Diagnosis and Surgical Management of Primary Hyperparathyroidism

Alexander L. Shifrin and David J. Terris

Contents

A. L. Shifrin et al. (eds.), *Endocrine Surgery Comprehensive Board Exam Guide*,
https://doi.org/10.1007/978-3-030-84737-1_13

Case Presentation

Patient Primary hyperparathyroidism (PHPT) patient history is a 53-year-old female who presented with incidental findings of elevated calcium level on a routine blood test. She reported no significant complaints besides symptoms of tiredness and fatigue. Past medical history was significant for the absence of kidney stones or fractures. She mentioned that she was treated for acne with radiation to her face in her early teenage years. No family history of cancer or hypercalcemia. No significant comorbidities. Medication includes only multivitamin which contains 500 mg of calcium daily. Prior surgery included cholecystectomy. On physical examination, vital signs are within normal range, no other abnormalities detected. She presented with laboratory data from the last 4 years which includes several total calcium measurements ranging between 10.4 mg/dL (2.75 mmol/L) and 11.2 mg/dL (2.85 mmol/L) (normal 8.5–10.2 mg/dL and 2.2 to 2.7 mmol/L, resp.), ionized calcium level 6.5 mg/dL (1.45 mmol/L) (normal 4.64–5.28 mg/dL and 1.14–1.34 mmol/L, resp.), PTH level on two occasions was 85 pg/mL (8.5 pmol/l) and 125 pg/mL (12.5 pmol/l) (normal 25–65 pg/mL and 1.6–6.9 pmol/L, resp.). Creatinine level was 0.95 mg/dL (84 μmol/L) (normal 0.6–1.0 mg/dL and 45–90 μmol/L, resp.), glomerular filtration rate (GFR) was 90 mL/min/1.73 m^2 (normal above 60 mL/min/1.73 m^2), phosphorus level was within normal range, and vitamin D25OH level was 15 ng/mL (37.5 nmol/L) (normal above 50 ng/mL and 125 nmol/L, resp.).

Questions

1. What are criteria to establish the diagnosis of primary hyperparathyroidism?
   1. Findings of a parathyroid adenoma on CT scan or neck ultrasound
   2. History of kidney stones and findings of a parathyroid adenoma on sestamibi scan
   3. Findings of normal serum calcium level and high serum PTH level
   4. Elevated 24-hour urine calcium level
   5. Findings of elevated serum calcium and PTH levels
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (3) and (5) are correct.
      (c) Only (4) and (5) are correct.
      (d) Only (2) and (4) and (5) are correct.
      (e) All are correct.
2. In which of the following would you establish the diagnosis of primary hyperparathyroidism?
   1. Elevation of both serum calcium and serum PTH levels
   2. Elevation of serum PTH but high normal serum calcium level
   3. Elevation of serum calcium but high normal serum PTH level
   4. Elevation of serum PTH level, normal serum calcium but elevation of ionized calcium level
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.

3. In which of the following would you establish the diagnosis of normohormonal primary hyperparathyroidism?
   1. Elevation of both serum calcium and serum PTH levels
   2. Elevation of serum PTH but high normal serum calcium level
   3. Elevation of serum calcium but high normal serum PTH level
   4. Elevation of serum PTH level, normal serum calcium but elevation of ionized calcium level
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (3) is correct.
      (d) Only (1) and (2) are correct.
      (e) All are correct.
4. In which of the following would you establish the diagnosis of normocalcemic primary hyperparathyroidism?
   1. Elevation of both serum calcium and serum PTH levels
   2. Elevation of serum PTH but high normal serum calcium level
   3. Elevation of serum calcium but high normal serum PTH level
   4. Elevation of serum PTH level, normal serum calcium but elevation of ionized calcium level
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (2) and (4) are correct.
      (d) Only (2) is correct.
      (e) All are correct.
5. What are recommendations for surgical management of asymptomatic PHPT based on the Summary Statement from the Fourth International Workshop?
   1. Serum calcium 1.0 mg/dL (0.25 mmol/L) above upper limit of normal
   2. Presence of osteoporosis defined as BMD by DEXA scan, a T-score of less than −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 of the radius
   3. Presence of vertebral fracture by imaging studies such as x-ray, CT scan, MRI, or Vertebral Fracture Assessment (VFA) by the DEXA scan
   4. 24-h urine for calcium above 400 mg/d (10 mmol/d)
   5. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT scan
   6. Individuals less than 50 years of age
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) and (5) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) and (5) are correct.
      (e) All are correct.

6. What statements regarding preoperative management of her calcium supplementation and vitamin D level are correct?
   1. Preoperative dietary calcium intake should be restricted, and her daily calcium supplementation should be stopped to prevent worsening of hypercalcemia.
   2. If daily dietary calcium intake is lower than 450 mg a day, she can continue daily calcium supplementation.
   3. Her low vitamin D level should be repleted by giving her the regiment of small doses of vitamin D such as 600–1000 IU of cholecalciferol to achieve the goal of the serum 25-OH vitamin D level in between 50 and 75 nmol/L.
   4. Her vitamin D supplementation should not be performed at this time, but should be postponed until after the surgery to prevent uncontrollable increase of preoperative serum calcium level and urinary calcium excretion that could result in the development of kidney stones.
      (a) Only (1) and (4) are correct.
      (b) Only (1) and (3) are correct.
      (c) Only (2) and (4) are correct.
      (d) Only (2) and (3) are correct.
      (e) All are correct.
7. Which statement(s) regarding PHPT is correct?
   1. About 85% of the patients with PHPT will have findings of a single adenoma.
   2. About 10% of patients with PHPT may have one of the familial syndromes such as MEN type 1, MEN 2, or other familial endocrine syndromes.
   3. Conservative follow-up for patients with normocalcemic PHPT showed that about 20% of them will become hypercalcemic.
   4. 15-years follow-up for patients who do not meet criteria for parathyroidectomy showed that after nonsurgical observation 40% of patients develop at least one indication for the surgery.
      (a) Only (1) and (2) and (3) are correct.
      (b) Only (1) and (2) and (4) are correct.
      (c) Only (1) and (3) and (4) are correct.
      (d) Only (2) and (3) and (4) are correct.
      (e) All are correct.
8. At what age MEN 1 and MEN 2 mutational analyses are indicated in patient with PHPT based on current guidelines?
   1. 10 years of age
   2. 20 years of age
   3. 30 years of age
   4. 40 years of age

(a) Only (1) and (2) and (3) are correct.
(b) Only (2) and (3) and (4) are correct.
(c) Only (3) and (4) are correct.
(d) Only (4) is correct.
(e) All are correct.

9. What is the best and the most cost-effective strategy to localize a solitary parathyroid adenoma?
   1. Sestamibi scan
   2. Neck ultrasound
   3. 4D CT scan
   4. Spect CT sestamibi scan
   5. Ultrasound plus Spect CT sestamibi scan
      (a) Only (1) and (2) are correct.
      (b) Only (1) and (3) are correct.
      (c) Only (2) and (3) are correct.
      (d) Only (5) is correct.
      (e) All are correct.
10. Which patient with PHPT would have high likelihood of multiglandular parathyroid hyperplasia?
    1. Patient with history of radiation exposure to the neck during childhood
    2. Patient with long history of Lithium therapy
    3. Patient with history of MEN 1 syndrome
    4. Patient with history of MEN 2 syndrome
    5. Patient with truly negative Spect CT sestamibi scan
    6. Patient presented with normohormonal PHPT
       (a) Only (2) and (3) and (4) are correct.
       (b) Only (2) and (3) and (5) and (6) are correct.
       (c) Only (1) and (3) and (4) and (6) are correct.
       (d) Only (2) and (3) and (4) and (6) are correct.
       (e) All are correct.
11. Taking in consideration that this patient has no history of kidney stones and no family history of hypercalcemia, but she mentioned that she was treated for acne with radiation to her face in early teenager years, which of the following is correct?
    1. Order bone density (DEXA) study, if no osteoporosis is present, then conservative follow-up is recommended since there are no complications of PHPT, unless patient wants to have a surgery.
    2. Advise patient to have parathyroidectomy.
    3. Perform neck ultrasound and order Spect CT sestamibi scan.
    4. Advise patient that she may have parathyroid hyperplasia due to prior history of radiation exposure.
    5. Advise patient that even with findings of one parathyroid gland, future recurrence is possible due to prior history of radiation exposure.
       (a) Only (1) and (2) and (3) are correct.
       (b) Only (2) and (3) and (4) and (5) are correct.

(c) Only (1) and (3) and (4) are correct.
(d) Only (2) and (3) and (5) are correct.
(e) All are correct.

