

## Para thyroidectomy failures and causes evaluation

Mohamed Baayou<sup>1,2</sup>, Mohamed Bashagha<sup>3</sup>, Mostafa Sgheir<sup>4,5</sup>, Eltaher Elshagmani<sup>6,7</sup>

- 1- Department of Medicine, Faculty of Medicine, Misurata university, Libya
- 2- Department of Medicine, Misurata Medical Center Misrata, Libya
- 3- Department of radiology, Faculty of Medicine, Misurata university, Libya
- 4- Department of Surgery, Misurata Medical Center Misrata, Libya
- 5- Department of Surgery, Faculty of Medicine, Misurata university, Libya
- 6- Department of medical laboratory, Faculty of Medical Technology, Misurata, Libya
- 7- Department of medical laboratory, National cancer institute, Misurata, Libya

| Article information                                                                                                                                                                                                          | Abstract                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Key words:</b> Persistent hyperparathyroidism, reoperative parathyroid surgery, adenoma, Sestamibi scan, hormone (PTH).</p> <hr/> <p>Received: 27-07-2025</p> <p>Accepted: 30-07-2025</p> <p>Available: 10-08-2025</p> | <p><b>Background:</b> Persistent primary hyperparathyroidism (PHPT) after surgery is often due to missed ectopic or supernumerary glands. Reoperation is challenging and requires precise imaging, anatomical understanding, and surgical expertise.</p> <p><b>Methods:</b> A 34-year-old woman with classic PHPT symptoms and biochemical evidence (Ca: 12.75 mg/dL, PTH: 891 pg/mL) underwent two failed parathyroidectomies. Imaging was inconclusive; histology showed nodular hyperplasia in the first and absence of parathyroid tissue in the second. A third surgery, guided by high-resolution ultrasound and intraoperative endoscopy, located an ectopic retroesophageal adenoma, which was excised.</p> <p><b>Results:</b> Immediate postoperative laboratory confirmed cure (Ca: 7.2 mg/dL, PTH: &lt;1.2). The patient developed transient hungry bone syndrome. No complications were noted.</p> <p><b>Conclusion:</b> Persistent PHPT requires high suspicion for ectopic or supernumerary glands. Third-time parathyroidectomy, when planned with expert imaging and surgical collaboration, can be safe and curative.</p> |

### I) Introduction

The parathyroid glands were first identified by Sir Richard Owen in the Great Indian Rhinoceros in 1850 [1]. They were identified in humans by Ivar Sandstrom, a Swedish medical student, in 1880 [2]. The first parathyroidectomy was reported by Mandl in 1929, 30 years prior to the isolation of human parathyroid hormone [3].

The success of the surgical management of parathyroid disease is based on accurate biochemical diagnosis and the surgeon's expert understanding of the significant embryologic variations in parathyroid anatomy. Knowledge of the unusual anatomic locations for enlarged parathyroid glands is crucial to operative success during both initial and reoperative parathyroid surgery [3].

Bone disease in severe primary hyperparathyroidism (PHPT) is described classically as osteitis fibrosa cystica (OFC). Bone pain, skeletal deformities and pathological fractures are features of OFC. Bone mineral density is usually extremely low in OFC, but it is reversible after surgical cure. The signs and symptoms of severe bone disease include bone pain, pathologic fractures, proximal muscle weakness with hyperreflexia. Bone involvement is typically characterized as salt-and-

pepper appearance in the skull, bone erosions and bone resorption of the phalanges, brown tumors and cysts. Severe symptomatic PHPT, marked by elevation of the serum calcium and PTH concentrations and sometimes nephrolithiasis and nephrocalcinosis [4].

Normal glands are usually approximately 5 x 4 x 2 millimetres in size and weigh 35-50 mg. Enlarged gland can be 50 mg to 20 grams in weight. The superior parathyroid glands are derived from the fourth branchial pouch. The inferior parathyroid glands are derived from the third branchial pouch [4]. Most (84 %) individuals have four parathyroid glands, two superior and two inferior glands [5]. Additional glands are found in 13 % of patients and  $\leq 3$  % only three glands [5]. The superior glands are symmetric in 80 % of cases, and inferior glands are symmetric 70 % of cases [5].

During parathyroid exploration, deductive reasoning based on the embryologic origin of identified parathyroid glands helps the surgeon identify missing glands [4]. The ectopic gland may be one of the four parathyroid glands, or it may be a supernumerary gland. In one series of 102 patients with persistent or recurrent hyperparathyroidism who required reoperation, ectopic glands were found in the paraesophageal position (28 %), in the mediastinum (26 %), intrathymic (24 %), intrathyroidal (11 %), in the carotid sheath (9 %), and in a high cervical position (2 %) [7].

An ectopic superior parathyroid gland may be undescended and located at the piriform sinus or intrathyroidal. Ectopic inferior parathyroid glands can be undescended at the carotid bulb. More typically they will be found lateral and inferior to the middle to lower thyroid lobe adjacent to the thyrothymic tract. Ectopic inferior parathyroid glands are most often found in the thymus or mediastinum (9 %) [8]. An undescended inferior parathyroid gland may be located anywhere within the carotid sheath (2 %). They can also be located intrathyroidally (1 %).

