International Journal of Community Medicine and Public Health
Almottowa HA et al. Int J Community Med Public Health. 2024 Dec;11(12):4984-4989
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20243413

Review Article

The role of surgery in managing recurrent hyperparathyroidism

Hisham Abdullah Almottowa[1]*, Manal Hussein Aldaihani[2], Ali Mohammad Alkandari[3], Mohammad Mahroos Alghabban[4], Abdullatif Hassan Aljabr[5], Monirah Khaled Alotaibi[5], Madhawi Fahad Alduosari[6], Abdulmajeed Muslih Alamri[4], Bader Hussain Almogheer[7], Danah Mohammad Alrasheedi[8]

[1]Department of General Surgery, King Fahad General Hospital, Jeddah, Saudi Arabia
[2]Kuwait Institute for Medical Specialization, Kuwait City, Kuwait
[3]Department of General Surgery, Al Sabah Hospital, Kuwait City, Kuwait
[4]Department of General Surgery, King Fahad General Hospital, Medina, Saudi Arabia
[5]College of Medicine, Arabian Gulf University, Manama, Bahrain
[6]Department of Otolaryngology, Ministry of Health, Saad Alabdullah, Kuwait
[7]Department of General Surgery, King Abdulaziz Hospital, Al Ahsa, Saudi Arabia
[8]Department of Family Medicine, Farwaniya Hospital, Farwaniya, Kuwait

Received: 12 October 2024
Accepted: 28 October 2024

***Correspondence:**
Dr. Hisham Abdullah Almottowa,
E-mail: hishamalmottowa@gmail.com

ABSTRACT

Recurrent hyperparathyroidism (RHPT) presents a complex surgical challenge after initial treatment for primary hyperparathyroidism (PHPT). Characterized by hypercalcemia following a previously successful parathyroidectomy, RHPT requires accurate diagnosis and careful management to avoid complications. Preoperative imaging advancements and intraoperative parathyroid hormone (PTH) monitoring have reduced recurrence rates from 30% to 2.5%-5%, though they can be as high as 14% in some cases. Persistent hyperparathormonemia, multigland disease (MGD), and conditions such as parathyroid carcinoma contribute to recurrence. Factors such as age, imaging results, and PTH levels influence recurrence risk, with studies identifying older age and double adenomas as predictors. Surgical reintervention carries significant risks, including recurrent laryngeal nerve (RLN) palsy and permanent hypocalcemia. Monitoring biochemical markers over time, including calcium and PTH levels, remains essential. This review explores the causes of RHPT, surgical management strategies, and factors predicting recurrence, with a focus on individualized patient care and minimizing surgical risks. Successful management requires a balance between reoperation necessity and potential complications.

Keywords: RHPT, Parathyroidectomy, MGD, Surgical management, Reoperation

INTRODUCTION

Hyperparathyroidism (HPT) is characterized by elevated levels of parathyroid hormone (PTH) in the bloodstream, either due to a disorder within the parathyroid glands which called primary hyperparathyroidism (PHPT) or in response to external factors which called secondary hyperparathyroidism (SHPT). The symptoms arise from elevated or persistently normal calcium levels in the blood, which are released from the bones as a result of excessive PTH production. In healthy individuals, elevated blood calcium typically suppresses PTH secretion.[1] Chronic hyperparathyroidism often leads to kidney stones as the most common symptom, along with bone pain, weakness, depression, confusion, and

increased urination. Both primary and SHPT can also lead to osteoporosis, weakening the bones.[2]

PHPT is the third most common endocrine disorder.[3] It occurs sporadically in 90%-95% of cases and is hereditary in 5%-10%, often linked to multiple endocrine neoplasia (MEN) syndromes. The primary causes of PHPT include single parathyroid adenoma (80%-85%), double adenomas (4%-5%), diffuse hyperplasia (10%-15%), and parathyroid carcinoma (<1%).[4] Successful management is defined as a return to normal calcium levels lasting for at least six months, with current cure rates ranging from 95% to 99%.[3] However, normocalcemia occurs before the initial surgery in 10% of PHPT cases, and patients with normal calcium but elevated PTH post-parathyroidectomy should be evaluated for secondary HPT or recurrence.[5]