12. What statements are correct regarding PTH and calcium kinetics?
    1. PTH half-life after the adenoma removal is approximately 3 to 4 minutes.
    2. Calcium measurements are not beneficial during the parathyroidectomy because ionized calcium level started to decrease only at 30 min after the adenoma removal.
    3. PTH elimination is proportional to its initial preoperative plasma concentration. Usually, the lowest drop of PTH level occurs at five hours after the adenoma removal.
    4. PTH levels start to increase after parathyroidectomy again at postoperative day 2.
    (a) Only (1) and (2) and (3) are correct.
    (b) Only (1) and (2) and (4) are correct.
    (c) Only (1) and (3) and (4) are correct.
    (d) Only (2) and (3) and (4) are correct.
    (e) All are correct.

13. What are the best criteria for intraoperative PTH monitoring to achieve a long-term cure?
    1. Drop of PTH level more than 50% from pre-excision (T baseline) and stimulation (during the manipulation of the gland) (T-0) levels at 5 and 10 minutes after the excision of the parathyroid adenoma
    2. Drop of PTH level more than 50% from pre-excision (T baseline) and stimulation (T-0) levels at 5 and 10 minutes and to the level of below 40 pg/mL (4.2 pmol/L) (normal 25–65 pg/mL and 1.6–6.9 pmol/L, resp.) after the excision of the parathyroid adenoma
    3. Drop of PTH level more than 50% from pre-excision (T baseline) and stimulation (T-0) levels at 1 hour after the excision of the parathyroid adenoma
    4. Drop of PTH level from 80 pg/mL (8.4 pmol/L) (normal 25–65 pg/mL and 1.6–6.9 pmol/L, resp.) at pre-excision (T baseline) and stimulation (T-0) 120 pg/mL (12.7 pmol/L) (normal 25–65 pg/mL and 1.6–6.9 pmol/L, resp.) levels to below 40 pg/mL (4.2 pmol/L) (normal 25–65 pg/mL and 1.6–6.9 pmol/L, resp.) at 10 minutes after the excision of the parathyroid adenoma
    (a) Only (1) and (2) and (3) are correct.
    (b) Only (1) and (2) and (4) are correct.
    (c) Only (1) and (3) and (4) are correct.
    (d) Only (2) and (4) are correct.
    (e) All are correct.

14. Which statements are correct regarding utilization of intraoperative parathyroid hormone (IOPTH) monitoring?
    1. Operative failure of minimally invasive surgical approach utilizing IOPTH monitoring related to the surgeons' misinterpretation of the IOPTH result and the failure to identify all abnormal parathyroid glands rather than IOPTH results itself.
    2. Bilateral parathyroid exploration could be considered in perioperative planning of patients with either normohormonal or normocalcemic PHPT.
    3. There is no difference in recurrence rate between minimally invasive (focused) approach utilizing IOPTH monitoring in patients with localized adenoma preoperatively and open four glands exploration approach.
    4. Minimally invasive parathyroidectomy can achieve a cure rate in up to 97–99% of patients when IOPTH monitoring is used.
       (a) Only (1) and (2) and (3) are correct.
       (b) Only (1) and (2) and (4) are correct.
       (c) Only (1) and (3) and (4) are correct.
       (d) Only (2) and (3) and (4) are correct.
       (e) All are correct.

15. Benefits of minimally invasive (focused) approach utilizing IOPTH monitoring are:
    1. To minimize the risk of complications, compare to more extensive exploratory surgery
    2. To decrease postoperative pain and discomfort
    3. To decrease surgical operative time
    4. To obtain the best cosmetic result
       (a) Only (1) and (2) and (3) are correct.
       (b) Only (1) and (2) and (4) are correct.
       (c) Only (1) and (3) and (4) are correct.
       (d) Only (2) and (3) and (4) are correct.
       (e) All are correct.
16. Which statements regarding surgical management of patient with PHPT are correct?
    1. Parathyroidectomy is indicated for all symptomatic patients and should be considered for most asymptomatic patients.
    2. Parathyroidectomy is more cost-effective in younger patients than observation or pharmacologic therapy.
    3. Parathyroidectomy is recommended regardless of the results of preoperative localizing studies for all patients who have met the surgical criteria.
    4. Minimally invasive parathyroidectomy using intraoperative PTH monitoring can achieve cure rate similar to open bilateral neck exploration in up to 99% of patients.

(a) Only (1) and (2) and (3) are correct.
(b) Only (1) and (2) and (4) are correct.
(c) Only (1) and (3) and (4) are correct.
(d) Only (2) and (3) and (4) are correct.
(e) All are correct.

17. What PTH level following parathyroidectomy increases the risk for symptomatic postoperative hypocalcemia?
    1. 10 pg/mL (1.06 pmol/L)
    2. 20 pg/mL (2.12 pmol/L)
    3. 30 pg/mL (3.18 pmol/L)
    4. 50 pg/mL (4.24 pmol/L)
    (a) Only (1) and (2) and (3) are correct.
    (b) Only (1) and (2) are correct.
    (c) Only (1) is correct.
    (d) Only (2) and (3) and (4) are correct.
    (e) All are correct.
18. What surgical steps can be undertaken to find an ectopic superior parathyroid gland adenoma?
    1. Dissect lower pole of the thyroid lobe in the plane to the RLN.
    2. Look at the intrathyroidal location at the inferior pole of the thyroid lobe.
    3. Look in the carotid sheath at the level of carotid bifurcation and above the bifurcation at the level of the skull base.
    4. Dissect down into paraesophageal, retroesophageally, retrolaryngeal, or retrotracheal space.
    (a) Only (1) and (4) are correct.
    (b) Only (1) and (2) are correct.
    (c) Only (1) and (3) and (4) are correct.
    (d) Only (4) is correct.
    (e) All are correct.
19. What surgical steps can be undertaken to locate an ectopic inferior parathyroid gland?
    1. Dissect deep under tubercle of Zuckerkandl.
    2. Dissect along and into the thyrothymic ligament or posterior thymus.
    3. Dissect a plane deep and posterior to the recurrent laryngeal nerve along the esophagus toward the posterior mediastinum.
    4. Dissect lateral to the recurrent laryngeal nerve along the medial border of the common carotid artery into the carotid sheath.
    (a) Only (1) and (4) are correct.
    (b) Only (2) is correct.
    (c) Only (1) and (3) and (4) are correct.
    (d) Only (4) is correct.
    (e) All are correct.

20. Following successful parathyroidectomy, the patient may expect:
    1. Bone mineral density will improve as early as 6 months after the parathyroidectomy.
    2. Quality of life may improve after the successful parathyroidectomy based on two scoring systems, PAS and SF-36.
    3. Since both scoring systems (PAS and SF-36) are easy to quantify, showing patients improvement after the parathyroidectomy in 6 months to up to 10 years after the surgery, they can be used as a part of the workup to recommend surgery in patients with PHPT.
    4. Despite the fact that nephrolithiasis risk decreases following parathyroidectomy, surgery has not been shown to improve renal function.
    (a) Only (1) and (2) and (3) are correct.
    (b) Only (1) and (2) and (4) are correct.
    (c) Only (1) and (3) and (4) are correct.
    (d) Only (2) and (3) and (4) are correct.
    (e) All are correct.
21. A 32-year-old female at her eighth week of pregnancy was found to have elevated calcium level 10.4 (2.59 mmol/L) and 10.8 mg/dL (2.69 mmol/L). She has no symptoms, no history of kidney stones. Which statements are correct regarding the management of pregnant patient who was diagnosed with PHPT?
    1. PHPT may have serious consequences to the mother and to the fetus if it remains unrecognized and untreated.
    2. PHPT remains undiagnosed during pregnancy in up to 80% of cases due to physiological changes that may mask gestational hypercalcemia.
    3. If clinically necessary, sestamibi scan can be safely used during pregnancy.
    4. Ultrasound scan can be safely used during pregnancy.
    (a) Only (1) and (2) and (4) are correct.
    (b) Only (1) and (2) and (3) are correct.
    (c) Only (1) and (3) and (4) are correct.
    (d) Only (2) and (3) and (4) are correct.
    (e) All are correct.
22. Which statements regarding the management of the pregnant patient with PHPT are correct?
    1. Management of PHPT during pregnancy should be individualized based on symptoms and severity of hypercalcemia.
    2. Bisphosphonates do not cross the placenta and appear to be safe during the pregnancy.