Supernumerary (>4) parathyroid glands occur in 2.5 to 15 % of individuals [5,9]. They can range from five to eight in number [6]. Most supernumerary glands are small, rudimentary, or divided, when enlarged, may be responsible for persistent hyperparathyroidism after failed parathyroid exploration [5,10,11]. Supernumerary glands were found in 15 % of cases of persistent hyperparathyroidism after parathyroidectomy [9]. The most common location of supernumerary glands is within the thymus or in relation to the thyrothymic ligament (two-thirds of cases) [6,11].

Missed parathyroid adenoma is the most common cause for a failed initial parathyroid operation and persistent hyperparathyroidism [12]. Understanding the embryology and anatomy of the parathyroid glands will help determine which one of the four parathyroid glands is missing or if it is a supernumerary gland. In this study, a case report will be demonstrated and the causes parathyroidectomy failure will be discussed.

## **II) Case history**

A 34-year Libyan lady from southeast of Libya not known to have any chronic illness presented to my clinic on 10/04/2021. Anamnesis revealed generalized bone pain, history of non-union fracture of right femur and humorous, limping gait and worsening symptoms of depression. The patient was alert but slow and complained of nausea. Serial of laboratory investigations was requested (see Tab-1).

| Blood tests             | Results                  |
|-------------------------|--------------------------|
| WBC                     | $5.8 \times 10^9 /L$     |
| HB                      | 13.2 g/dl                |
| Platlets                | $283.000 \times 10^9 /L$ |
| Serum creatinine        | 0.6 mg/dl                |
| Blood urea              | 23 mg/dl                 |
| Serum corrected calcium | 12.75 mg/dl              |
| Serum phosphorus        | 2.4 mg/dl                |
| Serum magnesium         | 2.58 mg/dl               |
| 24-hour urinary calcium | 31 mg/dl                 |
| Intact PTH              | 891 pg/ml                |
| 25-OHD                  | 67.4 ng/mL               |
| TSH                     | 1.8 $\mu$ U/mL           |
| Arterial blood gases    | Normal no acidosis       |
| Prolactin               | 14.8 ng/ml               |

A diagnosis of PHPT was made (high calcium and high PTH). Chest and abdominal X-ray was normal. Electrocardiogram normal and QTc: 408 ms. Neck USG showed sub centimetric iso-echoic thyroid nodules with peripheral vascularization, and no enlarged parathyroid glands. Abdominal ultrasound did not show kidney stones. X-ray hands (see Figure 1-A-B), distal clavicles (figure 2-A-B) and skull (Fig-3).



Fig-1 (A and B), anteroposterior (AP) hands. Note the radial margins of the proximal and middle phalanges bilaterally are frayed, irregular, and lace-like (arrows) owing to characteristic subperiosteal resorption. Also note the brown tumor (small arrowhead) and osteolysis of the distal phalanges (large arrowheads).



Fig. -2 (A) Detail view of the hands shows subperiosteal resorption in the phalanges (arrows). (B) Detail views of both distal clavicles show subchondral resorption bilaterally (arrows).



Fig3- Skull radiograph shows the typical "salt and pepper" appearance caused by osteitis fibrosa cystica.

Dual-energy X-ray absorptiometry revealed osteopenia: wrist (T score:  $-1.9$ ) and lumbar spine (T score:  $-1.3$ ). Jaw X-ray was revealed no areas of bone rarefaction which would have put the patient to high risk of developing osteonecrosis.

The operation day fixed and did on 15/04/2021, no postoperative complications. Few days later, the patient was reexamined and she was still suffering from the same complains. Series of serum calcium and PTH levels were unchanged (calcium 13.6 mg/dL, PTH 765.7), proved erratic and showed an upward trend over the preoperative levels. The patient denied any improvement. Histopathological report of parathyroidectomy revealed nodular hyperplasia of the two excised parathyroid glands.

Long-term clinical and biochemical follow-up was scheduled, the patient returned to her city. After an open discussion with the operating surgeon and review of operation procedure (he removed only 2 hypertrophied gland, and the remaining 2 gland were normal shape and size and not excised). After revision of post-operative laboratory and histopathological results, it was conclude that the cause of her hyperparathyroidism was most likely a diffuse hyper-parathyroidism. Regarding the severity of metabolic symptoms and post-operative conclusion, it was decided that a second surgery is the only curable possibility. Few days later and after the patient consent, a second parathyroidectomy was done on 06/07/2021 with hope to excise the remnant two parathyroid glands. No postoperative complications were documented. Few days later, the patient came with same complains and no improvement noted. Post second operation laboratory results (calcium 1272 mg/dL, PTH 1070 pg/ml), reveals still high level of her calcium and PTH which could be related to manipulation during the operation.

After receiving the terrible histopathology result (The three specimens show thyroid tissue with nodular hyperplasia and absence of any parathyroid tissue). Due to the lack of facility for 99m technetium-sestamibi (SESTAMIBI) scintigraphy in our country and difficulty to do it abroad, our best diagnostic option available was a repeated another parathyroid ultrasound by another expert radiologist which reported that "right sided lateral to and infero-lateral to the lower pole of the right thyroid, and just behind the right common carotid artery origin 2X1.5 cm hypoechoic solid nodule with medial sided feeding vessels, its long axis is along axis of the neck. Ultrasound findings are highly suggestive of right parathyroid adenoma".