Recurrent PHPT (R-PHPT) is characterized by hypercalcemia that reappears after at least six months of normal calcium levels following a successful surgery for PHPT.[6] R-PHPT tends to manifest more than six months later in most cases. Prior to considering a reoperation, the surgeon must confirm PHPT diagnosis. Once persistence or recurrence is verified, appropriate management should be discussed with the patient, taking into account the surgical risks of reoperation-such as permanent hypocalcemia and RLN palsy)-against the potential benefits. A single adenoma is identified in 68% of cases, multiglandular disease in 28%, and parathyroid carcinoma in 3%, while other causes, including parathyromatosis and graft recurrence, account for less than 1%.[7] The cure rate for R-PHPT at expert centers is estimated to be between 93% and 97%.[8] Patients with MEN syndromes are at a higher risk of recurrence and should receive management tailored to their hereditary condition.

In 1990, the incidence of RHPT was approximately 30%. With improvements in preoperative imaging, intraoperative PTH monitoring (IPM), and reduced use of bilateral neck exploration (BNE), the current incidence has decreased to 2.5%-5%,[8] though some recent reports suggest rates as high as 10% or even 14%.[9] Early postoperative transient hypercalcemia does not necessarily predict persistent PHPT (P-PHPT), as it occurs in nearly 10% of cases after successful parathyroidectomy and typically resolves within two weeks.[10]

METHODS

This study is based on a comprehensive literature search conducted on October 1, 2024, in the Medline and Cochrane databases, utilizing the medical subjects heading (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the role of surgery in managing RHPT. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

Diagnosing PHPT requires careful evaluation of total calcium and PTH levels, ruling out other conditions like vitamin D deficiency, renal dysfunction, and benign familial hypocalciuric hypercalcemia (BFHH). Misdiagnosis contributes to 2-10% of surgical failures. Differential diagnoses such as SHPT due to renal failure or vitamin D deficiency must be excluded before reoperation for recurrent PHPT.[8]

Diagnosis of recurrence

Once PHPT has been confirmed, distinguishing between persistent P-PHPT and persistent hyperparathormonemia, where calcium levels are typically normal or low, is essential. Wang et al noted that 15% of patients undergoing surgery for PHPT experienced elevated PTH levels postoperatively, with 66% of these patients showing normocalcemia.[11] While elevated PTH can be an early indicator of P-PHPT, it may also result from adaptive responses such as vitamin D deficiency or renal failure.

Vitamin D deficiency contributes to 4.7% of suspected recurrent or P-PHPT cases, necessitating its systematic investigation. Renal failure also plays a role in postoperative hyperparathormonemia, as confirmed in studies.[12] Elevated PTH levels post-surgery may also be linked to bone remineralization, often seen in hungry bone syndrome, which can overstimulate residual parathyroid tissue. Nonetheless, persistent hyperparathormonemia might still be an early sign of R-PHPT. Estimating how many patients with persistent hyperparathormonemia will eventually develop hyperparathyroidism or determining the appropriate follow-up duration remains challenging.

In the absence of an identified adaptive cause, patients should be monitored over several months or years, with periodic assessments of calcium, PTH, vitamin D, creatinine, and calciuria levels. Although no consensus exists for monitoring, annual checks of calcium and PTH are commonly recommended.[8]

Additionally, PPHPT or RPHPT must be differentiated from BFHH. In 1980, Marx et al found that at least 9% of patients referred after failed parathyroidectomy had BFHH.[13] In BFHH, calcium levels rarely exceed 2.7 mmol/L, making surgery unnecessary. Genetic testing of calcium-sensing receptor gene (CASR), adaptor-related protein complex 2, sigma 1 subunit gene (AP2S1), and G protein subunit alpha 11 gene (GNA11) genes is advised, especially when the urinary calcium-to-creatinine

clearance ratio (UCCR) falls between 0.01 and 0.02, to differentiate BFHH from PHPT.

