Secondary hyperparathyroidism (SHPT) affects a majority of patients with chronic kidney disease (CKD) of stage 3 or worse. Despite the development of calcimimetics and their effectiveness in treating SHPT, many patients continue to fail medical management and should be referred to a parathyroid surgeon. In this narrative review, we summarize the indications for surgical referral, preoperative planning, intraoperative strategies to guide resection, and postoperative management. In the absence of universal guidelines, it can be difficult to determine when it is appropriate to make this referral. The majority of studies evaluating parathyroidectomy (PTX) for SHPT use the criteria of parathyroid hormone level (PTH) >800 pg/ml with hypercalcemia and/or hyperphosphatemia, which may be accompanied by symptoms such as bone pain and pruritis that can improve after surgery. Although the reported utility of the various imaging modalities (i.e., 99m-technetium-sestamibi scintigraphy with computed tomography [SPECT/CT], CT, or ultrasound) is highly variable in SHPT, SPECT/CT appears to be the most sensitive. Intraoperatively, PTH monitoring is effective in predicting long-term cure of SHPT but not in predicting hypoparathyroidism. Ectopic and supernumerary parathyroid glands are common in these patients and are often implicated in persistent or recurrent disease. Postoperatively, patients are at risk of severe hypocalcemia and hungry bone syndrome requiring close monitoring and replenishment.

**Keywords:** parathyroidectomy; renal hyperparathyroidism; secondary hyperparathyroidism

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### Indications for Referral to Surgical Management

The majority of patients undergoing PTX for SHPT are on dialysis (76% in the United States between 2002 and 2011). This likely reflects the increased severity of SHPT in later-stage CKD, however, and dialysis is not a requirement to be considered for PTX. Referral to a surgeon is considered when patients have failed medical management with cinacalcet, and modifiable factors, such as hypocalcemia, vitamin D deficiency, and hyperphosphatemia, have been addressed to the greatest extent possible. At this point, these patients are considered to have refractory hyperparathyroidism.

Figure 1 proposes a decision-making algorithm for managing SHPT patients. At the time of publication, there is no universally accepted serum PTH level used to define “refractory” hyperparathyroidism. The Kidney Disease: Improving Global Outcomes guidelines suggest a target range for PTH of 2- to 9-fold the upper limit of normal (130–585 pg/ml if the upper limit of normal is 65 pg/ml). As a threshold for PTX, some physicians use PTH >800 pg/ml (indicating “severe” hyperparathyroidism according to the Kidney Disease Outcomes Quality Initiative guidelines) associated with hypercalcemia and/or hyperphosphatemia.

Overtreating hyperparathyroidism carries its own risks. In particular, lower PTH levels (usually <200 pg/ml) are associated with adynamic bone disease, accelerated vascular calcification, and increased fracture risk. Complicating matters, SHPT with PTH levels greater than around 800 pg/ml carries these same risks, and vascular calcification and fracture risk have been shown to decrease in some patients after PTX.

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**Figure 1.** Clinical algorithm for managing secondary hyperparathyroidism in renal disease. Sources: Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease and Kidney Disease: Improving Global Outcomes 2017 Clinical Practice Update. CT, computed tomography; ESRD, end-stage renal disease; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.
Beyond PTH level, symptoms and complications attributable to SHPT must also be considered for each patient. Symptoms such as bone pain, pruritis, and generalized weakness are nonspecific and may or may not be caused by hypercalcemia in SHPT. Therefore, these symptoms alone in the absence of significantly elevated PTH are generally not considered an indication for PTX. Symptoms including bone pain and severe pruritis have been shown to improve significantly after PTX in patients with PTH >800 pg/ml. In a cohort of SHPT patients with PTH >649 pg/ml, a significant increase in bone mineral density was seen as early as 6 months after PTX. Furthermore, in a large case–control study of patients receiving dialysis with no prior fragility fracture, PTX was associated with a significantly lower risk of hip fracture (5.3% vs. 8.5% over a 10-year period).

Calcemic uremic arteriolopathy, or calciphylaxis, is a rare, debilitating condition mostly seen in patients receiving dialysis, who present with painful and necrotic skin ulcers, and carries a very poor prognosis. Development of this condition has traditionally been attributed to longstanding hyperphosphatemia and hyperparathyroidism; however, the largest study of calciphylaxis patients to date (n = 207) showed unexpectedly low PTH levels, suggesting that factors such as warfarin use, as opposed to severe SHPT, are greater culprits in disease development. Few studies have evaluated the role of PTX for treating calciphylaxis specifically; one recent meta-analysis showed no mortality benefit in patients with calciphylaxis undergoing PTX, but a borderline reduced risk of wound deterioration was observed (P = 0.05).

