REVIEW

Recent advances in the understanding and management of primary hyperparathyroidism [version 1; peer review: 2 approved]

Melanie Goldfarb ¹, Frederick R. Singer²

¹Center for Endocrine Tumors and Disorders, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA, 90404, USA

²Endocrine/Bone Disease Program, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA, 90404, USA

V1 First published: 25 Feb 2020, 9(F1000 Faculty Rev):143
<https://doi.org/10.12688/f1000research.21569.1>

Latest published: 25 Feb 2020, 9(F1000 Faculty Rev):143
<https://doi.org/10.12688/f1000research.21569.1>

Abstract

Primary hyperparathyroidism is a hormonal disorder whose prevalence is approximately 1–2% in the United States of America. The disease has become more recognizable to clinicians in an earlier phase and, at present, patients can be diagnosed with “classic”, “normocalcemic”, “normohormonal”, or “mild, asymptomatic” primary hyperparathyroidism. Surgery, with a focused parathyroidectomy when possible, or a four-gland exploration, is the only way to cure the disease. Cure is determined by use of intra-operative parathyroid hormone monitoring with long-term cure rates ranging from 90–95%. Newer adjuncts to surgery include CT or PET imaging and near-infrared immunofluorescence. This article highlights updates in parathyroid disease and advances in parathyroid surgery; it does not provide a comprehensive summary of the disease process or a review of surgical indications, which can be found in the AAES guidelines or NIH Symposium on primary hyperparathyroidism.

Keywords

primary hyperparathyroidism

Open Peer Review

Approval Status

	1	2
version 1		
25 Feb 2020		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Francisco Bandeira**, Hospital Agamenon Magalhães, University of Pernambuco Medical School, Recife, Brazil
2. **Scott Wilhelm**, University Hospitals Cleveland, University Hospitals, Cleveland, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Melanie Goldfarb (melaniegoldfarbmd@gmail.com)

Author roles: **Goldfarb M:** Conceptualization, Investigation, Methodology, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Singer FR:** Conceptualization, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2020 Goldfarb M and Singer FR. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Goldfarb M and Singer FR. **Recent advances in the understanding and management of primary hyperparathyroidism [version 1; peer review: 2 approved]** F1000Research 2020, 9(F1000 Faculty Rev):143 <https://doi.org/10.12688/f1000research.21569.1>

First published: 25 Feb 2020, 9(F1000 Faculty Rev):143 <https://doi.org/10.12688/f1000research.21569.1>

Introduction

Primary hyperparathyroidism (PHPT) is a hormonal disorder whose prevalence is approximately 1–2% in the United States of America and is less prevalent in countries where biochemical screening is less common. It is most often diagnosed in postmenopausal women, though prevalence has been reported to be as high as 0.5–1% in older men. Recognition of this problem more than 90 years ago was originally in patients with severe symptomatology, such as impaired cognition, peptic ulcers, constipation, muscle weakness, and arthralgias, with the first parathyroidectomy carried out by Sir John Bland-Sutton before 1917¹. Previously, Felix Mandl of Germany had long been credited with performing the first parathyroidectomy in 1926². Over the years, as biochemical, pathological, and radiological technology has evolved, the clinical state of patients has changed radically. Initially, serum calcium and parathyroid hormone (PTH) levels were markedly elevated with kidney stones and fractures prominent. Over time, PHPT became more recognizable to clinicians in an earlier phase as routine chemistry became widely used and osteoporosis diagnosis increased with the advent of bone densitometry³. At present, a significant number of patients have “no symptoms”, although bone density may be decreased and occult nephrolithiasis may be present^{4–6}. Older adults are frequently underdiagnosed and undertreated, perhaps because of a lack of understanding of the consequences of the disorder⁷. A large survey of primary care patients has concluded that health cost savings associated with fracture risk could be achieved by appropriate screening and treatment of patients with a life expectancy of 16 years⁸.

Classification of primary hyperparathyroidism

PHPT is not a single entity. In most normal subjects, four glands are present and one or more may become pathologic. Other endocrine disorders may be present depending upon

genetic abnormalities, which may be inherited. Table 1 summarizes the types of PHPT that have been reported. A single parathyroid adenoma is found in about 80% of cases. Double adenomas and sporadic hyperplasia account for the majority of the remaining cases, and all the other multi-gland cases account for the rest. Parathyroid carcinomas are rare.