After a discussion with this radiologist and another expert surgeon and after a consent of patient and her husband, a third operation was done on 21/08/2021 with aid of intraoperative endoscopy (no facility of intra-operative PTH assessment). With intra-operative ultrasound exploration, a right side parathyroid adenoma was excised along with accidental suprasternal soft tissue mass excision with morphological features compatible with thymic hyperplasia. Post-operative hungry bone syndrome (calcium 7.2 mg/dL, PTH <1.2 ng/ml) was documented treated by high calcium supplementation, no other significant postoperative complications.

### III) Discussion

After initial parathyroidectomy, some patients develop persistent or recurrent disease. This operation failure should be confirmed biochemically and the indications for operation considered [2,7]. Because the risks of complications, these operations should be performed by experienced surgeons with reoperative neck surgery [8]. Several studies have demonstrated higher cure rates, fewer complications, lower cost, and shorter length of stay when parathyroid surgery is performed by high-volume surgeons and in high-volume centers It is the authors' recommendation that parathyroidectomy be performed by surgeons who perform no fewer than 10 procedures and ideally  $\geq 50$  procedures per year [2,60-62].

It is generally recommended that two concordant imaging studies for localization be obtained prior to re-exploration. Ultrasound-guided fine needle aspiration of a suspected gland(s) with both histology and parathyroid hormone (PTH) assay could be helpful in localization of affected gland [7].

The best candidate for re-do parathyroid surgery is a patient who (A) has severe or symptomatic primary hyperparathyroidism (serum calcium >11.5 mg/dl). (B) has a clear target on imaging and those with symptoms such as kidney stones, loss of kidney function, and osteoporosis have a strong motivation to pursue additional surgery.[9,10]

Ectopic thyroid tissue, thyroid nodules, and lymph nodes can easily resemble an enlarged parathyroid gland, especially in a reoperative case or when the patient has concomitant thyroiditis [66]. If the second parathyroid gland ipsilateral to the first is enlarged, the diagnosis of multigland disease is made, and multigland resection should be performed after a four-gland exploration [2].

In patients with four-gland hyperplasia, all but a portion of one enlarged gland is removed, leaving a well-vascularized parathyroid remnant of 50 to 100 mg size. This is referred to as a subtotal or three-and-half-gland resection. [76-74-68-67]. Sometimes, all the parathyroid glands cannot be identified readily. A systematic search is performed based on the knowledge of the path of descent of superior and inferior parathyroid glands.

#### **A) Steps suggested to avoid operative failure**

- 1- The operative report should detail the findings and events of parathyroidectomy .
- 2- The excised gland can be photographed or the surgeon can include a drawing of the operative findings in the written operative report .[63]
- 3- Preoperative localization is an integral part of a focused parathyroid exploration .
- 4- Commonly used localization studies include:
  - i. cervical ultrasound, sestamibi scan.
  - ii. Multiphase contrast-enhanced computed tomography (CT) of the neck (four-dimensional CT) .
- 5- Intraoperative parathyroid hormone (IOPTH) monitoring provides real-time confirmation of surgical cure [94]. The use of IOPTH is suggested to avoid high operative failure rates .[2]
- 6- IOPTH monitoring takes advantage of the short plasma half-life of PTH (three to five minutes) and a rapid assay that produces measurements while the patient is still in the operating room [34,95-97]. A baseline PTH value is obtained at the start of the procedure, prior to skin incision. PTH levels are then measured following removal of the suspected adenoma [71]. A reduction of at least 50 % in PTH level from the baseline is an accepted standard for intraoperative confirmation of success [ 2,98,99 100.]
- 7- One to two weeks postoperatively, patients should be seen to review pathology and obtain a baseline postoperative biochemical assessment.
- 8- At six months postoperatively, patients should have a repeat clinic visit with biochemical assessment .[2,113]
- 9- At six months to one year following documented cure, a follow-up visit along with a repeat biochemical assessment and a comparative bone mineral density study is suggested [2,114].

Failure to achieve durable cure of hypercalcemia is the most common complication of parathyroid surgery (reported at rates of 1 to 5 %).

The classic calcium nadir occurs within the first 24 to 48 hours after a parathyroidectomy, and a serum PTH value can be obtained on the first postoperative day prior to discharge[117].

The success rate of initial parathyroid surgery by an expert surgeon is about 98%. [30,40,120-121].

The success rate of re-do parathyroid surgery by an expert surgeon is 80-95%.

Re-do parathyroid surgery is risky. In experienced hands, the risk of permanent hoarseness (recurrent laryngeal nerve injury) during initial parathyroid surgery should be less than 1 in 200. In re-do parathyroid surgery, the risk is 1-3%[122-124-125].

In most reoperations for persistent or recurrent PHPT, the hyperfunctional parathyroid gland is identified in a usual and expected anatomic location.

The cure rate of reoperations may be improved using intraoperative parathyroid hormone monitoring to confirm excision of all hyperfunctioning tissue and, in some cases, to guide laterality of dissection [126-127-128].

### **B) Causes of recurrent hyperparathyroidism**

- 1- Dormant (sleeping) second parathyroid adenoma, also known as subordinate adenoma.
- 2- Missed parathyroid hyperplasia.
- 3- Incomplete removal of a single parathyroid adenoma.
- 4- Parathyromatosis occurs when the initial surgeon breaks open the capsule of a parathyroid adenoma, causing abnormal parathyroid cells to spill out and seed the nearby soft tissues of the neck.
- 5- Parathyroid carcinoma.