Anemia has also been correlated with SHPT. As many as 10% of ESRD patients are extremely resistant to erythropoietin therapy, which may be in part due to the fibrous replacement of bone marrow tissue that occurs with osteitis fibrosis cystica. In a small case series of patients with severe SHPT who underwent PTX, hemoglobin improved from a mean level of 8.6 g/dl to 9.4 g/dl, which was statistically significant but unlikely to change overall management. Overall, there is insufficient evidence to recommend PTX specifically to alleviate severe calciphylaxis or anemia.

Preoperative Planning

Imaging
As with primary hyperparathyroidism, the diagnosis of SHPT is a biochemical one and does not require imaging confirmation. Theoretically, preoperative imaging could be helpful for operative planning by localizing the parathyroid glands, particularly in cases of ectopic glands. Commonly used imaging modalities in hyperparathyroidism include 99m-technetium-sestamibi scintigraphy, often combined with computed tomography (i.e., SPECT/CT), and ultrasound. Figure 2 demonstrates the use of these modalities in a single patient.

The reported sensitivity and specificity of sestamibi scanning in SHPT varies greatly. A 2012 meta-analysis reported a pooled sensitivity of 58% and specificity of 93%; more recent studies have reported 43% to 88% sensitivity and 60% to 75% specificity, respectively. Despite this variability, studies do seem to agree that there is minimal benefit in surgical outcomes with preoperative sestamibi alone, even for cases involving ectopic glands. For example, at one high-volume endocrine surgery center, all ectopic glands (in 20 of 72 patients) were found by the surgeon during the operation, regardless of preoperative sestamibi.

Combined SPECT/CT has greater sensitivity (66%–88%) than sestamibi alone in SHPT but still performs poorly in identifying the ectopic glands, with the potential to prolong surgery. Many surgeons perform a focused neck ultrasound as this can be done easily and quickly in the office. However, the reported ability of ultrasound to identify parathyroid glands in SHPT is extremely variable and likely very user-dependent; thus, it does not appear to influence surgical outcomes and is again particularly poor for localizing ectopic glands.

It is important to note that these imaging studies are largely restricted to tertiary care centers with dedicated endocrine surgeons. In many cases, the experience of the surgeon likely plays a far greater role in the success of surgery than the preoperative imaging.

Surgical Planning
Given that all 4 glands are typically enlarged in SHPT, the surgeon should plan for a bilateral neck dissection. Although a total 4-gland PTX was once frequently performed in an attempt to avoid recurrence, this operation has fallen out of favor at many centers due to the risk of permanent hypocalcemia and hungry bone syndrome (HBS). Most patients undergo a subtotal PTX (sPTX) or total PTX (tPTX) with parathyroid tissue autotransplantation (tPTX+AT). The tPTX+AT carries the advantage of an easy reoperation in case of persistent disease. The parathyroid tissue is typically fragmented, then autotransplanted by injection into the arm, where in can be easily accessed under local anesthesia at a later time. In contrast, with sPTX, approximately half of the most normal-appearing gland is left behind in its anatomic position. However, because autotransplanted parathyroid tissue will not be functional until it has undergone neovascularization, some surgeons opt to mobilize a portion of 1
parathyroid gland on its vascular pedicle and autotransplant the tissue anteriorly, superficial to the strap muscles. The blood supply to the parathyroid remnant is maintained, the gland is easily accessed in case of reoperation, and placement of a surgical clip allows for easy identification on X-ray.

The relative complications of the 2 approaches are summarized in Table 1. A 2019 meta-analysis of >3600 patients found no statistically significant difference between tPTX+AT and sPTX in terms of rates of hypocalcemia, radiologic improvement of bone disease, improvement of symptoms attributable to hyperparathyroidism, rate of persistent disease, or time to recurrence.

Significant differences favoring sPTX included shorter operative time (120 vs. 150 minutes) and shorter hospital stay (4.1 vs. 5.0 days). In addition, the tPTX+AT group tended to have a greater need for long-term calcium and vitamin D supplementation, although the difference did not reach significance. A more recent study of 46 patients receiving dialysis did show a significantly higher risk of long-term calcium requirement in the tPTX+AT group (71%) compared with the sPTX group (37%).

Bilateral neck exploration is typically performed under general anesthesia, a potential barrier for CKD patients who are at high risk of perioperative complications. In addition to impaired renal function, patients frequently have interrelated comorbidities and risk factors, such as coagulopathies, diabetes, cardiovascular disease, and smoking histories. This increases their risk of bleeding, infections, hyperkalemia, arrhythmias, and other life-threatening complications. Although many have demonstrated the feasibility of a local anesthesia approach (cervical block with light sedation) for primary hyperparathyroidism (PHPT) patients undergoing a focused PTX, there is a paucity of literature on the feasibility of this approach in bilateral neck explorations and/or SHPT patients specifically.