Unlike classical PHPT, some patients are normocalcemic despite elevated serum PTH and others are hypercalcemic with serum PTH levels in the normal range⁹. In a 573-patient study of patients with PHPT, 405 patients were classic (70.7%), 96 were normohormonal (16.8%), and 72 were normocalcemic (12.5%)¹⁰. Normocalcemic hyperparathyroidism was associated with multi-gland disease (MGD) in 45% of patients, but only 10% in the normohormonal group and 9% in classic PHPT. Twelve months after surgery, the biochemistry was normal in >98% in all three groups.

It is important to distinguish PHPT from the rare disorder familial hypocalciuric hypercalcemia, of which there are three subtypes: FHH1, FHH2, and FHH3¹¹. Generally, these require no treatment. The diagnosis can be achieved by measuring 24-hour urinary calcium excretion. A calcium/creatinine level of less than 0.01 is found in most patients. Serum PTH levels are usually normal but may be elevated, and serum magnesium is usually elevated. These autosomal dominant disorders are caused by a loss-of-function mutation in the calcium-sensing receptor gene (*CaSR*) in the case of FHH1, loss of function in G-protein subunit alpha-1 (*GNA11*) in FHH2, and loss of function in adaptor protein-2 sigma 1 subunit (*GNA11*) in FHH3.

Indications for parathyroidectomy

Today, parathyroidectomy is recommended for the majority of patients diagnosed with PHPT. National and international guidelines recommend the minimum indications for surgical

Table 1. Classification of primary hyperparathyroidism.

Parathyroid adenomas
Normohormonal and normocalcemic subsets
Double parathyroid adenomas
Hyperparathyroidism-jaw tumor syndrome
Familial isolated hyperparathyroidism
Parathyroid carcinomas
Parathyroid hyperplasia
Sporadic
Normocalcemic and normohormonal subsets
Multiple endocrine neoplasia
Type 1: primary hyperparathyroidism, pancreatic neuroendocrine tumors, pituitary adenomas
Type 2A: primary hyperparathyroidism, medullary thyroid carcinoma, pheochromocytoma
Type 2B or 3: medullary thyroid carcinoma, pheochromocytoma, ganglioneuromas, marfanoid
habitus, primary hyperparathyroidism (uncommon)
Type 4: primary hyperparathyroidism, pituitary tumors
Familial isolated hyperparathyroidism
Neonatal severe primary hyperparathyroidism
Parathyromatosis
Lithium

treatment of PHPT, but ultimately it is a decision reached by the patient, surgeon, and endocrinologist^{12,13}. Surgery remains the most cost-effective long-term strategy, even in mild, asymptomatic patients, when incorporating fracture risk, in addition to decreasing cardiovascular risk factors and kidney stone formation and producing sustained benefits in quality of life (QOL) and neurocognition^{14–19}. Frailty, based on either co-morbid conditions or an actual frailty score, not age itself, appears to be the main contra-indication for surgery, since parathyroidectomy can be beneficial even in the very elderly^{20,21}. For patients who refuse, cannot medically have surgery, or who are not cured by surgery, cinacalcet, an inhibitor of the calcium-sensing receptor, can produce long-term normocalcemia²². A bisphosphonate can also be added to prevent bone loss.

Recent QOL studies using either older scoring measures or a new PHPT-specific health-related QOL questionnaire, PHPQoL, have demonstrated decreased symptomatology and recovery not only for patients with classical PHPT but also in patients with normocalcemic and mild PHPT^{23–27}. Improvements in QOL factors were measured as early as the first week after surgery and were sustained long term in areas of mental health, sleep quality, somatic and cognitive depression domains, and neurocognition. The updated AAES management guidelines cite neurocognitive symptoms as another surgical indication in addition to kidney stones, osteoporosis, decreased kidney function, and hypercalcemia that are dictated in the NIH guidelines.

Pre-operative imaging

Imaging for parathyroid localization should be performed only after the diagnosis of PHPT has been confirmed *and* the decision has been made to proceed with surgery. Localization is *not* to be used for diagnosis and should *not* be used to decide if a patient should proceed with surgery. Moreover, the old adage still holds true: the best localization is an experienced parathyroid surgeon. With that said, the primary role of pre-operative imaging is to decide if a patient is a candidate for a focused, minimally invasive parathyroidectomy.