Causes of RHPT

RHPT can arise from various underlying causes, often complicating the management of PHPT after initial surgery. Key factors contributing to recurrence include MGD, parathyroid carcinoma, and rare conditions such as parathyromatosis. Recognizing these causes is essential for improving diagnostic accuracy and guiding appropriate surgical or medical interventions in RHPT cases (Table 1).[14]

Table 1: The most common causes of RHPT, highlighting their characteristics and recurrence patterns.[14]

Cause	Description	Recurrence rate
MGD	Common cause due to hereditary multigland hyperplasia; recurs post-surgery from residual or grafted hyperplasia.	Similar recurrence to single gland disease.
Double adenoma	Distinct from MGD; recurrence may suggest asymmetric hyperplasia.	7.3% (higher than MGD: 4.4%).
Parathyroid carcinoma	Recurs in 50% of patients, often locoregional; higher with metastases.	50%, with metastases.
Parathyromatosis	Rare, caused by parathyroid tissue implantation post-surgery.	Extremely rare.

Predictive factors for persistent hyperparathyroidism and RHPT

Several studies have assessed demographic, clinical, radiological, and biochemical factors to predict the persistence and recurrence of HPT. Shirali et al. found that age over 66.5 years, calcium levels of 9.8 mg/dL, and PTH levels of 80 pg/mL at 6 months were independent factors associated with increased recurrence risk. For patients undergoing minimally invasive parathyroidectomy (MIP), at least one preoperative imaging result that was inconsistent with intraoperative findings was linked to a higher recurrence risk (HR 4.93, 95% CI 1.25-16.53, p=0.016).[15] Additionally, an increase in PTH with normocalcemia at 6 months was an independent risk factor for late recurrence.[16] Conversely, another study found that advanced age was a protective factor against recurrence (HR 0.97, 95% CI 0.940.99, p=0.034), while an intraoperative PTH drop greater than 70% (HR 0.45, 95% CI 0.20-0.98, p=0.046) was a protective factor for recurrence. Double adenoma was again identified as an independent risk factor for recurrence (HR 3.52, 95% CI 1.23-10.08, p=0.019).[17]

Similarly, a greater decrease in intraoperative PTH was protective against recurrence (HR=0.96, 95% CI=0.93-0.99, p=0.03), and a higher PTH value at 1-2 weeks postoperatively was significantly associated with recurrence (HR=1.03, 95% CI=1.02-0.05, p<0.01).[18] In a recent study, while the lowest intraoperative PTH level was a weak predictor of recurrence, the early biochemical response was determined to be the strongest predictor. Compared to patients with complete early postoperative response (within 2 weeks), those with an early partial response, characterized by increased PTH and calcium levels, had a 2.727-fold increased recurrence risk (95% CI 1.490-4.991, p<0.02), while those with increased PTH and normal calcium levels had a 4.297-fold increased risk (95% CI 2.570-7.186, p<0.02).[19] According to Lim et al normocalcemic HPT and a family history were significant predictive factors for MGD, which is a key factor in persistent and recurrent disease.[20]

Surgical approaches and risks in RHPT

Successful parathyroid surgery requires the surgeon to accurately identify the parathyroid glands, possess in-depth knowledge of their anatomical location and variations, and differentiate between normal and abnormal glands. In 85% of cases, the superior parathyroids are found within 1 cm of the thyroid's inferior angle, while the inferior parathyroids are typically located in the lower third of the junction between the posterior thyroid and anterior thymus in over 50% of cases, though they may also be found in the mediastinum or within the thyroid parenchyma.[5] The six recognized types of parathyroid anatomical locations are listed (Table 2).[5]

