, we collected the peak preoperative levels of PTH and ionized calcium. In addition, patients with persistent hyperparathyroidism and/or hypercalcemia postoperatively, were excluded from the study.

Conclusion

We found a strong positive correlation between the preoperative PTH level and the parathyroid adenoma weight and volume, while the relation with the preoperative ionized calcium level was relatively weak. Revealing such a correlation can help the surgeon to predict the size of the adenoma according to the preoperative values of these biomarkers and minimize the need for the re-exploration.

Conflict of interest: *The authors declare no conflict of interest.*

References

Adami S, Marcocci C, Gatti D. Epidemiology of primary hyperparathyroidism in Europe. J Bone Miner Res 17, N18–N23, 2002.

Akerstrom G, Malmaeus J, Bergstrom R. Surgical anatomy of human parathyroid glands. Surgery 95, 14–21, 1984.

Baloch ZW, LiVolsi VA. Pathology of the parathyroid glands in hyperparathyroidism. Semin Diagn Pathol 30, 165–177, 2013.

Bindlish V, Freeman JL, Witterick IJ, Asa SL. Correlation of the biochemical parameters with single parathyroid adenoma weight and volume. Head Neck 24, 1000–1003, 2002.

Botushanova AD, Botushanov NP, Yaneva MP. Nuclear medicine methods for evaluation of abnormal parathyreoid glands in patients with primary and secondary hyperparathyroidism. Folia Med 59, 396–404, 2017.

Casas AT, Burke GJ, Sathyanaryana N, Mansberger Jr AR, Wei JP. Prospective comparison of technetium 99 m sestamibi/iodine 123 scan versus high resolution ultrasonography for the preoperative localization of abnormal parathyroid glands in patients with previously unoperated primary hyperparathyroidism. Am J Surg 166, 369–373, 1993.

Clarck OH, Duh QY. Primary hyperparathyroidism, a surgical perspective. Endocrinol Metab Clin North Am 18, 701–714, 1989.

Dubost C, Bordier PJ, Ferry J, Gueris J. Le dosage de la parathormone dans l'hyperparathyroïdie primaire [The estimation of parathormone in primary hyperparathyroidism (author's transl)]. Nouv Presse Med 7, 21–25, 1978.

Farmer PE, Kim JY. Surgery and global health: A view from beyond the OR. World J Surg 32, 533–536, 2008.

Hamidi S, Aslani A, Nakhjavani M, Pajouhi M, Hedayat A, Kamalian N. Are biochemical values predictive of adenoma's weight in primary hyperparathyroidism? ANZ J Surg 76, 882–885, 2006.

Hedback C, Oden A, Tisell LE. Parathyroid adenoma weight and the risk of death after treatment for primary hyperparathyroidism. Surgery 117, 134–139, 1995.

Kamani F, Najafi A, Mohammadi SS, Tavassoli S, Shojaei SP. Correlation of biochemical markers of primary hyperparathyroidism with single adenoma weight and volume. Indian J Surg 7, 102–105, 2013.

Kirkby-Bott J, El-Khatib Z, Soudan B, Caiazzo R, Arnalsteen L, Carnaille B. 25-hydroxy Vitamin D deficiency causes parathyroid incidentalomas. Langenbecks Arch Surg 395, 919–924, 2010.

Lappas D, Noussios G, Anagnostis P, Adamidou F, Chatzigeorgiou A, Skandalakiset P. Location, number and morphology of parathyroid glands: results from a large anatomical series. Anat Sci Int 87, 160–164, 2012.

LiVolsi VA. Parathyroids: Morphology and Pathology. In: The Parathyroids: Basic and Clinical Concepts 2nd ed. Academic Press, 1–16, 2001.

Moretz WH 3rd, Watts TL, Virgin FW Jr., Chin E, Gourin CG, Terris DJ. Correlation of intraoperative parathyroid hormone levels with parathyroid gland size. Laryngoscope 117, 1957–1960, 2007.

Mozes G, Curlee KJ, Rowland CM, van Heerden JA, Thompson GB, Grant CS, Farley DR. The predictive value of laboratory findings in patients with primary hyperparathyroidism. J Am Coll Surg 194, 126–130, 2002.

Randhawa PS, Mace AD, Nouraei SAR, Stearns MP. Primary hyperparathyroidism: do perioperative biochemical variables correlate with parathyroid adenoma weight or volume? Clin Otolarygol 32, 179–184, 2007.

Rosen JE, Costouros NG, Lorang D, Burns AL, Alexander HR, Skarulis MC, Cochran C, Pingpank JF, Marx SJ, Spiegel AM, Libutti SK. Gland size is associated with changes in gene expression profiles in sporadic parathyroid adenomas. Ann Surg Oncol 12, 412–416, 2005.

Rutledge R, Stiegel M, Thomas CG, Wild RE. The relation of serum calcium and immunoparathormone levels to parathyroid size and weight in primary hyperparathyroidism. Surgery 98, 1107–1112, 1985.

Sadler TW, Thomas W, Langman J. Langman's medical embryology. 11th ed. Philadelphia, USA: Wolters Kluwer, Lippincott Williams & Wilkins, 2010.

Saxe AW, Lincenberg S, Hamburger SW. Can the volume of abnormal parathyroid tissue be predicted by preoperative biochemical measurement? Surgery 102, 840–845, 1987.

Sosa J, Powe NR, Levine MA, Udelsman R, Zeiger MA. Profile of a clinical practice: thresholds for surgery and surgical outcomes for patients with primary hyperparathyroidism: a national survey of endocrine surgeons. J Clin Endocrinol Metab 83, 2658–2665, 1998.

Stern S, Mizrachi A, Strenov Y, Knaanie A, Benbassat C, Shpitzer T, Bachar G. Parathyroid adenoma: a comprehensive biochemical and histological correlative study. Clin Otolaryngol 42, 381–386 2017.

Summers R, Macnab R. Thyroid, parathyroid hormones and calcium homeostasis. Anaesthesia Intensive Care Medicine 18, 10, 522–526, 2017.

Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 235, 665–670, 2002.

Wagner PK, Rothmund M. Correlation of tumor weight and typical pathologic laboratory parameters in primary hyperparathyroidism. Langenbeck Arch Chir 360, 133–139, 1983.

Wheeler MH. Primary hyperparathyroidism: A surgical perspective. Ann R Coll Surg Engl 80, 305–312, 1998.