Ultrasound (US) is the most cost-effective and a fairly sensitive localization technique and should be the first imaging test ordered for a patient. Surgeon-performed US has the greatest sensitivity and should be standard for any surgeon performing parathyroidectomies, in both the clinic and the operating room. US is best at detecting enlarged inferior glands, and understandably less so for superior glands owing to their location behind the thyroid gland or ectopic glands. If the US is negative or equivocal, in the United States, a CT scan is the most sensitive and cost-effective first- or second-line localization test^{28,29}. Sestamibi remains inferior because of the false positive rates with nodules and especially thyroiditis, which are present in many individuals³⁰. Although some centers report almost equivalent efficacy with a two-phase compared to four-phase CT scans, the most common technique is a three-phase scan³¹. No imaging, including CT scans, has a high accuracy in patients with MGD^{32–34}. In the re-operative setting, multimodal imaging

with at least two of Sestamibi, CT, MRI, and US has improved successful localization to 91.6% in one study of almost 350 patients³⁵.

Newer imaging techniques

Though not traditionally used for localization of parathyroid adenomas, dynamic MRIs, with or without ¹⁸F PET, have been trialed by some institutions and demonstrated reasonable sensitivity and positive predictive value (PPV)^{36–38}. Mayo clinic has trialed a novel radiotracer, carbon-11-choline, with PET/CT. In a small study, it had 100% sensitivity for the detection of abnormal single parathyroid glands, including abnormal glands as small as 6 mm or 50 mg. Unlike other nuclear medicine scans, imaging was completed in only 15 minutes and the radiation dose was lower than that of 4D CT³⁹.

Parathyroid surgery

Parathyroidectomy, regardless of the surgical technique (minimal access, video-assisted, robotic, or transoral) and whether it is a focused or a bilateral neck exploration (BNE), can be performed as an outpatient procedure. If the abnormal parathyroid gland(s) can be localized pre-operatively, a focused approach can be performed, resulting in decreased operative and anesthesia time, incision size (usually), and the amount of dissection, and therefore scar tissue, in the patient. In both the primary and the re-operative setting, parathyroidectomies should be performed by a high-volume surgeon and a multidisciplinary team engaged for complicated cases^{12,40,41}. When parathyroidectomy is performed by high-volume surgeons, rates of nerve injury are low, but post-operative hypercalcemia and hypocalcemia rates are reported to be 5% for index parathyroidectomies and 10% for re-operative parathyroidectomies⁴².

Determination of “cure”: intraoperative parathyroid hormone

Intraoperative PTH (IOPTH) continues to be the gold standard for confirmation of “cure” in the operating room. PTH has a half-life of 3.5 minutes that allows almost immediate evidence of a cure after removal of the abnormal inciting gland(s). IOPTH continues to add value in upwards of 15–20% of parathyroidectomies, depending on the patient cohort^{27,43}. However, even with localized imaging and a significant IOPTH fall well into the normal range, there is a 2–3% failure rate for unexplained reasons. Most commonly, IOPTH levels are drawn pre-incision, at 0, 5, and 10 minutes; other variations include levels at 0, 5, and 15 minutes or at 5, 10, and 20 minutes. The Miami criteria state that a 50% decrease from pre-operative or pre-excision PTH levels at 10 minutes correlates with a cure.

Further refinement of the criteria dictates that the final IOPTH level falls into the “normal” range, and some studies report improved cure rates when final IOPTH levels fall below 40⁴⁴. Baseline PTH does not seem to affect cure rate if the >50% drop is achieved, which is important given the increased number of patients with “normohormonal” PHPT having surgery⁴⁵. Patients who have been on long-term bisphosphonates or certain other medications or have a decreased creatinine clearance may have different PTH kinetics, taking 20–30 minutes

or longer to fall to its final value and/or require stricter criteria to declare a “cure”, though there is debate with regard to the extent of chronic kidney disease that causes altered PTH kinetics^{46–48}.

Prediction of multi-gland disease

As the definition and surgical referral of PHPT has expanded over the past decade or so, a greater percentage of patients, possibly as high as 25%, appear to have MGD, either double adenomas or four-gland hyperplasia. As mentioned above, pre-operative imaging is notoriously poor at recognizing and localizing MGD^{32,43}. Currently, IOPTH is the best test surgeons have for determining the presence of MGD. However, experiments with machine learning report a 94.1% accuracy, 94.1% sensitivity, 83.8% specificity, and 94.1% PPV for predicting MGD^{49,50}. Patients with normocalcemic PHPT, normal baseline PTH, and mild biochemical profiles appear to have higher rates of MGD^{10,51–53}.