3. Calcitonin and Cinacalcet cross the placenta and are contraindicated during the pregnancy.
4. In case of a mild form of PHPT in an asymptomatic patient, the risk of maternal and obstetrical complications is low and patients can be safely managed conservatively during the pregnancy, and parathyroidectomy can be delayed until after the delivery.
5. In cases of severe hypercalcemia when calcium level is above 11 mg/dL (2.74 mmol/L), or in symptomatic patient, the risk of preeclampsia and preterm delivery is high, and parathyroidectomy is indicated which should be performed in the second trimester.
   (a) Only (1) and (4) and (5) are correct.
   (b) Only (2) and (4) and (5) are correct.
   (c) Only (1) and (3) and (5) are correct.
   (d) Only (2) and (3) and (4) are correct.
   (e) All are correct.

13.1 Introduction

Primary hyperparathyroidism (PHPT) is defined by persistent elevation of serum calcium level with corresponding elevation of serum parathyroid hormone (PTH) level. Etiology of PHPT is mostly idiopathic due to autonomous overproduction of PTH by the abnormal parathyroid gland or glands. Normocalcemic PHPT is defined as an elevation of serum PTH level but inappropriately normal serum total and ionized calcium levels, when secondary causes are excluded such as vitamin D deficiency, primary hypercalciuria, chronic kidney disease, calcium malabsorption, and medications that can cause elevation of the PTH level (thiazides, lithium, anticonvulsants, bisphosphonates, and denosumab) [1]. Normohormonal PHPT is defined by inappropriately normal non-suppressed serum PTH level and high serum calcium level. Follow-up of patients with normocalcemic PHPT showed that in approximately 4 years, 22% of them will become hypercalcemic [1–4]. Approximately 85% of patients with PHPT will have a single parathyroid adenoma, and 15% of the patients will have either double adenoma or hyperplasia. Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop reported that more than 10% of patients with PHPT will have a mutation in 1 of 11 genes (MEN1, RET, CDKN1A, CDKN1B, CDKN2B, CDKN2C, CASR, CDC73, GNA11, AP2S1, and PTH) and may have familial syndromes such as multiple endocrine neoplasia (MEN) type 1, MEN 2, MEN 3, MEN 4, hyperparathyroidism jaw-tumor syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHPT), neonatal severe PHPT (NSPHPT), Familial Hypocalciuric Hypercalcemia (FHH)

type 1, FHH 2, FHH 3, and nonsyndromic PHPT (nsPHPT) [5–8].

13.2 Diagnosis of PHPT

Diagnosis of PHPT is biochemical and established by measuring of serum total and ionized calcium levels, and parathyroid hormone (PTH) level. Additional measurements include vitamin D25-OH level, phosphate, creatinine levels, glomerular filtration rate (GFR), alkaline phosphatase activity, and 24-hr urine calcium level [1, 5, 6]. The measurement of Bone Mineral Density (BMD) by DEXA scan should be included to evaluate for the presence of osteoporosis in the lumbar spine, femoral hip, and the wrist. Imaging studies may be ordered to evaluate for the presence of nephrolithiasis, such as kidney ultrasonography, abdominal X-ray, or abdominal CT scan [1], and to evaluate for possible bone stress fractures [1–4]. The patients with hyperparathyroidism who are less than 40 years of age, patients with positive family history for familial syndromes, the presence of multiglandular disease, and findings of parathyroid carcinoma or atypical adenoma should be considered for genetic testing [1, 5].

13.3 Indications for Surgical Treatment of PHPT

The Fourth International Workshop for the Management of Asymptomatic PHPT and the American Association of Endocrine Surgeons (AAES) Guidelines for Definitive Management of Primary Hyperparathyroidism have established the following criteria for surgical treatment of PHPT [1, 5, 6]:

1. Serum calcium 1.0 mg/dL (0.25 mmol/L) above upper limit of normal
2. Presence of osteoporosis defined as BMD by DEXA scan as T-score of less than −2.5 at lumbar spine, total hip, femoral neck, and especially, distal 1/3 of the radius (Z-scores should be used instead of T-scores in premenopausal women and men younger than 50 years of age)
3. Presence of vertebral fracture by imaging studies such as X-ray, CT scan, MRI, or Vertebral Fracture Assessment (VFA) by the DEXA scan
4. 24-h urine for calcium above 400 mg/d (10 mmol/d) and increased kidney stone risk by biochemical stone risk analysis
5. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT scan
6. Individuals less than 50 years of age

In addition to above criteria, the improved outcomes have been shown in all patients with asymptomatic PHPT who underwent a curative parathyroidectomy. Parathyroidectomy was more cost-effective than observation or pharmacologic therapy [5]. Therefore, the American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism stated that parathyroidectomy is indicated for all symptomatic patients and should be considered for most asymptomatic patients, even those who do not meet criteria for surgery [5].

13.4 Preoperative Radiological Studies and Surgical Treatment of PHPT

Radiological localization is important to help with localization of parathyroid adenoma in order to perform minimally invasive surgical approach. Minimally invasive surgical approach helps to decrease surgical time and the rate of complications, and to avoid extensive neck dissection. Radiological studies should not be used to establish the diagnosis of PHPT. The finding of the parathyroid adenoma on radiological studies does not serve as an indication for the parathyroidectomy, unless biochemical diagnosis of primary hyperparathyroidism has been established and the patient met the above-mentioned criteria. Diagnosis of PHPT should be established based on biochemical values of serum calcium and PTH levels. When parathyroid adenoma is not localized by any imaging studies, but surgical criteria are met, the patient is still a candidate for parathyroid exploration [5].

Out of all radiological studies, neck ultrasound is the safest and the least expensive imaging study for preoperative localization of parathyroid adenoma with no risk of radiation exposure. It was recommended that ultrasound should always be performed prior to a parathyroidectomy for operative planning of all patients with PHPT. Neck ultrasound is helpful not only in preoperative localization of parathyroid adenoma but also in evaluation of the thyroid gland, and visualization of the soft tissue of the neck. Findings of thyroid nodules or neck lymph nodes may change preoperative and operative plans. Thyroid nodules and lymph nodes that show worrisome features and sizes may require preoperative evaluation by fine needle aspiration biopsy (FNA). If the thyroid is very large and multinodular, and/or FNA biopsy will show findings suspicious for the cancer (Bethesda category V) or a diagnosis of the cancer (Bethesda category VI), the surgical procedure may be changed to include thyroidectomy or thyroid lobectomy.

It has been shown that the neck ultrasound is more sensitive when performed by the surgeon. When high-resolution neck

ultrasound was interpreted by radiologists, the sensitivity was reported between 51 and 89%, while surgeons-performed ultrasonography correctly identified a parathyroid adenoma in 74–90% of patients with a sensitivity 87% and specificity 88% [9–11].

The second study which is recommended to use for preoperative localization of parathyroid adenoma is dual-isotope subtraction single-photon emission computed tomography-computed tomography scan (SPECT-CT) that showed superior result compared with the regular sestamibi scan. Recent study showed that the sensitivity of the SPECT-CT scan was 95%, and specificity 89% for the detection and localization of a parathyroid adenoma. The positive predictive value was estimated to be 97% and the negative predictive value to be 83%. The accuracy of the technique was reported from 80% to 94% in detecting parathyroid adenoma and 92% in accurate localization to the appropriate gland and not only the laterality [1, 9, 12]. Similar to ultrasonography, sestamibi images should always be interpreted by the surgeon preoperatively. Sensitivity of technetium-99 m sestamibi scan is shown to be between 39% and 90% if the study is interpreted by the radiologist [10]. Preoperative assessment of the sestamibi scan by the surgeon, looking for subtleties or "shadows," may lead to the finding of parathyroid adenoma in imaging studies that were initially described as "negative" by the radiologist. Surgeons' evaluation of the "negative" sestamibi study reported findings 41% subtleties or "shadows," and evaluation of "indeterminate" sestamibi study reported findings of 76% subtleties or "shadows." In this group of patients, 91% underwent successful minimally invasive parathyroidectomy with a curative rate of 99% [13].

When the patient is presented with a truly negative sestamibi scan, then the likelihood of intraoperative findings of multiglandular disease is much higher [14]. When preoperative sestamibi scan shows persistent uptake on one side, but preoperative US failed to localize the adenoma, then the patient more likely has posteriorly located upper parathyroid gland adenoma [15]. It is important to know in planning for surgery if the patient had a history of lithium therapy or radiation exposure. Patients treated with lithium will most likely have multiglandular disease with an asymmetrical hyperplasia rather than a single adenoma. Therefore, the preoperative imaging studies could be misleading by showing only a single adenoma. Bilateral neck exploration is therefore recommended [16]. In contrast, the patient with radiation exposure (especially radioactive iodine ablation for Graves' disease) will most likely present with a single adenoma, but metachronous disease may develop several years after a successful parathyroidectomy.