Planning for re-do parathyroid surgery involves a combination of detective work (analysing what was done before), routinely request all prior operation reports, lab reports, pathology reports, and imaging reports, pathology slides for re-analysis.

### **IV) Conclusion:**

Reoperation is technically challenging with higher rates of morbidity and higher incidences of recurrent laryngeal nerve (RLN) injury and permanent hypoparathyroidism as well as higher rates of failure to cure. Thus, indications for reoperations are more stringent than for initial surgery. Persistent or recurrent post-hyperparathyroidism disease may be the result of supernumerary glands, or unrecognized multigland disease but the leading cause is surgeon inexperience.

### **V) References**

- [1]. Sandström I. On a new gland in man and several mammals (glandulae parathyroideae). Ups Läk Förh 1880; 15:441.
- [2]. Mandl F. Therapeutischer versuch bein einem falle von ostitis fibrosa generalisata mittels extirpation eines epithelk orperchen tumors. Zentrabl Chir 1926; 5:260.
- [3]. Bliss RD, Gauger PG, Delbridge LW. Surgeon's approach to the thyroid gland: surgical anatomy and the importance of technique. World J Surg 2000; 24:891.
- [4]. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery 1984; 95:14.
- [5]. Wang C. The anatomic basis of parathyroid surgery. Ann Surg 1976; 183:271.
- [6]. Shen W, Düren M, Morita E, et al. Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg 1996; 131:861.
- [7]. Richards ML, Thompson GB, Farley DR, Grant CS. Reoperative parathyroidectomy in 228 patients during the era of minimal-access surgery and intraoperative parathyroid hormone monitoring. Am J Surg 2008; 196:937.
- [8]. Carter WB, Carter DL, Cohn HE. Cause and current management of reoperative hyperparathyroidism. Am Surg 1993; 59:120.
- [9]. Arveschoug AK, Brøchner-Mortensen J, Bertelsen H, Vammen B. Supernumerary parathyroid glands in recurrent secondary hyperparathyroidism. Clin Nucl Med 2002; 27:599.
- [10]. Edis AJ, Levitt MD. Supernumerary parathyroid glands: implications for the surgical treatment of secondary hyperparathyroidism. World J Surg 1987; 11:398.
- [11]. Flament JB, Delattre JF, Pluot M . Arterial blood supply to the parathyroid glands: Implications for thyroid surgery. Surgical and Radiologic Anatomy 1982; 3:279.

- [12]. Jaskowiak N, Norton JA, Alexander HR, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. *Ann Surg* 1996; 224:308. Shah KN, Racine J, Jones LC, Aaron RK. Pathophysiology and risk factors for osteonecrosis. *Curr Rev Musculoskelet Med*. 2015;8(3):201–9.5.
- [13]. Bilezikian JP, Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. *N Engl J Med* 2004; 350:1746.
- [14]. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg* 2016; 151:959.
- [15]. Perrier ND. Asymptomatic hyperparathyroidism: a medical misnomer? *Surgery* 2005; 137:127.
- [16]. Udelsman R, Pasieka JL, Sturgeon C, et al. Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab* 2009; 94:366.
- [17]. Yu N, Leese GP, Donnan PT. What predicts adverse outcomes in untreated primary hyperparathyroidism? The Parathyroid Epidemiology and Audit Research Study (PEARS). *Clin Endocrinol (Oxf)* 2013; 79:27.
- [18]. Bilezikian JP, Khan AA, Potts JT Jr, Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab* 2009; 94:335.
- [19]. Carty SE, Norton JA. Management of patients with persistent or recurrent primary hyperparathyroidism. *World J Surg* 1991; 15:716.
- [20]. Karakas E, Müller HH, Schlosshauer T, et al. Reoperations for primary hyperparathyroidism--improvement of outcome over two decades. *Langenbecks Arch Surg* 2013; 398:99.
- [21]. Li W, Zhu Q, Lai X, et al. Value of preoperative ultrasound-guided fine-needle aspiration for localization in Tc-99m MIBI-negative primary hyperparathyroidism patients. *Medicine (Baltimore)* 2017; 96:e9051.
- [22]. Owens CL, Rekhtman N, Sokoll L, Ali SZ. Parathyroid hormone assay in fine-needle aspirate is useful in differentiating inadvertently sampled parathyroid tissue from thyroid lesions. *Diagn Cytopathol* 2008; 36:227.
- [23]. Bilezikian JP, Silverberg SJ. Normocalcemic primary hyperparathyroidism. *Arq Bras Endocrinol Metabol* 2010; 54:106.
- [24]. Bilezikian JP, Potts JT Jr, Fuleihan GH, et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Bone Miner Res* 2002; 17 Suppl 2:N2.
- [25]. Lundgren E, Hagström EG, Lundin J, et al. Primary hyperparathyroidism revisited in menopausal women with serum calcium in the upper normal range at population-based screening 8 years ago. *World J Surg* 2002; 26:931.
- [26]. Pinney SP, Daly PA. Parathyroid cyst: an uncommon cause of a palpable neck mass and hypercalcemia. *West J Med* 1999; 170:118.
- [27]. McCoy KL, Yim JH, Zuckerbraun BS, et al. Cystic parathyroid lesions: functional and nonfunctional parathyroid cysts. *Arch Surg* 2009; 144:52.
- [28]. Lew JI, Solorzano CC, Irvin GL 3rd. Long-term results of parathyroidectomy for hypercalcemic crisis. *Arch Surg* 2006; 141:696.
- [29]. Khalid AN, Hollenbeak CS, Higginbotham BW, Stack BC Jr. Accuracy and definitive interpretation of preoperative technetium 99m sestamibi imaging based on the discipline of the reader. *Head Neck* 2009; 31:576.
- [30]. Weiser TG, Haynes AB, Dziekan G, et al. Effect of a 19-item surgical safety checklist during urgent operations in a global patient population. *Ann Surg* 2010; 251:976.
- [31]. Fujiwara S, Sposto R, Ezaki H, et al. Hyperparathyroidism among atomic bomb survivors in Hiroshima. *Radiat Res* 1992; 130:372.
- [32]. Stratton JR. Chronic left ventricular thrombi. *G Ital Cardiol* 1994; 24:269.
- [33]. Albert U, De Cori D, Aguglia A, et al. Lithium-associated hyperparathyroidism and hypercalcaemia: a case-control cross-sectional study. *J Affect Disord* 2013; 151:786.