Long-term outcomes

Historically, after surgical parathyroidectomy for “classic” PHPT, long-term cure rates were reported at close to 95% after either a focused parathyroidectomy or BNE. However, more recent long-term follow-up studies of more mixed PHPT populations with mild, normocalcemic, and normohormonal disease report that recurrence rates may be as high as 10% at 15+ years⁵⁴. The number of glands removed at the initial operation does not appear to impact recurrence rates, although double adenomas may have higher rates of persistent disease immediately after surgery⁵⁵. A recent study reported that besides the final IOPTH, patients with 6-month calcium levels <9.7 and concomitant normal PTH had the best long-term cure⁵⁴. Following surgery, PTH may remain elevated in up to 25% of patients who are cured from parathyroidectomy, which does not impact long-term cure rates and is more common in patients with pre-operative vitamin D deficiency and impaired renal function⁵⁶. Additionally, up to 10% of patients experience a delay in normalization of their calcium levels for up to two weeks, which also does not appear to impact rates of recurrent or persistent disease⁵⁷.

Parathyroid autofluorescence: a new intra-operative adjunct?

Intrinsic near-infrared (NIR) autofluorescence may improve intraoperative identification of both normal and abnormal parathyroid glands. This could negate the need for a frozen section during surgery to confirm parathyroid tissue, if the technology is proven, as well as potentially nullify the need for prophylactic thymectomy during four-gland explorations when an inferior gland has not been identified and the IOPTH remains elevated. In the past few years, single institution studies have reported on their positive experiences with mostly fiber-based probe technology. Sensitivity, specificity, PPV, and negative predictive value (NPV) were as high as 95.8%, 97.2%, 95.1%, and 99.1%, respectively, in one study for detecting or confirming parathyroid tissue, and the addition of NIR helped to identify the abnormal gland in 20% of PHPT patients as well as rule out soft tissue as not parathyroid in another 15% of

patients with PHPT^{58,59}. Trials that combined NIR with injections of either methylene blue or indocyanine green did not seem to provide additional benefit^{60–63}. Only one study thus far has looked at the different autofluorescence in hyperfunctioning versus normal parathyroid glands and reported that hyperfunctioning glands had a lower mean autofluorescence with a more heterogeneous pattern than normal parathyroid glands⁶⁴.

Updates in special patient populations

MEN1. A few centers have recently reported their experience with performing a less-than-subtotal (SPTX) or total (TPTX) parathyroidectomy for MEN1 patients. Given the high rate of post-operative hypocalcemia from those two procedures, especially TPTX, which can be debilitating, as well as the high rate of recurrent disease requiring reoperation after SPTX, a more limited initial approach seems reasonable in select patients^{65–67}. Patients with positive pre-operative localization would be offered a more focused approach, whether single-gland or unilateral (i.e. two gland) excision, and would be counseled on the likely need for another operation at a future date. It would not be a classic “re-operation” at that time given that all parathyroid gland(s) would be removed in any explored quadrant at the time of the primary operation⁶⁸. Of note, in a small study, autofluorescence does not appear to be a useful adjunct during surgery in these patients⁶⁹.

Pregnant females. Two published studies report that not only is parathyroidectomy during pregnancy safe and effective, but it also provides improved fetal and maternal outcomes compared to medical management during gestation^{70,71}.

Parathyromatosis. Parathyromatosis is a rare cause of hyperparathyroidism⁷². Type 1 is thought to be of embryonic origin and consists of multiple nodules of benign hyperfunctioning parathyroid tissue, mainly consisting of chief cells, scattered throughout the neck and superior mediastinum. Type 2 occurs mainly after parathyroid surgery in patients with parathyroid hyperplasia accompanying chronic renal failure. It is a consequence of gland fracture and autotransplantation of parathyroid tissue in the neck at the time of parathyroid surgery. Surgical cure is difficult, and patients may require cinacalcet therapy and a bisphosphonate for management.

Lithium-treated patients. The prevalence of hypercalcemia in lithium-treated patients is very high, and the long-term surgical cure rate is <50%, with most patients displaying hyperplasia on pathology⁷³.

Summary

PHPT is prevalent, although older adults are frequently underdiagnosed and undertreated, perhaps owing to a lack of understanding of the consequences of the disorder. We now recognize multiple phenotypes of the disease that do not all include significantly high calcium and PTH levels. Advances in pre-operative imaging and surgical adjuncts continue to advance our ability to cure the disease, but more research into the genetic and molecular landscape of the disease is needed to improve our understanding and disease cure rates.