Therefore, lifelong follow-up is essential which is usually done by an endocrinologist [17].

If a patient with PHPT presents with negative sestamibi scan and ultrasonography, or in patients that present with persistent or recurrent disease, four-dimensional computed tomography (4D CT) scan or thin-cut CT scan (2.5 mm cuts) can show superior results in localization of difficult to find parathyroid adenomas. Patients with negative preoperative sestamibi scans who subsequently had thin-cut CT scans had 85% sensitivity and 94% specificity for correctly lateralizing the side of the adenoma. Thin-cut CT scan also had 66% sensitivity and 89% specificity for predicting the exact location of the diseased gland [18]. Utilizing combination of different modalities, such as 4D CT scan and ultrasonography, helps maximize success of the minimally invasive approach in patients with PHPT [11, 19]. Patients who have precise localization of the parathyroid adenoma by preoperative 4D CT scan have less extensive surgical exploration directed to the parathyroid adenoma rather than the four-gland exploration. As a result of that, they have lower length of stay compared to those patients who did not have precise localization [20].

The cost of the healthcare became a significant burden not only to the patient but for healthcare systems. To assess cost utility, the analyses were performed to determine the best diagnostic and the least expensive diagnostic tests for preoperative localization of the parathyroid adenoma. While the least expensive test was an ultrasound, the most cost-effective strategy to localize a parathyroid adenoma was an ultrasound followed by the SPECT CT sestamibi scan plus/minus 4D-CT scan or ultrasound followed by 4D-CT scan. Ultrasound followed by 4D-CT scan was the least expensive strategy with an estimated cost reported as $5901 [11, 21]. The least cost-effective study was SPECT CT sestamibi alone [22]. The sensitivity and specificity of combination of both studies, ultrasound and SPECT CT sestamibi scan, were reported between 91% and 96% in localization of parathyroid adenoma [9]. Positive predictive value of SPECT CT was greater than 90% with accuracy at about 83%. It was also more accurate (36%) in predicting multiglandular disease [23, 24]. The risk of radiation exposure should be considered prior to ordering imaging studies. Sestamibi scan is contraindicated during the pregnancy and should be used very cautiously in children [25, 26].

13.5 Preoperative Management

Calcium intake influences PTH levels in patients with PHPT. If dietary calcium intake will be restricted, the urinary calcium excretion will also decrease which will lower the risk of kidney stones. However calcium restriction will increase PTH levels

with worsening of bone demineralization in patients with PHPT and further increases of calcium load to the kidneys. Studies of patients with PHPT and supplementation of calcium by giving 500 mg oral calcium daily for those with <450 mg of daily calcium intake, compared to those patients with an intake >450 mg without supplementation, showed a significant decrease in PTH levels and an increase in femoral neck bone mineral density. Therefore the recommendation was made not to restrict dietary calcium intake in patients with asymptomatic PHPT but rather provide some calcium supplementation under close monitoring [5, 27, 28].

If a patient with PHPT presents with low vitamin D level, the vitamin D depletion was associated with elevation of PTH level and more severe PHPT. Repletion of vitamin D was associated with reductions in serum PTH levels. Some patients may experience increased serum calcium levels and increased urinary calcium excretion. Therefore the recommendation was made to replenish vitamin D in patients with asymptomatic PHPT to prevent postoperative hypocalcemia due to the hungry bone syndrome but under close monitoring. Regimen of vitamin D repletion should include smaller doses of vitamin D such as 600–1000 IU of cholecalciferol to achieve the goal of the serum 25OHD levels to >50 ng/mL (125 nmol/L) and up to 75 ng/mL (187.5 nmol/L) [28].

13.6 Intraoperative PTH Monitoring

Intraoperative PTH (IOPTH) measurement became the gold standard approach for minimally invasive parathyroidectomy. The goal of the IOPTH assessment is to achieve an instant intraoperative conformation of biochemical cure of hyperparathyroidism. It allows the performance of targeted parathyroidectomy directed toward the removal of a single parathyroid adenoma rather than the need for a bilateral neck exploration [29–32]. The rationale to perform an intraoperative PTH measurement is the development of a new generation of PTH assay with two monoclonal antibodies specific for the N- and C-terminal regions of the hormone (1–84)PTH, while earlier assays were directed to either N-terminal, midregion, or C-terminal [33]. Current assay allows the measurement of PTH levels very quickly during the surgery because the half-life of PTH is approximately 3 to 4 minutes compared to the calcium measurements which is not beneficial during the parathyroidectomy because ionized calcium level starts to decrease only at 30 min after the adenoma removal. PTH elimination is proportional to its initial plasma concentration with the lowest drop of PTH level occurring at 5 hours after the adenoma removal. PTH levels subsequently start to increase again at postoperative day 2 [33, 34]. The most common estab-

lished protocol for the IOPTH assay is the 50% drop in PTH level at 5 and 10 minutes after the excision of the parathyroid adenoma [35–37]. It has been shown that using this timing accurately predicts operative success or failure in 96.3% of patients. Some authors also recommended to use additional measurements of IOPTH level at 20 minutes after the parathyroidectomy, which showed 97.3% operative success rate [38]. Therefore, the ideal time points for IOPTH measurements are the following: Tb, at baseline (before the parathyroidectomy); at the T0, during the parathyroid adenoma manipulation; T5, at 5 minutes after the adenoma removal; T10, at 10 minutes after the adenoma removal; T20 can be added if IOPTH levels are decreasing slowly as seen in the case of very high initial preoperative PTH level.

Earlier data on IOPTH measurements established that the goal of 50% IOPTH levels drop was enough to achieve the biochemical cure, even if final IOPTH levels were still above the upper limit of normal [39]. More recent data have shown that in addition to 50% IOPTH level drop, it is optimal if it falls into the normal range. It was therefore recommended to achieve the goal of IOPTH level less than 40 pg/mL (4.24 pmol/L). The study of patients 2 years after the parathyroidectomy has shown that patients with final IOPTH level less than 40 pg/mL (4.24 pmol/L) had lower rate of persistence and recurrence compared to patients with IOPTH level between 40 and 59 pg/mL (4.24 and 6.25 pmol/L). The patients with a final IOPTH level between 41 and 65 pg/mL (4.35 and 6.89 pmol/L) have a higher likelihood of persistent disease due to not identifying an additional parathyroid adenoma or hyperplasia. Patients with final IOPTH ≥60 pg/mL were reported to have recurrence rate of 5.9%, and persistence rate of 5.4% as compared to patients with IOPTH level <40 pg/mL (< 4.24 pmol/L) which had recurrence rate of 1.3% and the lowest persistence rate of 0.2% [40–42]. In addition, IOPTH level drop greater than 70% was protective against the recurrence [43].

It is important to look for multiglandular disease in patients with normocalcemic or normohormonal PHPT, and relying only on the IOPTH levels may not be sufficient. Patients presented with normocalcemic PHPT may have a chance of about 10% to have multigland disease, and patients presented with normohormonal PHPT may have up to 58% chance of multigland disease. Therefore, bilateral parathyroid exploration could be considered in perioperative planning [44, 45]. Patients with normohormonal PHPT most often had a negative sestamibi scan compared to classic PHPT (18.3% vs. 4.8%). Cure rate for normohormonal PHPT was 88% compared to 96% in the classic group. Patients with normohormonal PHPT with PTH ≤55 pg/mL (≤5.83 pmol/L) had 83% cure rate, and those with PTH 56–65 pg/mL (5.93–6.89 pmol/L) had cure rate of 96% [46]. The major cause of operative failure of minimally

invasive surgical approach utilizing IOPTH monitoring was not the failure of IOPTH technique itself, but rather the surgeons' misinterpretation of the IOPTH result and the failure to identify all abnormal parathyroid glands [47].

13.7 Surgical Approach

Minimally invasive parathyroidectomy is defined as a focused resection of the single parathyroid gland adenoma performed through a small incision with minimal surgical dissection. It is possible since 85% of the patients with PHPT will have a single parathyroid adenoma. The goal of minimally invasive surgery is to achieve a biochemical cure with minimal surgical trauma which facilitates faster recovery, minimizes postoperative pain, and reduces the size of the incision with good cosmetic result [5, 48–50].

Minimally invasive approach showed no differences in recurrence compared to open technique [51]. Parathyroidectomy is recommended regardless of the results of preoperative localizing studies for all patients who have met surgical criteria. Minimally invasive parathyroidectomy can achieve cure rate in up to 97–99% of patients when IOPTH monitoring is used [5].