- [34]. Awad SS, Miskulin J, Thompson N. Parathyroid adenomas versus four-gland hyperplasia as the cause of primary hyperparathyroidism in patients with prolonged lithium therapy. *World J Surg* 2003; 27:486.
- [35]. Yip L, Ogilvie JB, Challinor SM, et al. Identification of multiple endocrine neoplasia type 1 in patients with apparent sporadic primary hyperparathyroidism. *Surgery* 2008; 144:1002.
- [36]. Stang MT, Yim JH, Challinor SM, et al. Hyperthyroidism after parathyroid exploration. *Surgery* 2005; 138:1058.
- [37]. Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; 99:3580.
- [38]. Solorzano CC, Carneiro-Pla D. Minimizing cost and maximizing success in the preoperative localization strategy for primary hyperparathyroidism. *Surg Clin North Am* 2014; 94:587.
- [39]. Alonso S, Ferrero E, Donat M, et al. The usefulness of high pre-operative levels of serum type I collagen bone markers for the prediction of changes in bone mineral density after parathyroidectomy. *J Endocrinol Invest* 2012; 35:640.
- [40]. Rajeev P, Movseysan A, Baharani A. Changes in bone turnover markers in primary hyperparathyroidism and response to surgery. *Ann R Coll Surg Engl* 2017; 99:559.
- [41]. Bilezikian JP, Potts JT Jr, Fuleihan Gel-H, et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Clin Endocrinol Metab* 2002; 87:5353.
- [42]. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Ann Surg* 2002; 235:665.
- [43]. Kiernan CM, Wang T, Perrier ND, et al. Bilateral Neck Exploration for Sporadic Primary Hyperparathyroidism: Use Patterns in 5,597 Patients Undergoing Parathyroidectomy in the Collaborative Endocrine Surgery Quality Improvement Program. *J Am Coll Surg* 2019; 228:652.
- [44]. Järhult J, Ander S, Asking B, et al. Long-term results of surgery for lithium-associated hyperparathyroidism. *Br J Surg* 2010; 97:1680.
- [45]. Carchman E, Ogilvie J, Holst J, et al. Appropriate surgical treatment of lithium-associated hyperparathyroidism. *World J Surg* 2008; 32:2195.
- [46]. Delbridge LW, Dolan SJ, Hop TT, et al. Minimally invasive parathyroidectomy: 50 consecutive cases. *Med J Aust* 2000; 172:418.
- [47]. Smit PC, Borel Rinkes IH, van Dalen A, van Vroonhoven TJ. Direct, minimally invasive adenomectomy for primary hyperparathyroidism: An alternative to conventional neck exploration? *Ann Surg* 2000; 231:559.
- [48]. Sackett WR, Barraclough B, Reeve TS, Delbridge LW. Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. *Arch Surg* 2002; 137:1055.
- [49]. Irvin GL 3rd, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. *World J Surg* 2004; 28:1287.
- [50]. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. *Ann Surg* 2002; 236:543.
- [51]. Day KM, Elsayed M, Monchik JM. No Need to Abandon Focused Unilateral Exploration for Primary Hyperparathyroidism with Intraoperative Monitoring of Intact Parathyroid Hormone. *J Am Coll Surg* 2015; 221:518.
- [52]. Westerdahl J, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. *Ann Surg* 2007; 246:976.
- [53]. Russell CF, Dolan SJ, Laird JD. Randomized clinical trial comparing scan-directed unilateral versus bilateral cervical exploration for primary hyperparathyroidism due to solitary adenoma. *Br J Surg* 2006; 93:418.
- [54]. Miccoli P, Bendinelli C, Berti P, et al. Video-assisted versus conventional parathyroidectomy in primary hyperparathyroidism: a prospective randomized study. *Surgery* 1999; 126:1117.