References

1. Delbridge LW, Palazzo FF: **First parathyroid surgeon: Sir John Bland-Sutton and the parathyroids.** *ANZ J Surg.* 2007; 77(12): 1058–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Cope O: **The study of hyperparathyroidism at the Massachusetts General Hospital.** *N Engl J Med.* 1966; 274(21): 1174–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Cipriani C, Bilezikian JP: **Three generational phenotypes of sporadic primary hyperparathyroidism: evolution defined by technology.** *Lancet Diabetes Endocrinol.* 2019; 7(10): 745–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. **F** Lemos ALP, Andrade SRL, Pontes LLH, *et al.*: **High Rate of Occult Urolithiasis in Normocalcemic Primary Hyperparathyroidism.** *Kidney Blood Press Res.* 2019; 44(5): 1189–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
5. Monchik JM, Gorgun E: **Normocalcemic hyperparathyroidism in patients with osteoporosis.** *Surgery.* 2004; 136(6): 1242–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Walker MD, Silverberg SJ: **Primary hyperparathyroidism.** *Nat Rev Endocrinol.* 2018; 14: 115–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. **F** Dombrowsky A, Borg B, Xie R, *et al.*: **Why Is Hyperparathyroidism Underdiagnosed and Undertreated in Older Adults?** *Clin Med Insights Endocrinol Diabetes.* 2018; 11: 1179551418815916.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
8. **F** Nguyen-Lee JJ, Paciuc M, Guerra R, *et al.*: **Derivation of a cost-saving screening strategy for asymptomatic primary hyperparathyroidism.** *Surgery.* 2020; 167(1): 155–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
9. Cusano NE, Cipriani C, Bilezikian JP: **Management of normocalcemic primary hyperparathyroidism.** *Best Pract Res Clin Endocrinol Metab.* 2018; 32(6): 837–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Lim JY, Herman MC, Bubis L, *et al.*: **Differences in single gland and multigland disease are seen in low biochemical profile primary hyperparathyroidism.** *Surgery.* 2017; 161(1): 70–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Lee JY, Shoback DM: **Familial hypocalciuric hypercalcemia and related disorders.** *Best Pract Res Clin Endocrinol Metab.* 2018; 32(5): 609–19.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. 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(10): 959–968.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Bilezikian JP, Brandi ML, Eastell R, *et al.*: **Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop.** *J Clin Endocrinol Metab.* 2014; 99(10): 3561–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Zanolco KA, Wu JX, Yeh MW: **Parathyroidectomy for asymptomatic primary hyperparathyroidism: A revised cost-effectiveness analysis incorporating fracture risk reduction.** *Surgery.* 2017; 161(1): 16–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. **F** Koubaity O, Mandry D, Nguyen-Thi PL, *et al.*: **Coronary artery disease is more severe in patients with primary hyperparathyroidism.** *Surgery.* 2020; 167(1): 149–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
16. **F** Kizilgöl M, Çalışkan M, Beyse S, *et al.*: **Effect of parathyroidectomy on epicardial fat thickness as a cardiovascular risk factor in patients with primary hyperparathyroidism.** *Turk J Med Sci.* 2019; 49(4): 1165–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
17. **F** Ejlsmark-Svensson H, Rolighed L, Rejnmark L: **Effect of Parathyroidectomy on Cardiovascular Risk Factors in Primary Hyperparathyroidism: A Randomized Clinical Trial.** *J Clin Endocrinol Metab.* 2019; 104(8): 3223–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
18. Karakose M, Caliskan M, Arslan MS, *et al.*: **The impact of parathyroidectomy on serum ADAMTS1, ADAMTS4 levels, insulin resistance, and subclinical cardiovascular disease in primary hyperparathyroidism.** *Endocrine.* 2017; 55(1): 283–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. McMahon DJ, Carrelli A, Palmeri N, *et al.*: **Effect of Parathyroidectomy Upon Left Ventricular Mass in Primary Hyperparathyroidism: A Meta-Analysis.** *J Clin Endocrinol Metab.* 2015; 100(12): 4399–407.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Seib CD, Chomsky-Higgins K, Gosnell JE, *et al.*: **Patient Frailty Should Be Used to Individualize Treatment Decisions in Primary Hyperparathyroidism.** *World J Surg.* 2018; 42(10): 3215–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. **F** Mascarella MA, Milad D, Richardson K, *et al.*: **Preoperative Risk Index Among Patients Undergoing Thyroid or Parathyroid Surgery.** *JAMA Otolaryngol Head Neck Surg.* 2020; 146(1): 7–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