Accurate localization of parathyroid adenoma helps to achieve the following goals by using the minimally invasive approach: to minimize the risk of complications secondary to more extensive exploratory surgery, to decrease postoperative pain and discomfort, to decrease surgical operative time, and to obtain the best cosmetic result.

The recurrence rate after minimally invasive approach is similar to bilateral standard open neck exploration (2.5% vs. 2.1%) [43, 51].

The concept of minimal dissection is especially important when we encounter the recurrent or persistent disease that was reported to occur in 2.5–5% of patients with PHPT [24, 48]. Patients who were presented for reoperative surgery with persistent or recurrent disease after initial standard four-glands neck exploration had complication rates of 44% which are significantly higher compared to 15% of patients with an initial minimally invasive parathyroidectomy [52].

Several recent guidelines on the management of asymptomatic PHPT have established indications for surgery [1, 5]. In addition, 15-year follow-up data showed that after non-surgical observation 40% of patients develop at least one indication for the surgery [53].

The benefits include a targeted surgical approach to the parathyroid adenoma, and the ability to perform a neck exploration with possible thyroid lobectomy without the need to convert to a standard open procedure. This allows for cosmetically pleasing and curative results [54, 55].

Looking at the long-term recurrence risk after a parathyroidectomy, a retrospective study reported a 10-year recurrence rate of 14.8% with median recurrence time of 6.3 years. Forty-one percent of recurrences were detected by 5 years, 65.5% by 10 years, and 34.5% at more than 10 years after the initial parathyroidectomy [43]. Another retrospective study reported the outcome of 1371 patients after a parathyroidectomy over the period of more than 10 years. Recurrence rate was dependent on final IOPTH values. With an IOPTH drop of less than 40 pg/mL (4.24 pmol/L) 1 year recurrence rate was 0.5%, 2 years recurrence rate was 1.5%, and 5 years recurrence rate was 4.3%. In contrast, with IOPTH level above 60 pg/mL (6.36 pmol/L), recurrence rate at 1 year was 3.7%, at 2 years was 9.5%, and at 5 years was 25.2% [42].

13.8 PHPT During Pregnancy

Prevalence of PHPT during pregnancy was reported between 0.15% and 1.4%. PHPT may have serious consequences to the mother and to the fetus if it remains unrecognized or untreated. In up to 80% of patients, it is not recognized due to physiological changes during pregnancy that mask gestational PHPT, such as hemodilution related to intravascular fluid expansion, hypoalbuminemia, increased glomerular filtration rate resulting in hypercalciuria, and transplacental transfer of calcium. Clinical presentation of PHPT may range from hyperemesis, lethargy, hypertension, thirst, abdominal pain, depression, constipation, bone fracture, maternal heart rhythm disorders, maternal hypertension to preeclampsia, nephrolithiasis, pancreatitis, hyperemesis gravidarum, and hypercalcemic crisis. Because the understanding of this concept and standard monitoring of all pregnant patients in developed countries, the presentation of PHPT during pregnancy is very mild, and it is diagnosed in earlier stages [25, 56–62]. As it was mentioned earlier, sestamibi scan is contraindicated during pregnancy due to radiation exposure risk to the fetus [25, 26]. Ultrasound is the only diagnostic option since it carries no risk of radiation exposure and is easy to perform [25]. Management of PHPT during pregnancy should be individualized based on symptoms and severity of hypercalcemia. Parathyroidectomy is indicated in symptomatic patients and patients with severe hypercalcemia, when calcium level is elevated above 11 mg/dL (2.74 mmol/L). Parathyroidectomy should be performed only in the second trimester to prevent miscarriage and anesthetic drugs exposure in the first trimester or spontaneous delivery in the third trimester [62]. Mild form of PHPT causes low risk of maternal and obstetrical complications; therefore the patients can be managed conservatively, and parathyroidectomy can be deferred until after the delivery. Some medications, such as

bisphosphonates, are contraindicated during pregnancy [63]. Calcitonin showed limited data and poor effectiveness, but it does not cross the placenta and appears to be safe [64]. Cinacalcet has shown good results in several studies, although safety data are limited [65, 66]. Recent paper published by Rigg et al. retrospectively reviewed data of 28 pregnant patients with PHPT (22 managed medically and 6 surgically by elective parathyroidectomies) showed that 30% of those who were managed medically developed preeclampsia, and 66% managed medically had preterm deliveries [67].

13.9 Location of Ectopic Parathyroid Glands

Since embryological development of the inferior parathyroid glands is closely related to the thymus, both derived from the third pharyngeal pouch, the location of the inferior parathyroid glands usually can be found within the proximity to the inferior pole of the thyroid lobe: inferiorly, laterally, or posteriorly [68]. The inferior parathyroid gland can be found in the superior horn of the thymus or thyrothymic ligament in about 25% cases [69]. It could be medial to the inferior pole on the trachea in 8% or lateral in about 12% [70].

Ectopic location of the inferior parathyroid gland is related to the failure of the gland to detach from the thymus. They could be found anywhere along the line of descent of the thymus. Ectopic migration of parathyroid gland could be either high or low.

From undescended or incompletely descended (1% of cases), much higher in the neck at the level of angle of mandible, such as at the level or above the carotid bifurcation; 2–3 cm lateral to or above the superior pole of the thyroid lobe; in proximity to the submandibular salivary gland (that makes it very difficult to evaluate by sestamibi scan which usually shows persistent uptake at the salivary glands); intrathyroidal (1% of cases); to excessively descended, in about 3% cases can be found very low in the upper chest at the level of aortic arch, below it, or at pericardium [69, 71].

Surgical steps can be undertaken to locate a missing inferior parathyroid gland: dissect lower pole of the thyroid lobe in the plane to the RLN, dissect along and into the thyrothymic ligament or posterior thymus; look into the intrathyroidal location at the inferior pole of the thyroid lobe; look for undescended lower gland in the carotid sheath at the level of carotid bifurcation and above the bifurcation at the level of the skull base [72].

Superior parathyroid glands originated from dorsal wing of the fourth pharyngeal pouch and migrate down a shorter distance compared to inferior glands that makes an ectopic location more predictable [72]. Ectopic superior parathyroid glands

can be found between the thyroid gland and carotid artery, or adjacent to the carotid artery. Superior parathyroid gland also could be intrathyroidal but less likely than inferior. The surgical steps that could be undertaken to locate a missing superior parathyroid gland include as follows: mobilize the superior pole of the thyroid lobe with rotation of the thyroid medially, looking superiorly, medially or posteriorly to the upper pole of the thyroid lobe; dissect deep under tubercle of Zuckerkandl; dissect a plane deep and posterior to the recurrent laryngeal nerve along the esophagus toward the posterior mediastinum; dissect down paraesophageal or retroesophageally; dissect lateral to the recurrent laryngeal nerve along the medial border of the common carotid artery; dissect into the carotid sheath caudally; dissect deep to the inferior thyroid artery; dissect into retrolaryngeal retrotracheal space [71, 72].

13.10 Prediction and Treatment of Postoperative Hypocalcemia

Complications of parathyroid surgery include hypocalcemia and recurrent laryngeal nerve injury. Collaborative Endocrine Surgery Quality Improvement Program (CESQIP) data from 2014 to 2017 showed that hypocalcemia develops in 2.4% of patients after first time parathyroidectomy, and in 10.5% of patients after remedial parathyroidectomy [73]. Temporary hypoparathyroidism and hungry bone syndrome can develop in 1.8–42% of patients after parathyroidectomy [74, 75]. The rate of permanent hypoparathyroidism is reported in up to 3.6% of patients after initial surgery, and the rate increases in patients having bilateral neck exploration [5]. To predict development of hypocalcemia, immediate postoperative PTH level can be measured and be predictive of the development of postoperative hypocalcemia symptoms [76]. A study of patients after a thyroidectomy showed that there was no statistically significant difference in predicting postoperative hypocalcemia when PTH levels were measured at 1 hour after the surgery versus at 24 hours after the surgery [77]. Another study of patients after a thyroidectomy showed that PTH levels less than 10 pg/mL (1.06 pmol/L) at 4 hours after the surgery accurately predict postoperative drop of serum calcium level below 8.02 mg/dL (2.0 mmol/L) [78]. Intraoperative or early postoperative intact PTH levels less than 15 pg/mL (1.59 pmol/L) increase the risk for symptomatic postoperative hypocalcemia. The reduction of the IOPTH level by 85% is predictive of the development of post-parathyroidectomy hypocalcemia in patients with PHPT [79]. An intact PTH level measured on postoperative day 1 after the parathyroidectomy showed the highest ability to predict temporary hypoparathyroidism, but