- [55]. Slepavicius A, Beisa V, Janusonis V, Strupas K. Focused versus conventional parathyroidectomy for primary hyperparathyroidism: a prospective, randomized, blinded trial. *Langenbecks Arch Surg* 2008; 393:659.
- [56]. Aarum S, Nordenström J, Reihner E, et al. Operation for primary hyperparathyroidism: the new versus the old order. A randomised controlled trial of preoperative localisation. *Scand J Surg* 2007; 96:26.
- [57]. Mihai R, Barczynski M, Iacobone M, Sitges-Serra A. Surgical strategy for sporadic primary hyperparathyroidism an evidence-based approach to surgical strategy, patient selection, surgical access, and reoperations. *Langenbecks Arch Surg* 2009; 394:785.
- [58]. Jinih M, O'Connell E, O'Leary DP, et al. Focused Versus Bilateral Parathyroid Exploration for Primary Hyperparathyroidism: A Systematic Review and Meta-analysis. *Ann Surg Oncol* 2017; 24:1924.
- [59]. Henry JF, Sebag F, Tamagnini P, et al. Endoscopic parathyroid surgery: results of 365 consecutive procedures. *World J Surg* 2004; 28:1219.
- [60]. Miccoli P, Berti P, Materazzi G, et al. Results of video-assisted parathyroidectomy: single institution's six-year experience. *World J Surg* 2004; 28:1216.
- [61]. Hessman O, Westerdahl J, Al-Suliman N, et al. Randomized clinical trial comparing open with video-assisted minimally invasive parathyroid surgery for primary hyperparathyroidism. *Br J Surg* 2010; 97:177.
- [62]. Augustine MM, Bravo PE, Zeiger MA. Surgical treatment of primary hyperparathyroidism. *Endocr Pract* 2011; 17 Suppl 1:75.
- [63]. Fouquet T, Germain A, Zarnegar R, et al. Totally endoscopic lateral parathyroidectomy: prospective evaluation of 200 patients. ESES 2010 Vienna presentation. *Langenbecks Arch Surg* 2010; 395:935.
- [64]. Prades JM, Asanau A, Timoshenko AP, et al. Endoscopic parathyroidectomy in primary hyperparathyroidism. *Eur Arch Otorhinolaryngol* 2011; 268:893.
- [65]. Angelos P. Recurrent laryngeal nerve monitoring: state of the art, ethical and legal issues. *Surg Clin North Am* 2009; 89:1157.
- [66]. Avenia N, Sanguinetti A, Cirocchi R, et al. Antibiotic prophylaxis in thyroid surgery: a preliminary multicentric Italian experience. *Ann Surg Innov Res* 2009; 3:10.
- [67]. Leaper DJ, Melling AG. Antibiotic prophylaxis in clean surgery: clean non-implant wounds. *J Chemother* 2001; 13 Spec No 1:96.
- [68]. Gagliardi AR, Fenech D, Eskicioglu C, et al. Factors influencing antibiotic prophylaxis for surgical site infection prevention in general surgery: a review of the literature. *Can J Surg* 2009; 52:481.
- [69]. Fry DE. Surgical site infections and the surgical care improvement project (SCIP): evolution of national quality measures. *Surg Infect (Larchmt)* 2008; 9:579.
- [70]. Bratzler DW, Houck PM, Surgical Infection Prevention Guidelines Writers Workgroup, et al. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004; 38:1706.
- [71]. Braxton CC, Gerstenberger PA, Cox GG. Improving antibiotic stewardship: order set implementation to improve prophylactic antimicrobial prescribing in the outpatient surgical setting. *J Ambul Care Manage* 2010; 33:131.
- [72]. Stavrakis AI, Ituarte PH, Ko CY, Yeh MW. Surgeon volume as a predictor of outcomes in inpatient and outpatient endocrine surgery. *Surgery* 2007; 142:887.
- [73]. Chen H, Wang TS, Yen TW, et al. Operative failures after parathyroidectomy for hyperparathyroidism: the influence of surgical volume. *Ann Surg* 2010; 252:691.
- [74]. Sosa JA, Powe NR, Levine MA, et al. 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* 1998; 83:2658.
- [75]. Perrier ND, Edeiken B, Nunez R, et al. A novel nomenclature to classify parathyroid adenomas. *World J Surg* 2009; 33:412.
- [76]. Tublin ME, Yim JH, Carty SE. Recurrent hyperparathyroidism secondary to parathyromatosis: clinical and imaging findings. *J Ultrasound Med* 2007; 26:847.
- [77]. Kollmorgen CF, Aust MR, Ferreiro JA, et al. Parathyromatosis: a rare yet important cause of persistent or recurrent hyperparathyroidism. *Surgery* 1994; 116:111.