In SHPT patients who are not surgical candidates, thermal and chemical ablation can be considered. Thermal ablation uses microwave, radiofrequency, or laser ablation to induce thermal necrosis in the parathyroid gland.
A recent meta-analysis showed no difference in the risk of postprocedure hypocalcemia or hoarseness between thermal ablation \( (n = 157) \) and PTX \( (n = 169) \). However, the thermal ablation group had a significantly higher risk of persistent or recurrent hypoparathyroidism (10.5% vs. 3.3%). Chemical ablation of parathyroid glands with percutaneous ethanol injection has also been used successfully in SHPT patients, both as an initial procedure and in patients with recurrent or persistent SHPT after PTX. Both procedures are minimally invasive and repeatable and may be viable options for poor surgical candidates.

**Intraoperative Strategies Used to Guide Resection**

The role of intraoperative parathyroid hormone (ioPTH) monitoring in SHPT is less clear than in PHPT. Nonetheless, measuring ioPTH is useful for predicting cure of hyperparathyroidism. A drop in ioPTH of at least 60% to 70% from pre-excision to 10 to 30 minutes post-excision has been strongly correlated with resolution of hyperparathyroidism, whereas the Miami criterion (decrease in PTH by 50% from highest value pre-excision at 10 minutes post-excision) does not appear to be a useful metric. The timing of ioPTH measurement has been debated. One randomized trial showed no benefit in outcomes and increased cost when measuring ioPTH beyond 10 minutes, using a
Given the high prevalence of ectopic glands, which often blend in with surrounding tissues and can be difficult to isolate, many endocrine surgeons consider a bilateral cervical thymectomy necessary in all SHPT patients undergoing PTX. In one study, thymic parathyroid glands were found to be the culprit in 28% of reoperative PTXs for persistent or recurrent SHPT. A 2015 consensus report from the European Society of Endocrine Surgeons recommended universal BCT at the time of sPTX or tPTX+AT given the evidence that bilateral cervical thymectomy may spare a significant number of patients a second operation. Many centers do perform bilateral cervical thymectomy routinely on all SHPT patients, or selectively on patients in whom 4 glands were not identified.

To aid in localization of the parathyroid glands, some providers have begun to use intraoperative near-infrared fluorescence imaging. This technique involves i.v. injection of indocyanine green, a relatively safe water-soluble organic dye that binds to lipoproteins in the vasculature and can help identify pathologic parathyroid glands. It may be useful for identifying a gland remnant with good vascular supply in sPTX and for identifying ectopic glands in some patients.

In a study of 29 patients with SHPT undergoing total PTX (without AT), operative time was significantly reduced (130 vs. 156 minutes) in those receiving indocyanine green fluorescence imaging. Still, further studies are needed to establish whether near-infrared fluorescence imaging leads to improved surgical outcomes.

Intraoperative nerve monitoring is frequently used in various neck procedures to help identify and preserve the recurrent laryngeal nerves. Studies on PTX patients specifically have been conflicted on whether intraoperative nerve monitoring actually prevents recurrent laryngeal nerve injury, which can cause permanent voice changes and airway complications. Although its results may not be generalizable, a recent large meta-analysis of bilateral thyroidectomy patients showed a significantly decreased risk of both transient (risk ratio = 0.71) and permanent (risk difference = −0.0026) recurrent laryngeal nerve injury with intraoperative nerve monitoring. Use of this technology varies by institution and, to our knowledge, has not been studied in SHPT patients specifically.

### Postoperative Management

**Monitoring for Hypocalcemia**

Postoperatively, it is critical to monitor patients for HBS, defined as a drop in serum calcium to <2.1 mmol/L (8.4 mg/dl), usually with a nadir on postoperative days 2 to 4, and/or prolonged hypocalcemia beyond postoperative day 4. Patients may also develop

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**Table 1. Relative complications of the 2 operations for secondary hyperparathyroidism**

| Subtotal parathyroidectomy | Total parathyroidectomy with autotransplantation |
|----------------------------|-----------------------------------------------|
| • Among patients with recurrent disease, potentially increased risk of additional neck dissection (vs. removal of grafted tissue) | • Potentially greater risk of hypocalcemia |
| • Longer operating time | • Longer hospital stay |
| • Radiologic improvement in bone disease | | |
| • Improvement in symptoms attributable to SHPT | | |
| • Rate of persistent disease | | |
| • Time to recurrence | | |

SHPT, secondary hyperparathyroidism.
Sources: Yuan et al. and Zmijewski et al.