22. Cetani F, Saponaro F, Marcocci C: **Non-surgical management of primary hyperparathyroidism.** *Best Pract Res Clin Endocrinol Metab.* 2018; 32(6): 821–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Bannani S, Christou N, Guérin C, *et al.*: **Effect of parathyroidectomy on quality of life and non-specific symptoms in normocalcaemic primary hyperparathyroidism.** *Br J Surg.* 2018; 105(3): 223–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. **F** Ejlsmark-Svensson H, Sikjaer T, Webb SM, *et al.*: **Health-related quality of life improves 1 year after parathyroidectomy in primary hyperparathyroidism: A prospective cohort study.** *Clin Endocrinol (Oxf).* 2019; 90(1): 184–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
25. Dulfer R, Geilvoet W, Morks A, *et al.*: **Impact of parathyroidectomy for primary hyperparathyroidism on quality of life: A case-control study using Short Form Health Survey 36.** *Head Neck.* 2016; 38(8): 1213–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. **F** Horiuchi K, Yoshida Y, Okamoto T: **Effects of surgery on the patient-reported outcomes of primary hyperparathyroidism patients with mild hypercalcemia without classic symptoms: A systematic review of the literature.** *Surg Today.* 2019; 92: 1613.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
27. Bobanga ID, McHenry CR: **Is intraoperative parathyroid hormone monitoring necessary for primary hyperparathyroidism with concordant preoperative imaging?** *Am J Surg.* 2017; 213(3): 484–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. **F** Yeh R, Tay YD, Tabacco G, *et al.*: **Diagnostic Performance of 4D CT and Sestamibi SPECT/CT in Localizing Parathyroid Adenomas in Primary Hyperparathyroidism.** *Radiology.* 2019; 291(2): 469–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
29. Hamidi M, Sullivan M, Hunter G, *et al.*: **4D-CT is Superior to Ultrasound and Sestamibi for Localizing Recurrent Parathyroid Disease.** *Ann Surg Oncol.* 2018; 25(5): 1403–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Beck AC, Kashyap AK, Lal G, *et al.*: **Discordant findings on preoperative imaging for primary hyperparathyroidism and thyroid disease: Choosing the path to follow.** *Surgery.* 2019; 166(4): 678–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Ramirez AG, Shada AL, Martin AN, *et al.*: **Clinical efficacy of 2-phase versus 4-phase computed tomography for localization in primary hyperparathyroidism.** *Surgery.* 2016; 160(3): 731–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Shu S, Yuen AD, Yeh MW, *et al.*: **Factors Associated With Discordance Between Preoperative Parathyroid 4-Dimensional Computed Tomographic Scans and Intraoperative Findings During Parathyroidectomy.** *JAMA Surg.* 2017; 152(12): 1141–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. de Gregorio L, Lubitz CC, Hodin RA, *et al.*: **The Truth about Double Adenomas: Incidence, Localization, and Intraoperative Parathyroid Hormone.** *J Am Coll Surg.* 2016; 222(6): 1044–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Tian Y, Tanny ST, Einsiedel P, *et al.*: **Four-Dimensional Computed Tomography: Clinical Impact for Patients with Primary Hyperparathyroidism.** *Ann Surg Oncol.* 2018; 25(1): 117–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. **F** Patel SG, Saunders ND, Jamshed S, *et al.*: **Multimodal Preoperative Localization Improves Outcomes in Reoperative Parathyroidectomy: A 25-Year Surgical Experience.** *Am Surg.* 2019; 85(9): 939–43.
[PubMed Abstract](#) | **F1000 Recommendation**
36. Kluijfhout WP, Venkatesh S, Beninato T, *et al.*: **Performance of magnetic resonance imaging in the evaluation of first-time and reoperative primary hyperparathyroidism.** *Surgery.* 2016; 160(3): 747–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Kluijfhout WP, Vorselaars WM, van den Berk SA, *et al.*: **Fluorine-18 fluorocholine PET-CT localizes hyperparathyroidism in patients with inconclusive conventional imaging: A multicenter study from the Netherlands.** *Nucl Med Commun.* 2016; 37(12): 1246–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. **F** Beheshti M, Hehenwarter L, Paymani Z, *et al.*: **¹⁸F-Fluorocholine PET/CT in the assessment of primary hyperparathyroidism compared with ^{99m}Tc-MIBI or ^{99m}Tc-tetrofosmin SPECT/CT: A prospective dual-centre study in 100 patients.** *Eur J Nucl Med Mol Imaging.* 2018; 45(10): 1762–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
39. **F** Parvianian A, Martin-Macintosh EL, Goenka AH, *et al.*: **¹¹C-Choline PET/CT for Detection and Localization of Parathyroid Adenomas.** *AJR Am J Roentgenol.* 2018; 210(2): 418–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
40. **F** Iacobone M, Scerrino G, Palazzo FF: **Parathyroid surgery: an evidence-based volume-outcomes analysis: European Society of Endocrine Surgeons (ESES) positional statement.** *Langenbecks Arch Surg.* 2019; 404(8): 919–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**