- [78]. McCoy KL, Chen NH, Armstrong MJ, et al. The small abnormal parathyroid gland is increasingly common and heralds operative complexity. *World J Surg* 2014; 38:1274.
- [79]. Tominaga Y, Kakuta T, Yasunaga C, et al. Evaluation of Parathyroidectomy for Secondary and Tertiary Hyperparathyroidism by the Parathyroid Surgeons' Society of Japan. *Ther Apher Dial* 2016; 20:6.
- [80]. Liu ME, Qiu NC, Zha SL, et al. To assess the effects of parathyroidectomy (TPTX versus TPTX+AT) for Secondary Hyperparathyroidism in chronic renal failure: A Systematic Review and Meta-Analysis. *Int J Surg* 2017; 44:353.
- [81]. Wang C. The anatomic basis of parathyroid surgery. *Ann Surg* 1976; 183:271.
- [82]. Edis AJ, Levitt MD. Supernumerary parathyroid glands: implications for the surgical treatment of secondary hyperparathyroidism. *World J Surg* 1987; 11:398.
- [83]. Irvin GL 3rd, Prudhomme DL, Deriso GT, et al. A new approach to parathyroidectomy. *Ann Surg* 1994; 219:574.
- [84]. Henry JF. Reoperation for primary hyperparathyroidism: tips and tricks. *Langenbecks Arch Surg* 2010; 395:103.
- [85]. Borot S, Lapierre V, Carnaille B, et al. Results of cryopreserved parathyroid autografts: a retrospective multicenter study. *Surgery* 2010; 147:529.
- [86]. Akerström G, Stålberg P. Surgical management of MEN-1 and -2: state of the art. *Surg Clin North Am* 2009; 89:1047.
- [87]. Sharma J, Weber CJ. Surgical therapy for familial hyperparathyroidism. *Am Surg* 2009; 75:579.
- [88]. Lew JI, Solorzano CC. Surgical management of primary hyperparathyroidism: state of the art. *Surg Clin North Am* 2009; 89:1205.
- [89]. Fernandez-Ranvier GG, Khanafshar E, Jensen K, et al. Parathyroid carcinoma, atypical parathyroid adenoma, or parathyromatosis? *Cancer* 2007; 110:255.
- [90]. Wang CA, Gaz RD. Natural history of parathyroid carcinoma. Diagnosis, treatment, and results. *Am J Surg* 1985; 149:522.
- [91]. Wynne AG, van Heerden J, Carney JA, Fitzpatrick LA. Parathyroid carcinoma: clinical and pathologic features in 43 patients. *Medicine (Baltimore)* 1992; 71:197.
- [92]. Shane E. Clinical review 122: Parathyroid carcinoma. *J Clin Endocrinol Metab* 2001; 86:485.
- [93]. Xue S, Chen H, Lv C, et al. Preoperative diagnosis and prognosis in 40 Parathyroid Carcinoma Patients. *Clin Endocrinol (Oxf)* 2016; 85:29.
- [94]. Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: an update and review. *World J Surg* 1991; 15:738.
- [95]. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 1999; 86:538.
- [96]. Anderson BJ, Samaan NA, Vassilopoulou-Sellin R, et al. Parathyroid carcinoma: features and difficulties in diagnosis and management. *Surgery* 1983; 94:906.
- [97]. Kebebew E. Parathyroid carcinoma. *Curr Treat Options Oncol* 2001; 2:347.
- [98]. Givi B, Shah JP. Parathyroid carcinoma. *Clin Oncol (R Coll Radiol)* 2010; 22:498.
- [99]. Owen RP, Silver CE, Pellitteri PK, et al. Parathyroid carcinoma: a review. *Head Neck* 2011; 33:429.
- [100]. Villar-del-Moral J, Jiménez-García A, Salvador-Egea P, et al. Prognostic factors and staging systems in parathyroid cancer: a multicenter cohort study. *Surgery* 2014; 156:1132.
- [101]. McClenaghan F, Qureshi YA. Parathyroid cancer. *Gland Surg* 2015; 4:329.
- [102]. Schulte KM, Talat N, Galata G, et al. Oncologic resection achieving r0 margins improves disease-free survival in parathyroid cancer. *Ann Surg Oncol* 2014; 21:1891.
- [103]. Al-Kurd A, Mekel M, Mazeh H. Parathyroid carcinoma. *Surg Oncol* 2014; 23:107.
- [104]. Kassahun WT, Jonas S. Focus on parathyroid carcinoma. *Int J Surg* 2011; 9:13.
- [105]. Erovc BM, Goldstein DP, Kim D, et al. Parathyroid cancer: outcome analysis of 16 patients treated at the Princess Margaret Hospital. *Head Neck* 2013; 35:35.
- [106]. Desiato V, Melis M, Amato B, et al. Minimally invasive radioguided parathyroid surgery: A literature review. *Int J Surg* 2016; 28 Suppl 1:S84.