Table 2: Types of parathyroid anatomical locations.[5]

Type	Location
A1	Attached to the thyroid capsule
A2	Partially or completely embedded in the thyroid gland but outside the capsule
A3	Within the thyroid parenchyma
B1	Peripheral, with a natural gap space between the parathyroid and thyroid gland
B2	Within the thymus gland
B3	Blood supply from thymic or mediastinal vessels

Once a diagnosis is established, the surgeon must weigh the benefits and risks of reoperation. Not every patient requires reoperation, and mild asymptomatic hypercalcemia may be preferable to permanent hypocalcemia or RLN palsy. Early reoperation (within 24-72 hours) is possible if the adenoma was missed during the initial surgery. In these cases, new imaging should be performed immediately, and the location must be unequivocally identified. Early surgery is usually considered when preoperative imaging was of low quality and can be repeated at a specialized center, such as through methoxyisobutylisonitrile (MIBI) subtraction scanning. However, early reoperation for R-PHPT is often unnecessary, as it is crucial to reassess patient history, confirm the diagnosis, and perform new localization studies. Additionally, reoperation within weeks of primary surgery carries a higher risk of morbidity due to inflammatory scarring, so reoperations are generally delayed by 4-6 months.[21]

Morbidity of redo surgery

Before introduction of MIP, reoperation for R-PHPT carried a higher risk of permanent hypoparathyroidism (>10%) and RLN palsy (5 times more likely than in primary surgery).[22] Although redo surgery has become safer, the risks remain significant. Transient RLN palsy occurs in 11% of cases, with permanent RLN palsy reported in 6-9% of cases. This increased risk necessitates precise preop vocal cord assessment, and intraoperative nerve monitoring may be beneficial. Postop hypocalcemia is common (81% of cases), and permanent hypocalcemia occurs in 3-13% of cases. Other complications, such as wound infections/bleeding, are rare.[8]

Surgical approach and use of intraoperative PTH

The surgical approach depends on imaging results and suspected parathyroid disease. In cases of MGD, a revision cervicotomy with BNE is recommended. For single adenomas, a focused approach can be considered. En-bloc resection is crucial in cases of parathyromatosis, recurrent parathyroid carcinoma, intrathyroid adenoma, or graft recurrence. If imaging results are negative, the surgeon must carefully evaluate the benefits of reoperation. Mediastinal exploration using thoracic access is generally too invasive. Studies have demonstrated that intraoperative PTH (IOPTH) monitoring accurately predicts cure in 97-100% of reoperation cases and failure in 78%.[23,24] Therefore, IOPTH is highly recommended for P-PHPT and R-PHPT reoperations.[21]

Revision of cervicotomy and BNE

Revision cervicotomy and BNE is a technically demanding procedure requiring an experienced surgeon with extensive knowledge of anatomy and parathyroid embryology. It is the standard reoperation in cases of suspected MGD. The surgeon must review previous surgery and pathology reports to identify which parathyroid glands have been removed. Localization studies are useful but are often negative in MGD.[8] All parathyroid tissue must be located, including intrathymic parathyroids. Due to postoperative fibrosis, infra-hyoid muscles may fuse with the underlying thyroid and trachea, necessitating a lateral approach. Revision surgery carries a high risk of postoperative hypoparathyroidism, and autotransplantation of parathyroid tissue should be discussed preoperatively. The use of IOPTH has been suggested to guide decisions on autotransplantation with a PTH reduction cutoff of 84%.[23] However, the transplantation of hyperfunctional tissue may lead to recurrent disease in 7-17% of cases, and graft failure occurs in 6-50% of transplanted tissue. Immediate autotransplantation is generally avoided unless necessary, such as when three normal glands have been excised or when cryopreservation is unavailable.[21]