not hungry bone syndrome. The best time for the evaluation of hungry bone syndrome is between postoperative day 5 and 7. Most centers perform the parathyroidectomy on an outpatient basis as a same day surgery; therefore delayed assessment of PTH level is not always possible prior to patient discharge from the hospital. Since development of hungry bone syndrome is difficult to predict and in order to prevent postoperative hypocalcemia, a routine, empiric, prophylactic postoperative administration of oral calcium with vitamin D is recommended to avoid development of symptoms in the early postoperative period [5, 76, 80]. It also appeared to be the most cost-effective approach. Recent statement of the American Association of Clinical Endocrinologists and American College of Endocrinology recommended routine, prophylactic treatment with oral calcium with or without calcitriol for all patients after a parathyroidectomy to prevent transient hypocalcemia [81]. If a IOPTH value measured at 20 minutes or longer after the parathyroidectomy is >15 pg/mL (1.59 pmol/L), the patient can be discharged home on a prophylactic oral calcium dose of between 500 mg and 1000 mg 3 times a day. If IOPTH level < 15 pg/mL (<1.59 pmol/L), calcitriol at dose 0.5 to 1.0 mcg twice a day should be started in addition to calcium and, possibly, magnesium supplementation. Patients also can be observed in the hospital overnight. In order for calcitriol to be effective, it may take up to 72 hours. For patients who develop severe symptoms of postoperative hypocalcemia, intravenous calcium is administered as 1–2 gram boluses in 50 mL of 5% dextrose infused over 20 minutes. If symptoms of severe hypocalcemia persist despite supplementation, then an intravenous calcium infusion of a solution composed of 11 grams of calcium gluconate added to normal saline or 5% dextrose water, to provide a final volume of 1000 mL, is administered at 50 mL/hour intravenous infusion rate and adjusted to maintain the calcium level in the low normal range [81, 82].

13.11 Postoperative Follow-Up

Postoperative follow-up should include measurements of calcium and PTH level shortly after the surgery and in 6 months after the parathyroidectomy. Persistent PHPT is defined as a failure to achieve normocalcemia within 6 months of parathyroidectomy, while recurrent PHPT is defined by the recurrence of hypercalcemia after a normocalcemic interval at more than 6 months after the parathyroidectomy [5]. When a diagnosis of persistent or recurrent PHPT is established, the patient should be re-evaluated with confirmatory biochemical tests to confirm the diagnosis of PHPT, and then assess to determine indications for surgery. Prior surgical records should be obtained and

reviewed, new imaging studies should be obtained, and RLN function should be evaluated prior to surgery [5].

13.12 Long-Term Effect of Parathyroidectomy in Patients with PHPT

Successful parathyroidectomy will result in normalization of bone resorption markers within hours of surgery, with subsequent more gradual increase in bone mineral density as early as 6 months post parathyroidectomy at the lumbar spine and hip, and the distal 1/3 radius [83]. Parathyroidectomy was also associated with a 64% reduction in the absolute risk of hip fractures [50, 84, 85]. Despite the fact that nephrolithiasis risk decreases following parathyroidectomy, it has not been shown to improve renal function [53, 86].

Several studies have shown a positive effect of parathyroidectomy on left ventricular mass index, a predictor of cardiovascular mortality. They reported that the highest preoperative PTH levels were associated with the greatest improvements. The clinical significance of the left ventricular mass improvement is unclear; therefore the Proceedings of the Fourth International Workshop suggested that there are no data to support that cardiovascular evaluation should be part of the workup of PHPT, or that surgery should be undertaken to improve cardiovascular markers or function [83, 87, 88].

Quality of life of patients with PHPT have been studied as well, but most of the neurocognitive complaints are nonspecific and symptoms can be difficult to quantify. Several assessment scoring systems have been developed: the PAS (parathyroid assessment of symptoms) score, the PHPQoL (primary hyperparathyroidism quality of life) score, and SF-36. SF36 quality of life scale scores include vitality, physical functioning, body pain, general health, role physical, role emotional, role social, and role mental health. The PAS scores include feeling tired, feeling thirsty, mood swings, joint pains, irritability, feeling blue, feeling weak, itchy, forgetful, headache, abdominal pain, bone pain, and ability to move off chair. Based on those two scoring systems, the follow-up studies of patients with PHPT at 6 months and 12 months after a successful parathyroidectomy showed improvement of the quality of life that appeared to be stable for at least 10 years after the surgery [89–94].

Answers to the Questions

1. (b); 2. (e); 3. (c); 4. (d); 5. (e); 6. (d); 7. (e); 8. (e); 9. (d); 10. (b); 11. (d); 12. (e); 13. (d); 14. (e); 15. (e); 16. (e); 17. (c); 18. (d); 19. (b); 20. (b); 21. (a); 22. (a)

References

1. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–9.
2. Jolobe OM. Normal ionized serum calcium is a prerequisite for characterization of normocalcemic primary hyperparathyroidism. Am J Med Sci. 2012;343(6):512.
3. Babwah F, Buch HN. Normocalcaemic primary hyperparathyroidism: a pragmatic approach. J Clin Pathol. 2018;71(4):291–7.
4. Bilezikian JP, Silverberg SJ. Normocalcemic primary hyperparathyroidism. Arq Bras Endocrinol Metabol. 2010;54(2):106–9.
5. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, Doherty GM, Herrera MF, Pasieka JL, Perrier ND, Silverberg SJ, Solórzano CC, Sturgeon C, Tublin ME, Udelsman R, Carty SE. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016;151(10):959–68.
6. Udelsman R, Åkerström G, Biagini C, Duh QY, Miccoli P, Niederle B, Tonelli F. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3595–606.
7. Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3570–9.
8. Bilezikian JP, Cusano NE, Khan AA, Liu JM, Marcocci C, Bandeira F. Primary hyperparathyroidism. Nat Rev Dis Primers. 2016;2:16033.
9. Arora S, Balash PR, Yoo J, Smith GS, Prinz RA. Benefits of surgeon-performed ultrasound for primary hyperparathyroidism. Langenbeck's Arch Surg. 2009;394(5):861–7.
10. Deutmeyer C, Weingarten M, Doyle M, Carneiro-Pla D. Case series of targeted parathyroidectomy with surgeon-performed ultrasonography as the only preoperative imaging study. Surgery. 2011;150(6):1153–60.
11. Solorzano CC, Carneiro-Pla D. Minimizing cost and maximizing success in the preoperative localization strategy for primary hyperparathyroidism. Surg Clin North Am. 2014;94(3):587–605.
12. Keidar Z, Solomonov E, Karry R, Frenkel A, Israel O, Mekel M. Preoperative [99mTc]MIBI SPECT/CT interpretation criteria for localization of parathyroid adenomas-correlation with surgical findings. Mol Imaging Biol. 2017;19(2):265–70.
13. Neychev VK, Kouniavsky G, Shiue Z, Udall DN, Somervell H, Umbricht CB, Zeiger MA. Chasing "shadows": discovering the subtleties of sestamibi scans to facilitate minimally invasive parathyroidectomy. World J Surg. 2011;35(1):140–6.
14. Thier M, Daudi S, Bergenfelz A, Almquist M. Predictors of multiglandular disease in primary hyperparathyroidism. Langenbeck's Arch Surg. 2018;403(1):103–9.
15. Harari A, Mitmaker E, Grogan RH, Lee J, Shen W, Gosnell J, Clark O, Duh QY. Primary hyperparathyroidism patients with positive preoperative sestamibi scan and negative ultrasound are more likely to have posteriorly located upper gland adenomas (PLUGs). Ann Surg Oncol. 2011;18(6):1717–22.
16. Skandarajah AR, Palazzo FF, Henry JF. Lithium-associated hyperparathyroidism: surgical strategies in the era of minimally invasive parathyroidectomy. World J Surg. 2011;35(11):2432–9.
17. Ippolito G, Palazzo FF, Sebag F, Henry JF. Long-term follow-up after parathyroidectomy for radiation-induced hyperparathyroidism. Surgery. 2007;142(6):819–22; discussion 822.e1.