- [107]. Carneiro DM, Irvin GL 3rd. Late parathyroid function after successful parathyroidectomy guided by intraoperative hormone assay (QPTH) compared with the standard bilateral neck exploration. *Surgery* 2000; 128:925.
- [108]. Sokoll LJ, Drew H, Udelsman R. Intraoperative parathyroid hormone analysis: A study of 200 consecutive cases. *Clin Chem* 2000; 46:1662.
- [109]. Lee S, Ryu H, Morris LF, et al. Operative failure in minimally invasive parathyroidectomy utilizing an intraoperative parathyroid hormone assay. *Ann Surg Oncol* 2014; 21:1878.
- [110]. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. *Surgery* 1993; 114:1019.
- [111]. Chiu B, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. *Arch Surg* 2006; 141:483.
- [112]. Wharry LI, Yip L, Armstrong MJ, et al. The final intraoperative parathyroid hormone level: how low should it go? *World J Surg* 2014; 38:558.
- [113]. Westerdahl J, Bergenfelz A. Parathyroid surgical failures with sufficient decline of intraoperative parathyroid hormone levels: unobserved multiple endocrine neoplasia as an explanation. *Arch Surg* 2006; 141:589.
- [114]. Cayo A, Chen H. Radioguided reoperative parathyroidectomy for persistent primary hyperparathyroidism. *Clin Nucl Med* 2008; 33:668.
- [115]. Chen JS, Sambrook PN, March L, et al. Hypovitaminosis D and parathyroid hormone response in the elderly: effects on bone turnover and mortality. *Clin Endocrinol (Oxf)* 2008; 68:290.
- [116]. Chen H, Pruhs Z, Starling JR, Mack E. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. *Surgery* 2005; 138:583.
- [117]. Chen H, Mack E, Starling JR. A comprehensive evaluation of perioperative adjuncts during minimally invasive parathyroidectomy: which is most reliable? *Ann Surg* 2005; 242:375.
- [118]. Black MJ, Ruscher AE, Lederman J, Chen H. Local/cervical block anesthesia versus general anesthesia for minimally invasive parathyroidectomy: what are the advantages? *Ann Surg Oncol* 2007; 14:744.
- [119]. Shindo ML, Rosenthal JM, Lee T. Minimally invasive parathyroidectomy using local anesthesia with intravenous sedation and targeted approaches. *Otolaryngol Head Neck Surg* 2008; 138:381.
- [120]. Carling T, Donovan P, Rinder C, Udelsman R. Minimally invasive parathyroidectomy using cervical block: reasons for conversion to general anesthesia. *Arch Surg* 2006; 141:401.
- [121]. Pallotta JA, Sacks BA, Moller DE, Eisenberg H. Arteriographic ablation of cervical parathyroid adenomas. *J Clin Endocrinol Metab* 1989; 69:1249.
- [122]. Doppman, JL. Endocrine imaging. *Endocrinologist* 1997; 7:83.
- [123]. Stratigis S, Stylianou K, Mamalaki E, et al. Percutaneous ethanol injection therapy: a surgery-sparing treatment for primary hyperparathyroidism. *Clin Endocrinol (Oxf)* 2008; 69:542.
- [124]. Veldman MW, Reading CC, Farrell MA, et al. Percutaneous parathyroid ethanol ablation in patients with multiple endocrine neoplasia type 1. *AJR Am J Roentgenol* 2008; 191:1740.
- [125]. Stuart HC, Harvey A, Pasiaka JL. Normocalcemic hyperparathyroidism: preoperatively a disease, postoperatively cured? *Am J Surg* 2014; 207:673.
- [126]. Silva AM, Vodopivec D, Christakis I, et al. Operative intervention for primary hyperparathyroidism offers greater bone recovery in patients with sporadic disease than in those with multiple endocrine neoplasia type 1-related hyperparathyroidism. *Surgery* 2017; 161:107.
- [127]. Burkey SH, van Heerden JA, Thompson GB, et al. Reexploration for symptomatic hematomas after cervical exploration. *Surgery* 2001; 130:914.
- [128]. Rosenbaum MA, Haridas M, McHenry CR. Life-threatening neck hematoma complicating thyroid and parathyroid surgery. *Am J Surg* 2008; 195:339.
- [129]. Grubbs EG, Rafeeq S, Jimenez C, et al. Preoperative vitamin D replacement therapy in primary hyperparathyroidism: safe and beneficial? *Surgery* 2008; 144:852.
- [130]. Mittendorf EA, Merlino JI, McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. *Am Surg* 2004; 70:114.
- [131]. Rudofsky G Jr, Grafe IA, Metzner C, et al. Transient post-operative thyrotoxicosis after parathyroidectomy. *Med Sci Monit* 2009; 15:CS41.

- [132]. Powell AC, Alexander HR, Chang R, et al. Reoperation for parathyroid adenoma: a contemporary experience. *Surgery* 2009; 146:1144.
- [133]. Vázquez-Díaz O, Castillo-Martínez L, Orea-Tejeda A, et al. Reversible changes of electrocardiographic abnormalities after parathyroidectomy in patients with primary hyperparathyroidism. *Cardiol J* 2009; 16:241.
- [134]. Bartsch DK, Rothmund M. Reoperative surgery for primary hyperparathyroidism. *Br J Surg* 2009; 96:699.
- [135]. Patow CA, Norton JA, Brennan MF. Vocal cord paralysis and reoperative parathyroidectomy. A prospective study. *Ann Surg* 1986; 203:282.
- [136]. Thompson GB, Grant CS, Perrier ND, et al. Reoperative parathyroid surgery in the era of sestamibi scanning and intraoperative parathyroid hormone monitoring. *Arch Surg* 1999; 134:699.
- [137]. Silberfein EJ, Bao R, Lopez A, et al. Reoperative parathyroidectomy: location of missed glands based on a contemporary nomenclature system. *Arch Surg* 2010; 145:1065.
- [138]. Yen TW, Wang TS, Doffek KM, et al. Reoperative parathyroidectomy: an algorithm for imaging and monitoring of intraoperative parathyroid hormone levels that results in a successful focused approach. *Surgery* 2008; 144:611.
- [139]. Irvin GL 3rd, Molinari AS, Figueroa C, Carneiro DM. Improved success rate in reoperative parathyroidectomy with intraoperative PTH assay. *Ann Surg* 1999; 229:874.