41. Stack BC Jr, Tolley NS, Bartel TB, *et al.*: **AHNS Series: Do you know your guidelines? Optimizing outcomes in reoperative parathyroid surgery: Definitive multidisciplinary joint consensus guidelines of the American Head and Neck Society and the British Association of Endocrine and Thyroid Surgeons.** *Head Neck*. 2018; 40(8): 1617–29.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. **F** Kazaure HS, Thomas S, Scheri RP, *et al.*: **The devil is in the details: Assessing treatment and outcomes of 6,795 patients undergoing remedial parathyroidectomy in the Collaborative Endocrine Surgery Quality Improvement Program.** *Surgery*. 2019; 165(1): 242–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
43. **F** Shawky M, Abdel Aziz T, Morley S, *et al.*: **Impact of intraoperative parathyroid hormone monitoring on the management of patients with primary hyperparathyroidism.** *Clin Endocrinol (Oxf)*. 2019; 90(2): 277–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
44. **F** Clafin J, Dhir A, Espinosa NM, *et al.*: **Intraoperative parathyroid hormone levels ≤ 40 pg/mL are associated with the lowest persistence rates after parathyroidectomy for primary hyperparathyroidism.** *Surgery*. 2019; 166(1): 50–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
45. Trinh G, Noureldine SI, Russell JO, *et al.*: **Characterizing the operative findings and utility of intraoperative parathyroid hormone (iPTH) monitoring in patients with normal baseline iPTH and normohormonal primary hyperparathyroidism.** *Surgery*. 2017; 161(1): 78–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. **F** Liu SN, Yusufali AH, Mao ML, *et al.*: **Stricter iPTH criterion for successful parathyroidectomy in stage III CKD patients with primary hyperparathyroidism.** *Surgery*. 2018; 164(6): 1306–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
47. Sunkara B, Cohen MS, Miller BS, *et al.*: **Influence of concurrent chronic kidney disease on intraoperative parathyroid hormone monitoring during parathyroidectomy for primary hyperparathyroidism.** *Surgery*. 2018; 163(1): 42–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. **F** Egan RJ, Iliff H, Stechman MJ, *et al.*: **Intraoperative Parathyroid Hormone Assay Remains Predictive of Cure in Renal Impairment in Patients with Single Parathyroid Adenomas.** *World J Surg*. 2018; 42(9): 2835–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
49. Somnay YR, Craven M, McCoy KL, *et al.*: **Improving diagnostic recognition of primary hyperparathyroidism with machine learning.** *Surgery*. 2017; 161(4): 1113–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Imbus JR, Randle RW, Pitt SC, *et al.*: **Machine learning to identify multigland disease in primary hyperparathyroidism.** *J Surg Res*. 2017; 219: 173–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. **F** Pandian TK, Lubitz CC, Bird SH, *et al.*: **Normocalcemic hyperparathyroidism: A Collaborative Endocrine Surgery Quality Improvement Program analysis.** *Surgery*. 2020; 167(1): 168–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
52. Orr LE, McKenzie TJ, Thompson GB, *et al.*: **Surgery for Primary Hyperparathyroidism with Normal Non-suppressed Parathyroid Hormone can be Both Challenging and Successful.** *World J Surg*. 2018; 42(2): 409–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Applewhite MK, White MG, Tseng J, *et al.*: **Normohormonal primary hyperparathyroidism is a distinct form of primary hyperparathyroidism.** *Surgery*. 2017; 161(1): 62–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. **F** Mallick R, Nicholson KJ, Yip L, *et al.*: **Factors associated with late recurrence after parathyroidectomy for primary hyperparathyroidism.** *Surgery*. 2020; 167(1): 160–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. **F** Mazotas IG, Yen TWF, Doffek K, *et al.*: **Persistent/Recurrent Primary Hyperparathyroidism: Does the Number of Abnormal Glands Play a Role?** *J Surg Res*. 2020; 246: 335–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
56. Duke WS, Kim AS, Waller JL, *et al.*: **Persistently elevated parathyroid hormone after successful parathyroid surgery.** *Laryngoscope*. 2017; 127(7): 1720–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Lai V, Yen TW, Doffek K, *et al.*: **Delayed Calcium Normalization After Presumed Curative Parathyroidectomy is Not Associated with the Development of Persistent or Recurrent Primary Hyperparathyroidism.** *Ann Surg Oncol*. 2016; 23(7): 2310–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