18. Harari A, Zarnegar R, Lee J, Kazam E, Inabnet WB 3rd, Fahey TJ 3rd. Computed tomography can guide focused exploration in select patients with primary hyperparathyroidism and negative sestamibi scanning. Surgery. 2008;144(6):970–6; discussion 976–9.
19. Shifrin A, Thind P, Neistadt D eds. Atlas of Parathyroid Imaging and Pathology. Publisher: Springer Inc. 1st Edition, 2020, Hardcover, 120 pages, ISBN-10: 3030409589; ISBN-13: 978-3030409586.
20. Abbott DE, Cantor SB, Grubbs EG, Santora R, Gomez HF, Evans DB, Lee JE, Vu T, Perrier ND. Outcomes and economic analysis of routine preoperative 4-dimensional CT for surgical intervention in de novo primary hyperparathyroidism: does clinical benefit justify the cost? J Am Coll Surg. 2012;214(4):629–37; discussion 637–9.
21. Lubitz CC, Stephen AE, Hodin RA, Pandharipande P. Preoperative localization strategies for primary hyperparathyroidism: an economic analysis. Ann Surg Oncol. 2012;19(13):4202–9.
22. Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. Would scan, but which scan? A cost-utility analysis to optimize preoperative imaging for primary hyperparathyroidism. Surgery. 2011;150(6):1286–94.
23. McCoy KL, Ghodadra AG, Hiremath TG, Albarano A, Joyce JM, Yip L, Carty SE. Muthukrishnan A Sestamibi SPECT/CT versus SPECT only for preoperative localization in primary hyperparathyroidism: a single institution 8-year analysis. Surgery. 2018;163(3):643–7.
24. Madorin CA, Owen R, Coakley B, Lowe H, Nam K-H, Weber K, Kushnir L, Rios J, Genden E, Pawha PS, Inabnet WB. Comparison of radiation exposure and cost between dynamic computed tomography and sestamibi scintigraphy for preoperative localization of parathyroid lesions. JAMA Surg. 2013;148(6):500–3.
25. McMullen TP, Learoyd DL, Williams DC, Sywak MS, Sidhu SB, Delbridge LW. Hyperparathyroidism in pregnancy: options for localization and surgical therapy. World J Surg. 2010;34(8):1811–6.
26. Azarbar S, Salardini A, Dahdah N, Lazewatsky J, Sparks R, Portman M, Crane PD, Lee ML, Zhu Q. A phase I-II, open-label, multicenter trial to determine the dosimetry and safety of 99mTc-sestamibi in pediatric subjects. J Nucl Med. 2015;56(5):728–3.
27. Jorde R, Szumlas K, Haug E, Sundsfjord J. The effects of calcium supplementation to patients with primary hyperparathyroidism and a low calcium intake. Eur J Nutr. 2002;41:258–63.
28. Marcocci C, Bollerslev J, Aziz Khan A, Shoback D. Medical Management of Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. J Clin Endocrinol Metabol. 2014;99(10):3607–18.
29. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. Am J Surg. 1991;162(4):299–302.
30. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Clinical usefulness of an intraoperative "quick parathyroid hormone" assay. Surgery. 1993;114(6):1019–22; discussion 1022–3.
31. Irvin GL 3rd, Deriso GT 3rd. A new, practical intraoperative parathyroid hormone assay. Am J Surg. 1994;168(5):466–8.
32. Carneiro-Pla D. Contemporary and practical uses of intraoperative parathyroid hormone monitoring. Endocr Pract. 2011;17 Suppl 1:44–53.
33. Bieglmayer C, Prager G, Niederle B. Kinetic analyses of parathyroid hormone clearance as measured by three rapid immunoassays during parathyroidectomy. Clin Chem. 2002;48(10):1731–8.
34. Maier GW, Kreis ME, Renn W, Pereira PL, Häring HU, Becker HD. Parathyroid hormone after adenectomy for primary hyperparathyroidism. A study of peptide hormone elimination kinetics in humans. J Clin Endocrinol Metab. 1998;83(11):3852–6.

35. Carneiro DM, Irvin GL 3rd. New point-of-care intraoperative parathyroid hormone assay for intraoperative guidance in parathyroidectomy. World J Surg. 2002;26(8):1074–7.
36. Carneiro-Pla D. Recent findings in the use of intraoperative parathyroid hormone monitoring in parathyroid disease. Curr Opin Oncol. 2009;21(1):18–22.
37. Trinh G, Noureldine SI, Russell JO, Agrawal N, Lopez M, Prescott JD, Zeiger MA, Tufano RP. Characterizing the operative findings and utility of intraoperative parathyroid hormone (IOPTH) monitoring in patients with normal baseline IOPTH and normohormonal primary hyperparathyroidism. Surgery. 2017;161(1):78–86.
38. Calò PG, Pisano G, Loi G, Medas F, Barca L, Atzeni M, Nicolosi A. Intraoperative parathyroid hormone assay during focused parathyroidectomy: the importance of 20 minutes measurement. BMC Surg. 2013;13:36.
39. Carneiro-Pla DM, Solorzano CC, Lew JI, Irvin GL 3rd. Long-term outcome of patients with intraoperative parathyroid level remaining above the normal range during parathyroidectomy. Surgery. 2008;144(6):989–93; discussion 993–4.
40. Wharry LI, Yip L, Armstrong MJ, Virji MA, Stang MT, Carty SE, McCoy KL. The final intraoperative parathyroid hormone level: how low should it go? World J Surg. 2014;38(3):558–63.
41. Rajaei MH, Bentz AM, Schneider DF, Sippel RS, Chen H, Oltmann SC. Justified follow-up: a final ioPTH over 40 pg/mL is associated with an increased risk of persistence and recurrence in primary hyperparathyroidism. Ann Surg Oncol. 2015;22(2):454–9.
42. Rajaei MH, Bentz AM, Schneider DF, Sippel RS, Chen H, Oltmann SC. Justified follow-up: a final intraoperative parathyroid hormone (ioPTH) Over 40 pg/mL is associated with an increased risk of persistence and recurrence in primary hyperparathyroidism. Ann Surg Oncol. 2015;22(2):454–9.
43. Lou I, Balentine C, Clarkson S, Schneider DF, Sippel RS, Chen H. How long should we follow patients after apparently curative parathyroidectomy? Surgery. 2017;161(1):54–61.
44. Trinh G, Rettig E, Noureldine SI, Russell JO, Agrawal N, Mathur A, Prescott JD, Zeiger MA. Tufano RP surgical management of normocalcemic primary hyperparathyroidism and the impact of intraoperative parathyroid hormone testing on outcome. Otolaryngol Head Neck Surg. 2018;159(4):630–7.
45. Javid M, Callender G, Quinn C, Carling T, Donovan P, Udelsman R. Primary hyperparathyroidism with normal baseline intraoperative parathyroid hormone: a challenging population. Surgery. 2017;161(2):493–8.
46. Orr LE, McKenzie TJ, Thompson GB, Farley DR, Wermers RA, Lyden ML. Surgery for primary hyperparathyroidism with normal non-suppressed parathyroid hormone can be both challenging and successful. World J Surg. 2018;42(2):409–14.
47. Lee S, Ryu H, Morris LF, Grubbs EG, Lee JE, Harun N, Feng L, Perrier ND. Operative failure in minimally invasive parathyroidectomy utilizing an intraoperative parathyroid hormone assay. Ann Surg Oncol. 2014;21(6):1878–83.
48. Starker L, Fonseca A, Carling T, Udelsman R. Minimally Invasive Parathyroidectomy. International Journal of Endocrinology. 2011;206502:1–8.
49. Henry JF. Minimally invasive thyroid and parathyroid surgery is not a question of length of the incision. Langenbeck's Arch Surg. 2008;393(5):621–6.
50. Stephen AE, Mannstadt M, Hodin RA. Indications for surgical management of hyperparathyroidism: a review. JAMA Surg. 2017;152(9):878–82.