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criterion of >60% fall in PTH from preoperative to 10 minutes post-excision to conclude the operation. This conclusion was supported by another study that showed no significant difference between 10- and 20-minute post-excision values. One study in which the majority of patients underwent total PTX did show a significant drop in iOPTH from 10 to 20 minutes post-excision, but this result may not be generalizable to patients undergoing sPTX or tPTX+AT. There is no universal definition of “cure” in SHPT patients; many have PTH levels that fall by 70% or much more, but not into a normal range. In a study of 57 patients receiving dialysis and undergoing PTX, the average PTH level at last follow-up was 66 pg/ml (range 15–201 pg/ml, mean follow-up time 2.3 years). The study also showed no significant difference between sPTX and tPTX+AT in terms of PTH levels before intubation, 10 minutes post-excision, 20 minutes post-excision, or at postoperative follow-up. Notably, iOPTH does not reliably predict hypoparathyroidism postoperatively, and even patients with PTH levels >2-fold the upper limit of normal at 15 to 20 minutes post-excision can go on to develop undetectable PTH and severe hypocalcemia.

Supernumerary (5 or more) and ectopic parathyroid glands are common in SHPT. Supernumerary glands are found in 5% to 30% of patients and ectopically located glands in 28% to 46% of patients, posing an additional challenge to surgical exploration. Failure of iOPTH to fall by ≥70% after seemingly appropriate resection should prompt a search for additional glands, which account for a significant proportion of persistent or recurrent hyperparathyroidism cases requiring reoperation. As with PHPT, hyperfunctioning parathyroid glands may be found in the thymus, thyroid parenchyma, retroesophageal space, carotid sheath, and mediastinum.
hypomagnesemia and hypophosphatemia and/or hyperkalemia. The reported prevalence of HBS after PTX in SHPT varies, but it is generally accepted to be a very common complication. Risk factors include radiologic evidence of osteitis fibrosa cystica, higher bone-specific alkaline phosphatase, greater weight of resected parathyroid glands, and lower preoperative corrected serum calcium.

Studies are conflicted on whether higher preoperative PTH is an independent predictor of HBS. Symptoms of severe hypocalcemia include perioral paresthesias, tingling in the extremities, carpopedal spasm, severe muscle cramps, and/or positive Chvostek or Trousseau sign. All patients should be educated on these symptoms as they can develop after discharge if home calcium supplementation is insufficient. Treatment involves aggressive repletion with i.v. calcium, along with magnesium and phosphorus as needed. Hypocalcemia may persist for several days to several months, and very rarely for 1 year or more.

In all SHPT patients undergoing PTX, the KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD recommend that the blood level of ionized calcium be measured every 4 to 6 hours for the first 48 to 72 hours after surgery, and then twice daily until stable. Immediately postoperatively, i.v. calcium supplementation should be started to maintain normal levels. When able to take medications orally, KDOQI recommends 1 or 2 g of calcium carbonate 3 times per day (for a total of 1.2 g/day) to be adjusted to maintain normal ionized calcium. However, higher supplementation requirements may occur in clinical practice. One study reported an average daily elemental calcium requirement of 3.2 g during week 1 that downtrended to 2.4 g by week 6, with 0.5 to 1.0 µg/day of calcitriol supplementation. Another study reported a total calcium requirement of 11 g over an average hospital stay of 8 days (1.4 g/day), consistent with the KDOQI recommendation.

Adequate levels of activated vitamin D are essential to maintaining calcium. KDOQI recommends up to 2 µg/day of calcitriol postoperatively, but preoperative loading may also help maintain postoperative calcium levels. In one retrospective study, taking 0.5 µg of calcitriol twice daily for 5 days was associated with a significantly reduced risk of requiring i.v. calcium (given for symptoms, calcium <7.0 mg/dl, or according to surgeon preference). Calcitriol-loaded patients also had a significantly shorter hospital stay, by 2.0 days. Postoperatively, calcitriol administration of up to 4 µg/day significantly mitigated the decline in calcium levels in a small, placebo-controlled trial. It is unknown whether i.v. and oral calcitriol differed in their effectiveness. Finally, high-calcium dialysate can also be considered in patients receiving dialysis to help manage postoperative hypocalcemia.

Although KDOQI guidelines note that patients on phosphate binders preoperatively may need to have their dose reduced or discontinued, the decrease in serum phosphate levels appears to be minimal after PTX.

**Persistent or Recurrent Hyperparathyroidism**

The actual rates of persistent (often defined as within 6 months of surgery) and recurrent (>6 months postsurgery) SHPT are very difficult to estimate as studies used variable cutoffs in defining these conditions. Some studies used cutoffs of 200 to 235 pg/ml and reported failure rates of 21% to 28% whereas others simply used the PTH assay upper limit of normal (65 pg/ml), which may not be realistic. These cutoffs are significantly more conservative than the aforementioned KDIGO guideline that PTH be maintained under 9-fold the upper limit of normal (<585 pg/ml if the upper limit of normal is 65 pg/ml).