Focused approach

The most common cause of failed primary parathyroid surgery is a missed single adenoma.[8] With advances in imaging, most reoperations can now be performed using a unilateral or focused approach, reducing the risk of permanent RLN palsy and hypoparathyroidism. MIP has been shown to be superior to BNE. In a retrospective study, Nawrot et al reported a 94% cure rate with a focused approach in 66.3% of cases.[7] A cervical-focused approach is recommended when two concordant imaging modalities confirm a single adenoma missed during the primary surgery or a recurrence due to a single adenoma or MGD on a parathyroid stump. The initial incision is reused, and a lateral or thyrothymic approach is preferred to avoid dissection near the thyroid or trachea. For mediastinal adenomas (1-2% of cases), video-assisted thoracoscopy is indicated, as these adenomas are often inaccessible via cervicotomy.[21] The use of IOPTH and nerve monitoring is strongly recommended.

En-bloc resection

In cases of parathyromatosis, all remaining parathyroid tissue must be excised, though cure is difficult. Separating the RLN from parathyroid tissue can be challenging, and the patient must be informed of the high risk of RLN palsy.[25] For parathyroid carcinoma, en-bloc resection (thyroid lobectomy with central lymph node resection) is the treatment of choice, but it is often performed as a delayed procedure to prevent recurrence. Parathyroid carcinoma recurs in about 50% of cases. While some studies suggest no benefit to extensive resection,[26] it is still recommended to remove all affected tissues en-bloc. Graft recurrence after autotransplantation is possible in SHPT, and reoperations on grafts are complex due to tissue embedding in muscle. Intrathyroid adenomas (0.5-3.5% of cases) may require en-bloc lobectomy resection, but in most cases, they can be removed without lobectomy.[27] Prophylactic lobectomy is not recommended if the adenoma is not found.[21]