51. Schneider D, Mazeh H, Chen H, Sippel R. Predictors of recurrence in primary hyperparathyroidism: an analysis of 1,386 cases. Ann Surg. 2014;259(3):563–8.
52. Morris LF, Lee S, Warneke CL, Abadin SS, Suliburk JW, Romero Arenas MA, Lee JE, Grubbs EG, Perrier ND. Fewer adverse events after reoperative parathyroidectomy associated with initial minimally invasive parathyroidectomy. Am J Surg. 2014;208(5):850–5.
53. Walker MD, Silverberg SJ. Primary hyperparathyroidism. Nat Rev Endocrinol. 2018;14(2):115–25.
54. Fouquet T, Germain A, Zarnegar R, Klein M, De Talance N, Claude Mayer J, Ayav A, Bresler L, Brunaud L. Totally endoscopic lateral parathyroidectomy: prospective evaluation of 200 patients. ESES 2010 Vienna presentation. Langenbeck's Arch Surg. 2010;395(7):935–40.
55. Bakkar S, Matteucci V, Corsini C, Pagliaro S, Miccoli P. Less is more: time to expand the indications for minimally invasive video-assisted parathyroidectomy. J Endocrinol Investig. 2017;40(9):979–83.
56. Stringer K, Gough J, Gough I. Primary hyperparathyroidism during pregnancy: management by minimally invasive surgery based on ultrasound localization. ANZ J Surg. 2017;87(10):E134–7.
57. Dochez V, Ducarme G. Primary hyperparathyroidism during pregnancy. Arch Gynecol Obstet. 2015;291(2):259–63.
58. Dahlman T, Sjoberg HE, Bucht E. Calcium homeostasis in normal pregnancy and puerperium. A longitudinal study. Acta Obstet Gynecol Scand. 1994;73(5):393–8.
59. Kamenický P, Lecoq AL, Chanson P. Primary hyperparathyroidism in pregnancy. Ann Endocrinol (Paris). 2016;77(2):169–71.
60. Hosking DJ. Calcium homeostasis in pregnancy. Clin Endocrinol. 1996;45(1):1–6.
61. Hirsch D, Kopel V, Nadler V, Levy S, Toledano Y, Tsvetov G. Pregnancy outcomes in women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2015;100(5):2115–22.
62. Abood A, Vestergaard P. Pregnancy outcomes in women with primary hyperparathyroidism. Eur J Endocrinol. 2014;171(1):69–76.
63. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can. 2008;30(12):1146–8.
64. Krysiak R, Wilk M, Okopien B. Recurrent pancreatitis induced by hyperparathyroidism in pregnancy. Arch Gynecol Obstet. 2011;284(3):531–4.
65. Edling KL, Korenman SG, Janzen C, Sohsman MY, Apple SK, Bhuta S, Yeh MW. A pregnant dilemma: primary hyperparathyroidism due to parathyromatosis in pregnancy. Endocr Pract. 2014;20(2):e14–7.
66. Vera L, Oddo S, Di Iorgi N, Bentivoglio G, Giusti M. Primary hyperparathyroidism in pregnancy treated with cinacalcet: a case report and review of the literature. J Med Case Rep. 2016;10:361.
67. Rigg J, Gilbertson E, Barrett HL, Britten FL, Lust K. Primary hyperparathyroidism in pregnancy: maternofetal outcomes at a quaternary referral obstetric hospital, 2000 through 2015. J Clin Endocrinol Metab. 2019;104(3):721–9.
68. Fancy T, Gallagher D 3rd, Hornig JD. Surgical anatomy of the thyroid and parathyroid glands. Otolaryngol Clin N Am. 2010;43(2):221–7.
69. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery. 1984;95(1):14–21.
70. Bruining HA, Birkenhäger JC, Ong GL, Lamberts SW. Causes of failure in operations for hyperparathyroidism. Surgery. 1987;101(5):562–5.
71. Randolph GW. Surgery of the thyroid and parathyroid glands. Saunders; 2nd, 2012. ISBN-10: 9781437722277.
72. Cheatem D, Sturgeon C. Chapter 60 – Technique of parathyroidectomy. In: Clark O, Duh Q-Y, Kebebew E, Gosnell J, Shen W, editors. Textbook of endocrine surgery. 3rd ed. Jaypee; 2016.

73. Kazaure HS, Thomas S, Scheri RP, Stang MT, Roman SA, Sosa JA. 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. 2018. pii: S0039-6060(18)30526-9.
74. Allendorf J, DiGorgi M, Spanknebel K, Inabnet W, Chabot J, Logerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. World J Surg. 2007;31(11):2075–80.
75. Mittendorf EA, Merlino JI, McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. Am Surg. 2004;70(2):114–9; discussion 119–20.
76. Kaderli RM, Riss P, Geroldinger A, Selberherr A, Scheuba C, Niederle B. Primary hyperparathyroidism: dynamic postoperative metabolic changes. Clin Endocrinol. 2018;88(1):129–38.
77. Yetkin G, Citgez B, Yazici P, Mihmanli M, Sit E, Uludag M. Early prediction of post-thyroidectomy hypocalcemia by early parathyroid hormone measurement. Ann Ital Chir. 2016;87:417–21.
78. Barczyński M, Cichoń S, Konturek A. Which criterion of intraoperative iPTH assay is the most accurate in prediction of true serum calcium levels after thyroid surgery? Langenbeck's Arch Surg. 2007;392(6):693–8.
79. Crea N, Pata G, Casella C, Cappelli C, Salerni B. Predictive factors for postoperative severe hypocalcaemia after parathyroidectomy for primary hyperparathyroidism. Am Surg. 2012;78(3):352–8.
80. Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ 3rd, Shaha AR, Shindo ML, Snyder SK, Stack BC Jr, Sunwoo JB, Wang MB. American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults. Thyroid. 2018;28(7):830–41.
81. Stack BC Jr, Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, Pallota J, Snyder SK, Wong RJ, Randolph GW. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: Postoperative Hypoparathyroidism – Definitions and Management. Endocr Pract. 2015;21(6):674–85.
82. Campbell S, Corrigan T, Bilezikian J, Shifrin A. in 1. "Endocrine Emergencies". Editor: Alexander Shifrin. Chapter 11. "Hypocalcemic crisis: acute postoperative management". Publisher: Elsevier Inc, 1st Edition, Hardcover, 352 pages. ISBN-13: 9780323760973; ISBN-10: 032376097X. Published Date: 15th July 2021.
83. Silverberg SJ, Clarke BL, Peacock M, Bandeira F, Boutroy S, Cusano NE, Dempster D, Lewiecki EM, Liu JM, Minisola S, Rejnmark L, Silva BC, Walker MD, Bilezikian JP. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3580–94.
84. Cusano NE, Rubin MR, Silva BC, Tay YD, Williams JM, Agarwal S, Omeragic B, Guo XE, Bilezikian JP. Skeletal microstructure and estimated bone strength improve following parathyroidectomy in primary hyperparathyroidism. J Clin Endocrinol Metab. 2018;103(1):196–205.
85. Lee D, Walker MD, Chen HY, Chabot JA, Lee JA, Kuo JH. Bone mineral density changes after parathyroidectomy are dependent on biochemical profile. Surgery. 2019;165(1):107–13.
86. Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JE, Rejnmark L, Thakker R, D'Amour P, Paul T, Van Uum S, Shrayyef MZ, Goltzman D, Kaiser S, Cusano NE, Bouillon R, Mosekilde L, Kung AW, Rao SD, Bhadada SK, Clarke BL, Liu J, Duh Q, Lewiecki EM, Bandeira F, Eastell R, Marcocci C, Silverberg SJ, Udelsman R, Davison KS, Potts JT Jr, Brandi ML, Bilezikian JP. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int. 2017;28(1):1–19.

87. Pepe J, Cipriani C, Sonato C, Raimo O, Biamonte F, Minisola S. Cardiovascular manifestations of primary hyperparathyroidism: a narrative review. Eur J Endocrinol. 2017;177(6):R297–308.
88. McMahon DJ, Carrelli A, Palmeri N, Zhang C, DiTullio M, Silverberg SJ, Walker MD. Effect of parathyroidectomy upon left ventricular mass in primary hyperparathyroidism: a meta-analysis. J Clin Endocrinol Metab. 2015;100(12):4399–407.
89. Ejlsmark-Svensson H, Sikjaer T, Webb SM, Rejnmark L, Rolighed L. Health-related quality of life improves 1 year after parathyroidectomy in primary hyperparathyroidism: a prospective cohort study. Clin Endocrinol. 2019;90(1):184–91.
90. Pasieka JL, Parsons L, Jones J. The long-term benefit of parathyroidectomy in primary hyperparathyroidism: a 10-year prospective surgical outcome study. Surgery. 2009;146(6):1006–13.
91. Mihai R, Sadler GP. Pasieka's parathyroid symptoms scores correlate with SF-36 scores in patients undergoing surgery for primary hyperparathyroidism. World J Surg. 2008;32(5):807–14.
92. Greutelaers B, Kullen K, Kollias J, Bochner M, Roberts A, Wittert G, Pasieka J, Malycha P. Pasieka Illness Questionnaire: its value in primary hyperparathyroidism. ANZ J Surg. 2004;74(3):112–5.
93. Shah-Becker S, Derr J, Oberman BS, Baker A, Saunders B, Carr MM, Goldenberg D. Early neurocognitive improvements following parathyroidectomy for primary hyperparathyroidism. Laryngoscope. 2018;128(3):775–80.
94. Brito K, Edirimanne S, Eslick GD. The extent of improvement of health-related quality of life as assessed by the SF36 and Paseika scales after parathyroidectomy in patients with primary hyperparathyroidism–a systematic review and meta-analysis. Int J Surg. 2015;13:245–9.