Guidelines on the management of persistent or recurrent SHPT are lacking. Some surgeons defer to the same indications used for the original procedure and will consider re-exploration of patients with PTH >800 pg/ml and hypercalcemia and/or hyperphosphatemia unresponsive to drug therapy. KDOQI guidelines recommend imaging with ultrasound, sestamibi, and CT or magnetic resonance imaging to aid in localization of lingering parathyroid tissue before re-exploration. Preoperative localization, if possible, is particularly important in this scenario as the search can be complicated by significant adhesions and scar tissue from the previous operation.

If the only remaining parathyroid tissue is located subcutaneously in the forearm or the neck after tPTX+AT, a simple procedure under local anesthesia may suffice and a second neck exploration may be avoided. The Casanova test is one technique for diagnosing the site of recurrence if tissue was autotransplanted into the forearm. In essence, the grafted arm is briefly occluded and an ensuing significant reduction in PTH suggests hyperfunctioning of the graft. Similarly, comparing PTH levels in the bilateral arm veins was shown to be useful in predicting whether the recurrence was coming from the grafted arm as opposed to tissues in the neck. As one would expect, patients with hyperfunctioning grafted tissue had a significant PTH gradient between the 2 arms, whereas those with persistent or recurrent disease in the neck did not have a significant PTH gradient. In addition, several cases have been published describing successful use of sestamibi to identify hyperfunctioning autotransplanted parathyroid grafts in patients with recurrent SHPT.
Regardless of the initial operation performed, patients may have remnants of previously excised parathyroid glands or previously undiscovered ectopic glands that result in persistent hyperparathyroidism. The second operation may necessitate exploration of the thymus (if still present), thyroid parenchyma, retroesophageal space, carotid sheath, and/or mediastinum. Some centers have reported significantly greater drops in ioPTH during successful reoperations compared with the initial operation, which may help guide re-expansion.81,82

**Short- and Long-term Survival**

The reported 30-day mortality after PTX in SHPT patients, who have an elevated risk of multiple perioperative complications (as previously discussed), ranges from 0.8% to 3.1%, based on observational and US database studies.89–91 Respiratory complications, cardiac complications, and infection are some of the most common issues in the early postoperative period.92 In the longer term, however, PTX seems to have a favorable effect on survival. A systematic review of 13 observational studies showed a 28% decrease in all-cause mortality and a 37% decrease in cardiovascular mortality, with mean follow-up ranging from 1 to 8 years.89–91,93–95

**Open Questions That Exist in the Field**

Open questions on this topic are summarized in Table 2. At this time, there are no universal, evidence-based guidelines on the indications for PTX in SHPT. Randomized, controlled trials in SHPT populations are lacking but will be necessary to establish appropriate biochemical and clinical parameters for surgical referral and to define clinically significant persistence and recurrence of SHPT. Development of universal guidelines would likely need to involve a multidisciplinary effort across all specialties involved in the care of this patient cohort.

Localizing the ectopic and supernumerary glands commonly found in this population on preoperative imaging remains challenging. Although combined SPECT/CT has been and appears to be more sensitive than sestamibi alone or ultrasound in this population, no studies to date have evaluated the newer 4-dimensional CT (4D-CT).32,33,36,37 In PHPT patients, 4D-CT alone had greater sensitivity than when combined with sestamibi (SPECT/CT) in a subgroup analysis of multigland patients specifically.96 However, given the fundamental difference in pathophysiology of PHPT versus SHPT, studies in SHPT patients specifically are needed to determine whether preoperative 4D-CT is beneficial in operative planning.

Intraoperatively, there is the outstanding question of whether near-infrared fluorescence imaging imaging can decrease operating times and rates of persistent disease by aiding in the localization of glands that are grossly difficult to appreciate.64 Finally, further studies are needed to evaluate the long-term safety and efficacy of thermal ablation given its potential to alleviate SHPT in the many patients who are poor surgical candidates.45

**Table 2.** Parathyroidectomy for secondary hyperparathyroidism: outstanding questions

| Question                                                                 |
|-------------------------------------------------------------------------|
| What are the thresholds for serum PTH, calcium, and/or phosphate levels where the benefits outweigh the risks of PTX and the patient should be referred to a surgeon? |
| What is the optimal imaging for localizing ectopic and/or supernumerary glands? |
| Is there an optimal percent decrease in ioPTH level that is predictive of cure and allows the surgeon to avoid further exploration? |
| Does the use of NIRF imaging decrease rates of persistent or recurrent disease by aiding in gland localization? |
| Over long-term follow-up, how do outcomes after thermal and chemical ablation procedures compare to those with parathyroidectomy? |

**ioPTH,** intraoperative parathyroid hormone; **NIRF,** near-infrared immunofluorescence; PTH, parathyroid hormone; **PTX,** parathyroidectomy.