58. **F** Squires MH, Jarvis R, Shirley LA, *et al.*: **Intraoperative Parathyroid Autofluorescence Detection in Patients with Primary Hyperparathyroidism.** *Ann Surg Oncol*. 2019; 26(4): 1142–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
59. **F** Kose E, Rudin AV, Kahramangil B, *et al.*: **Autofluorescence imaging of parathyroid glands: An assessment of potential indications.** *Surgery*. 2020; 167(1): 173–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
60. Tummers QR, Schepers A, Hamming JF, *et al.*: **Intraoperative guidance in parathyroid surgery using near-infrared fluorescence imaging and low-dose Methylene Blue.** *Surgery*. 2015; 158(5): 1323–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Hillary SL, Guillermet S, Brown NJ, *et al.*: **Use of methylene blue and near-infrared fluorescence in thyroid and parathyroid surgery.** *Langenbecks Arch Surg*. 2018; 403(1): 111–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. DeLong JC, Ward EP, Lwin TM, *et al.*: **Indocyanine green fluorescence-guided parathyroidectomy for primary hyperparathyroidism.** *Surgery*. 2018; 163(2): 388–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Lerchenberger M, Al Arabi N, Gallwas JKS, *et al.*: **Intraoperative Near-Infrared Autofluorescence and Indocyanine Green Imaging to Identify Parathyroid Glands: A Comparison.** *Int J Endocrinol*. 2019; 2019: 4687951.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
64. **F** Kose E, Kahramangil B, Aydin H, *et al.*: **Heterogeneous and low-intensity parathyroid autofluorescence: Patterns suggesting hyperfunction at parathyroid exploration.** *Surgery*. 2019; 165(2): 431–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
65. **F** Manoharan J, Albers MB, Bollmann C, *et al.*: **Single gland excision for MEN1-associated primary hyperparathyroidism.** *Clin Endocrinol (Oxf)*. 2019; 92(1): 63–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
66. **F** Montenegro FLM, Brescia MDG, Lourenço DM Jr, *et al.*: **Could the Less-Than Subtotal Parathyroidectomy Be an Option for Treating Young Patients With Multiple Endocrine Neoplasia Type 1-Related Hyperparathyroidism?** *Front Endocrinol (Lausanne)*. 2019; 10: 123.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
67. Horiuchi K, Sakurai M, Hani K, *et al.*: **Impact of “Tailored” Parathyroidectomy for Treatment of Primary Hyperparathyroidism in Patients with Multiple Endocrine Neoplasia Type 1.** *World J Surg*. 2018; 42(6): 1772–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Kluijfhout WP, Beninato T, Drake FT, *et al.*: **Unilateral Clearance for Primary Hyperparathyroidism in Selected Patients with Multiple Endocrine Neoplasia Type 1.** *World J Surg*. 2016; 40(12): 2964–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. Squires MH, Shirley LA, Shen C, *et al.*: **Intraoperative Autofluorescence Parathyroid Identification in Patients With Multiple Endocrine Neoplasia Type 1.** *JAMA Otolaryngol Head Neck Surg*. 2019; 145(10): 897–902.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. **F** Rigg J, Gilbertson E, Barrett HL, *et al.*: **Primary Hyperparathyroidism in Pregnancy: Maternofetal Outcomes at a Quaternary Referral Obstetric Hospital, 2000 Through 2015.** *J Clin Endocrinol Metab*. 2019; 104(3): 721–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
71. **F** DiMarco AN, Meeran K, Christakis I, *et al.*: **Seventeen Cases of Primary Hyperparathyroidism in Pregnancy: A Call for Management Guidelines.** *J Endocr Soc*. 2019; 3(5): 1009–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. Jain M, Krasne DL, Singer FR, *et al.*: **Recurrent primary hyperparathyroidism due to Type 1 parathyromatosis.** *Endocrine*. 2017; 55(2): 643–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
73. **F** Meehan AD, Wallin G, Järhult J: **Characterization of Calcium Homeostasis in Lithium-Treated Patients Reveals Both Hypercalcaemia and Hypocalcaemia.** *World J Surg*. 2020; 44(2): 517–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. Scott Wilhelm

Department of Surgery, Endocrine Surgery, University Hospitals Cleveland, University Hospitals, Cleveland, OH, 44106, USA

Competing Interests: No competing interests were disclosed.

2. Francisco Bandeira

Division of Endocrinology, Diabetes and Metabolic Bone Diseases, , Hospital Agamenon Magalhães, University of Pernambuco Medical School, Recife, Brazil

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research