CONCLUSION

Surgical management of RHPT requires careful evaluation, including accurate preoperative imaging and risk assessment. Understanding recurrence predictors and surgical risks, such as nerve damage and hypocalcemia, is essential. Surgeons must balance the necessity of reoperation with potential complications, employing individualized treatment strategies to optimize outcomes and reduce the likelihood of recurrence.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Fraser WD. Hyperparathyroidism. Lancet (London, England). 2009;374(9684):145-58.
2. Michels TC, Kelly KM. Parathyroid disorders. American family physician. 2013;88(4):249-57.
3. Olguín Joseau S, Arias A, Garzón A, Peretti E, Guzmán L, Ruggieri M. Risk factors for surgical failure in patients undergoing surgery for primary hyperparathyroidism. Cirugia espanola. 2022;100(9):569-72.
4. Aygün N, Uludağ M. Surgical Treatment of Primary Hyperparathyroidism: Which Therapy to Whom? Sisli Etfal Hastanesi tip bulteni. 2019;53(3):201-4.
5. Pavlidis ET, Pavlidis TE. Update on the current management of persistent and recurrent primary hyperparathyroidism after parathyroidectomy. World J Clin Cases. 2023;11(10):2213-5.
6. Udelsman R. Approach to the patient with persistent or recurrent primary hyperparathyroidism. J Clin Endocrinol Metabol. 2011;96(10):2950-8.
7. Nawrot I, Chudziński W, Ciąćka T, Barczyński M, Szmidt J. Reoperations for persistent or recurrent primary hyperparathyroidism: results of a retrospective cohort study at a tertiary referral center. Med Sci Monitor. 2014;20:1604.
8. Guerin C, Paladino NC, Lowery A, Castinetti F, Taieb D, Sebag F. Persistent and recurrent hyperparathyroidism. Updates Surg. 2017;69(2):161-9.
9. Szabo Yamashita T, Mirande M, Huang CT, Ann K, Ria F-F, Ravinder S, et al. Persistence and Recurrence of Hypercalcemia After Parathyroidectomy Over 5 Decades (1965-2010) in a Community-based Cohort. Ann Surg. 2023;278(2):e309-13.
10. Lai V, Yen TW, Doffek K, Azadeh AC, Ty BC, Gilbert GF, et al. Delayed Calcium Normalization After Presumed Curative Parathyroidectomy is Not Associated with the Development of Persistent or Recurrent Primary Hyperparathyroidism. Ann Surg Oncol. 2016;23(7):2310-4.
11. Wang TS, Ostrower ST, Heller KS. Persistently elevated parathyroid hormone levels after parathyroid surgery. Surgery. 2005;138(6):1130-6.
12. Denizot A, Pucini M, Chagnaud C, Botti G, Henry J-F. Normocalcemia with elevated parathyroid hormone levels after surgical treatment of primary hyperparathyroidism. The American journal of surgery. 2001;182(1):15-9.
13. Marx SJ, Stock JL, Attie MF, Downs Jr RW, Gardner DG, Brown EM, et al. Familial hypocalciuric hypercalcemia: recognition among patients referred after unsuccessful parathyroid exploration. Ann Internal Med. 1980;92(3):351-6.
14. Uludag M, Unlu MT, Kostek M, Caliskan O, Aygun N, Isgor A. Persistent and Recurrent Primary Hyperparathyroidism: Etiological Factors and Pre-Operative Evaluation. Sisli Etf al Hastanesi tip bulteni. 2023;57(1):1-17.
15. Shirali AS, Wu S-Y, Chiang Y-J. Recurrence after successful parathyroidectomy-Who should we worry about? Surgery. 2022;171(1):40-6.
16. Mallick R, Nicholson KJ, Yip L, Carty SE, McCoy KL. Factors associated with late recurrence after parathyroidectomy for primary hyperparathyroidism. Surgery. 2020;167(1):160-5.
17. 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.
18. Schneider DF, Mazeh H, Chen H, Sippel RS. Predictors of recurrence in primary hyperparathyroidism: an analysis of 1386 cases. Ann Surg. 2014;259(3):563-8.
19. Ryder CY, Jarocki A, McNeely MM. Early biochemical response to parathyroidectomy for primary hyperparathyroidism and its predictive value for recurrent hypercalcemia and recurrent primary hyperparathyroidism. Surgery. 2021;169(1):120-5.
20. Lim JY, Herman MC, Bubis L. Differences in single gland and multigland disease are seen in low biochemical profile primary hyperparathyroidism. Surgery. 2017;161(1):70-7.
21. Henry J-F. Reoperation for primary hyperparathyroidism: tips and tricks. Langenbeck's Arch Surg. 2010;395:103-9.
22. Grant CS, Thompson G, Farley D, van Heerden J. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. Arch Surg. 2005;140(5):472-8.
23. Richards ML, Thompson GB, Farley DR, Grant CS. Reoperative parathyroidectomy in 228 patients during the era of minimal-access surgery and intraoperative parathyroid hormone monitoring. Am J Surg. 2008;196(6):937-42.
24. Yen TW, Wang TS, Doffek KM, Krzywda EA, Wilson SD. Reoperative parathyroidectomy: an algorithm for imaging and monitoring of intraoperative parathyroid hormone levels that results

in a successful focused approach. Surgery. 2008;144(4):611-9.
25. Jain M, Krasne DL, Singer FR, Giuliano AE. Recurrent primary hyperparathyroidism due to Type 1 parathyromatosis. Endocrine. 2017;55(2):643-50.
26. Young S, Wu JX, Li N, Yeh MW, Livhits MJ. More extensive surgery may not improve survival over parathyroidectomy alone in parathyroid carcinoma. Ann Surgical Oncol. 2016;23:2898-904.
27. Wheeler MH, Williams ED, Wade JS. The hyperfunctioning intrathyroidal parathyroid gland: a potential pitfall in parathyroid surgery. World J Surg. 1987;11(1):110-4.

Cite this article as: Almottowa HA, Aldaihani MH, Alkandari AM, Alghabban MM, Aljabr AH, Alotaibi MK, et al. The role of surgery in managing recurrent hyperparathyroidism. Int J Community Med Public Health 2024;11:4984-9.