**CONCLUSION**

Herein we have summarized the current evidence to guide the surgical management of SHPT. Despite advances in medical management, a significant number of patients have refractory disease and may benefit from surgical resection, particularly if there is a low likelihood of transplant. Both sPTX and tPTX + AT are effective in treating SHPT, although the surgeon should be aware of the high prevalence of ectopic and supernumerary glands and should perform a thorough neck exploration. Intraoperative PTH monitoring can help guide resection and avoid persistent hyperparathyroidism. In the immediate postoperative period, hypocalcemia is common and close monitoring is critical. There are a number of outstanding questions on this topic, and we have highlighted areas where evidence is lacking and further research is needed.

**DISCLOSURE**

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**REFERENCES**

1. Bureo JC, Arévalo JC, Antón J, Adrados G, Jiménez Morales JL, Robles NR. Prevalence of secondary hyperparathyroidism in patients with stage 3 and 4 chronic kidney disease seen in internal medicine. *Endocrinol Nutr.* 2015;62:300–305.
2. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int*. 2007;71:31–38.

3. Ramos AM, Albalate M, Vázquez S, Caramelo C, Egido J, Ortiz A. Hyperphosphatemia and hyperparathyroidism in incident chronic kidney disease patients. *Kidney Int Suppl*. 2008;(suppl):S88–S93.

4. Dialysis Outcomes Practice Patterns Study (DOPPS) practice monitor. Arbor Research Collective for Health. https://www.dopps.org/DPM. Accessed August 3, 2020.

5. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. *Clin J Am Soc Nephrol*. 2011;6:913–921.

6. van der Plas WY, Noltes ME, van Ginhoven TM, Kruijff S. Secondary and tertiary hyperparathyroidism: a narrative review. *Scand J Surg*. 2019;104:916–929.

7. Block GA, Bushinsky DA, Cunningham J, et al. Effect of etelcalcetide vs placebo on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: two randomized clinical trials. *JAMA*. 2017;317:146–155.

8. Parfrey PS, Chertow GM, Block GA, et al. The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of cinacalcet: the EVOLVE trial. *J Clin Endocrinol Metab*. 2013;98:4834–4844.

9. Gincherman Y, Moloney K, McKee C, Coyne DW. Assessment of adherence to cinacalcet by prescription refill rates in hemodialysis patients. *Hemodial Int*. 2010;14:68–72.

10. Park H, Rascati KL, Lawson KA, Barner JC, Richards KM, Malone DC. Adherence and persistence to prescribed medication among Medicare part D beneficiaries on dialysis: comparisons of benefit type and benefit phase. *J Manag Care Spec Pharm*. 2014;20:862–876.

11. Kim SM, Long J, Montez-Rath ME, Leonard MB, Norton JA, Chertow GM. Rates and outcomes of parathyroidectomy for secondary hyperparathyroidism in the United States. *Clin J Am Soc Nephrol*. 2016;11:1260–1267.

12. Ketteler M, Block GA, Evenepoel P, et al. Diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder: synopsis of the Kidney Disease: Improving Global Outcomes 2017 Clinical Practice Guideline Update. *Ann Intern Med*. 2018;168:422–430.

13. Lau WL, Obi Y, Kalantar-Zadeh K. Parathyroidectomy in the management of secondary hyperparathyroidism. *Clin J Am Soc Nephrol*. 2018;13:952–961.

14. Zhang Y, Lu Y, Feng S, Zhan Z, Shen H. Evaluation of laboratory parameters and symptoms after parathyroidectomy in dialysis patients with secondary hyperparathyroidism. *Renal Fail*. 2019;41:921–929.

15. Konstantinidis I, Nadkarni G, Divino CM, Lapsia V. Utilization of parathyroidectomy for secondary hyperparathyroidism in end-stage renal disease. *Clin Kidney J*. 2013;6:277–282.

16. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(suppl 3):S1–S201.

17. Hercz G, Pei Y, Greenwood C, et al. Aplastic osteodystrophy without aluminum: the role of “suppressed” parathyroid function. *Kidney Int*. 1993;44:860–866.

18. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol*. 2004;15:1943–1951.

19. Tomiyama C, Carvalho AB, Higa A, Jorgetti V, Draibe SA, Canziani ME. Coronary calcification is associated with lower bone formation rate in CKD patients not yet in dialysis treatment. *J Bone Miner Res*. 2010;25:499–504.

20. Danese MD, Kim J, Doan QV, Dylan M, Griffiths R, Chertow GM. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. *Am J Kidney Dis*. 2006;47:149–156.

21. Bleyer AJ, Burkart J, Piazza M, Russell G, Rohr M, Carr JJ. Changes in cardiovascular calcification after parathyroidectomy in patients with ESRD. *Am J Kidney Dis*. 2005;46:464–469.

22. Goldsmith DJ, Covic A, Sambrook PA, Ackrill P. Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. *Nephron*. 1997;77:37–43.

23. Ishimura E, Okuno S, Kitatani K, et al. Significant association between the presence of peripheral vascular calcification and lower serum magnesium in hemodialysis patients. *Clin Nephrol*. 2007;68:222–227.

24. Rudser KD, de Boer IH, Dooley A, Young B, Kestenbaum B. Fracture risk after parathyroidectomy among chronic hemodialysis patients. *J Am Soc Nephrol*. 2007;18:2401–2407.

25. Chou FF, Chen JB, Lee CH, Chen SH, Sheen-Chen SM. Parathyroidectomy can improve bone mineral density in patients with symptomatic secondary hyperparathyroidism. *Arch Surg*. 2001;136:1064–1068.

26. Udomkarnjananun S, Kongnathasate K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, Susantitaphong P. Treatment of calciphylaxis in CKD: a systematic review and meta-analysis. *Kidney Int Rep*. 2019;4:231–244.

27. Brandenburg VM, Kramann R, Rotte H, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. *Nephrol Dial Transplant*. 2017;32:126–132.

28. Chutia H, Ruram AA, Bhattacharyya H, Boruah P, Nath C. Association of secondary hyperparathyroidism with hemoglobin level in patients with chronic kidney disease. *J Lab Physicians*. 2013;5:51–54.

29. Chow TL, Chan TT, Ho YW, Lam SH. Improvement of anemia after parathyroidectomy in Chinese patients with renal failure undergoing long-term dialysis. *Arch Surg*. 2007;142:644–648.

30. Caldarella C, Treglia G, Pontecorvi A, Giordano A. Diagnostic performance of planar scintigraphy using 99mTc-MIBI in patients with secondary hyperparathyroidism: a meta-analysis. *Ann Nucl Med*. 2012;26:794–803.

31. Jones BA, Lindeman B, Chen H. Are Tc-99m-sestamibi scans in patients with secondary hyperparathyroidism and renal failure needed? *J Surg Res*. 2015;243:380–383.

32. Lee JB, Kim WY, Lee YM. The role of preoperative ultrasonography, computed tomography, and sestamibi scintigraphy localization in secondary hyperparathyroidism. *Ann Surg Treat Res*. 2015;89:300–305.

33. Hiramitsu T, Tomosugi T, Okada M, et al. Pre-operative localization of the parathyroid glands in secondary hyperparathyroidism: a retrospective cohort study. *Sci Rep*. 2019;9:14634.
64. Spartalis E, Ntokos G, Georgiou K, et al. Intraoperative indocyanine green (ICG) angiography for the identification of the parathyroid glands: current evidence and future perspectives. In Vivo. 2020;34:23–32.

65. Vidal Fortuny J, Sadowski SM, Belfontai V, Karenovics W, Guigard S, Trippez F. Indocyanine green angiography in subtotal parathyroidectomy: technique for the function of the parathyroid remnant. J Am Coll Surg. 2016;223:e43–e49.

66. Cui L, Gao Y, Yu H, et al. Intraoperative parathyroid localization with near-infrared fluorescence imaging using indocyanine green during total parathyroidectomy for secondary hyperparathyroidism. Sci Rep. 2017;7:8193.

67. Ghani U, Assad S, Assad S. Role of intraoperative nerve monitoring during parathyroidectomy to prevent recurrent laryngeal nerve injury. Cureus. 2018;8, e880.

68. Bai B, Chen W. Protective effects of intraoperative nerve monitoring (IONM) for recurrent laryngeal nerve injury in thyroidectomy: meta-analysis. Sci Rep. 2018;8:7761.

69. Jain N, Reilly RF. Hungry bone syndrome. Curr Opin Nephrol Hypertens. 2017;26:250–255.

70. Florescu MC, Islam KM, Plumb TJ, Smith-Shull S, Nieman J, Mandalapu P. Calcium supplementation after parathyroidectomy in dialysis and renal transplant patients. Int J Nephrol Renovasc Dis. 2014;7:183–190.

71. Goh BL, Yudisthra MG, Hisham AN. Alkaline phosphatase predicts calcium requirements after total parathyroidectomy in patients receiving dialysis. Br J Surg. 2010;97:185–188.

72. Lim CTS, Kalaisevam T, Kitan N, Goh BL. Clinical course after parathyroidectomy in adults with end-stage renal disease on maintenance dialysis. Clin Kidney J. 2018;11:265–269.

73. Wang M, Chen B, Zou X, et al. A nomogram to predict hungry bone syndrome after parathyroidectomy in patients with secondary hyperparathyroidism. J Surg Res. 2020;255:33–41.

74. Ho LY, Wong PN, Sin HK, et al. Risk factors and clinical course of hungry bone syndrome after total parathyroidectomy in dialysis patients with secondary hyperparathyroidism. BMC Nephrol. 2017;18:12.

75. Viana E, Evenepoel P, Bammens B, Claes K, Kuypers D, Vanrenterghem Y. Calcium requirements after parathyroidectomy in patients with refractory secondary hyperparathyroidism. Nephron Clin Pract. 2008;110:c80–c85.

76. Alsafan S, Sherman SK, Dahdaleh FS, et al. Preoperative calcitriol reduces postoperative intravenous calcium requirements and length of stay in parathyroidectomy for renal-organ hyperparathyroidism. Surgery. 2019;165:151–157.

77. Clair F, Leenhardt L, Bourdeau A, et al. Effect of calcitriol in the control of plasma calcium after parathyroidectomy. A placebo-controlled, double-blind study in chronic hemodialysis patients. Nephron. 1987;46:18–22.

78. Agha A, Loss M, Schlitt HJ, Scherer MN. Recurrence of secondary hyperparathyroidism in patients after total parathyroidectomy with autotransplantation: technical and therapeutic aspects. Eur Arch Otorhinolaryngol. 2012;269:1519–1525.

79. Kievit AJ, Tinnemans JG, Idu MM, Groothoff JW, Surachno S, Aronson DC. Outcome of total parathyroidectomy and autotransplantation as treatment of secondary and tertiary hyperparathyroidism in children and adults. World J Surg. 2010;34:993–1000.

80. Steffen L, Moffa G, Müller PC, Oertli D. Secondary hyperparathyroidism: recurrence after total parathyroidectomy with autotransplantation. Swiss Med Wkly. 2019;149:w20160.

81. Zhu L, Cheng F, Zhu X, et al. Safety and effectiveness of reoperation for persistent or recurrent drug refractory secondary hyperparathyroidism. Gland Surg. 2020;9:401–408.

82. Neyer U, Hoerandner H, Haid A, Zimmermann G, Niederle B. Total parathyroidectomy with autotransplantation in renal hyperparathyroidism: low recurrence after intra-operative tissue selection. Nephrol Dial Transplant. 2002;17:625–629.

83. Casanova D, Sarfati E, De Francisco A, Amado JA, Arias M, Dubost C. Secondary hyperparathyroidism: diagnosis of site of recurrence. World J Surg. 1991;15:546–549 [discussion 549–550].

84. Chou FF, Lee CH, Chen HY, Chen JB, Hsu KT, Sheen-Chen SM. Persistent and recurrent hyperparathyroidism after total parathyroidectomy with autotransplantation. Ann Surg. 2002;235:99–104.

85. Lightowler C, Carroll MJ, Chesser AM, et al. Identification of autotransplanted parathyroid tissue by Tc-99m methoxy isobutyl isonitrile scintigraphy. Nephrol Dial Transplant. 1995;10:1372–1375.

86. Ohta H, Komibuchi T, Nishimura M, et al. 99mTc-MIBI accumulation in the parathyroid autograft in a patient with recurrent hyperparathyroidism. Ann Nucl Med. 1996;10:247–249.

87. Ardito G, Revelli L, Giustozzi E, Giordano A. Radioguided parathyroidectomy in forearm graft for recurrent hyperparathyroidism. Br J Radiol. 2012;85:e1–e3.

88. Thelen MH, Kuwert T, Lerch H, Witting C, Winterberg B, Schober O. Double-phase Tc-99m MIBI scintigraphy in secondary hyperparathyroidism relapsing after parathyroidectomy and removal of a parathyroid autograft. Clin Nucl Med. 1996;21:609–611.

89. Sharma J, Raggi P, Kutner N, et al. Improved long-term survival of dialysis patients after near-total parathyroidectomy. J Am Coll Surg. 2012;214:400–407 [discussion 407–408].

90. Ma TL, Hung PH, Jong IC, et al. Parathyroidectomy is associated with reduced mortality in hemodialysis patients with secondary hyperparathyroidism. Biomed Res Int. 2015;2015:639587.

91. Kestenbaum B, Andress DL, Schwartz SM, et al. Survival following parathyroidectomy among United States dialysis patients. Kidney Int. 2004;66:2010–2016.

92. Tang JA, Salapatas AM, Bonzelar LB, Friedman M. Parathyroidectomy for the treatment of hyperparathyroidism: thirty-day morbidity and mortality. Laryngoscope. 2018;128:528–533.

93. Goldenstein PT, Elias RM, Pires de Freitas do Carmo L, et al. Parathyroidectomy improves survival in patients with severe hyperparathyroidism: a comparative study. PLoS One. 2013;8, e68870.

94. Ivarsson KM, Akaberi S, Isaksson E, et al. The effect of parathyroidectomy on patient survival in secondary hyperparathyroidism. Nephrol Dial Transplant. 2015;30:2027–2033.

95. Komaba H, Taniguchi M, Wada A, Iseki K, Tsubakihara Y, Yokota T. 99mTc-sestamibi scintigraphy for the localization of postoperative parathyroid remnants. Ann Nucl Med. 1997;11:205–209.

96. 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;291:469–476.