

Exploring surgical failures in primary hyperparathyroidism

Échec de la chirurgie dans l'hyperparathyroïdie primaire

Azza Mediouni, Maamoun Kriaa, Maha Mejbri, Rihab Lahmer, Maissa Lajhouri, Houda Chahed

University of Tunis el Manar, Faculty of Medicine of Tunis, postal code 1007, La Rabta Hospital, ENT department, Tunis, Tunisia.

ABSTRACT

Introduction: Parathyroidectomy is considered the most cost-effective treatment for primary hyperparathyroidism (PHPT), with a relatively low incidence of complications. Nonetheless, 5-10% of patients do not achieve cure after initial parathyroidectomy. We hereby report our experience to determine the causes of our uncured patients and explore factors that could be associated with failure.

Methods: We conducted a retrospective case series study and reviewed all the patients who underwent surgery for PHPT from 2004 to 2020. Cure was defined as re-establishment of normal calcium homeostasis lasting a minimum of 6 months. Persistent PHPT (perPHPT) was defined as ongoing hypercalcemia at any time within the 6 months after surgery.

Results: The overall failure-to-cure rate was 6%. Of the 165 patients, 155 underwent successful surgical treatment of PHPT at the initial operation and perPHPT occurred in 10 patients. Baseline factors including age, sex, preoperative laboratory values, imaging, and surgical approach did not differ significantly between cured and non-cured groups. The sensitivity of intraoperative PTH measurement (iOPHT) as an indicator of operative success was 88,5%. Of the 10 patients with perPHPT, multi-gland disease (MGD) was present in 7 and ectopic adenoma in one. The lack of iOPHT use contributed to failure in 2 cases.

Conclusion: Our study underscores the critical role of MGD as a significant cause of perPHPT. Other etiologies may include ectopic glands or technical problems during surgery. The use of iOPHT is crucial in reducing the incidence of perPHPT and should be a routine practice.

Key words: Primary hyperparathyroidism, Parathyroid hormone, Parathyroid Glands, Parathyroidectomy, Treatment Failure.

RÉSUMÉ

Introduction : La parathyroïdectomie est le traitement de référence de l'hyperparathyroïdie primaire (HPTP), avec un taux de complications relativement faible. Néanmoins, 5 à 10 % des patients présentent une persistance de la maladie après chirurgie. Notre objectif est de déterminer les causes d'échec thérapeutiques de nos patients et d'étudier les facteurs associés à cet échec.

Méthodes : Nous avons mené une étude rétrospective des cas de HPTP opérés entre 2004 et 2020. La guérison a été définie comme le rétablissement d'une calcémie normale durant au moins 6 mois. L'HPTP persistante (HPTPper) a été définie comme la persistance d'une hypercalcémie au cours des 6 mois après la chirurgie.

Résultats : Le taux global d'échec était de 6 %. Sur les 165 patients, 155 ont bénéficié d'un traitement chirurgical réussi, et une HPTPper est survenue chez 10 patients. Les facteurs étudiés tels que l'âge, le sexe, la biologie, l'imagerie et la technique chirurgicale étaient similaires entre les deux groupes. La sensibilité du dosage peropératoire de la PTH (iOPHT) était de 88,5 %. Les causes d'échec étaient une pathologie multiglandulaire dans 7 cas, et un adénome ectopique dans un cas. Le non-recours à la iOPHT a contribué à l'échec dans 2 cas.

Conclusion : Notre étude souligne le rôle majeur de la pathologie multiglandulaire dans l'échec thérapeutique des HPTP. Les autres étiologies peuvent inclure l'ectopie glandulaire ou des difficultés opératoires. L'utilisation de l'iOPHT est cruciale pour réduire le taux de HPTPper et devrait être une pratique courante.

Mots-clés : Hyperparathyroïdie primaire, Hormone parathyroïdienne, Glandes parathyroïdes, Parathyroïdectomie, Echec thérapeutique.

Correspondance

Maamoun Kriaa

University of Tunis el Manar, Faculty of Medicine of Tunis, postal code 1007, La Rabta Hospital, ENT department, Tunis, Tunisia.

Email: Maamoun.kriaa@gmail.com

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder, and the most common cause of hypercalcemia, with a prevalence of 0.1% to 1% of adults in the general population (1).

Parathyroidectomy (PTx) is considered the most cost-effective treatment for PHPT, with a relatively low incidence of complications. Nonetheless, 5-10% of patients do not achieve a long-term cure after initial parathyroidectomy (2). Causes of persistent PHPT (perPHPT) include failure to localize a pathologic gland during the first surgery or incomplete resection due to the presence of multi-glandular disease (MGD) (3).

The purpose of this study is to investigate surgery failure in our experience, explore uncured patients' characteristics, and review relevant literature.

METHODS

We performed a retrospective study of patients who underwent initial PTx between 2004 and 2020. Patients with secondary, or tertiary hyperparathyroidism were excluded, as well as those who had prior parathyroid surgeries, and those with post-operative follow-up of less than 6 months.

The information gathered covered demographics, preoperative and postoperative laboratory values (ionized calcium, parathyroid hormone (PTH), 25-OH vitamin D, alkaline phosphatase...), preoperative imaging results, intraoperative findings, intraoperative PTH (iOPTh) values, the extent of surgery, the final pathology, and long-term results.

The normal ranges of Ca and PTH were defined as 85–104 mg/L and 15–65 ng/L, respectively.

Preoperative imaging consisted of neck ultrasonography (US) and a Technetium (99m Tc) sestamibi scintigraphy (MIBI). We considered MIBI and US concordant if they both localized the adenoma on the same side of the neck. In addition, a CT scan was performed when the lesions were difficult to locate.

The use of intraoperative tools (frozen section and iOPTh) was variable and left to the treating surgeon's judgment (considering that iOPTh monitoring has been introduced in our department since 2012). Frozen section was used to confirm the nature of the excised tissue. To monitor PTH intraoperatively, two serum samples were collected. These were taken from a venous line 10 min after the induction of general anesthesia and positioning of the patient (baseline), and 10 minutes after the removal of the abnormal parathyroid tissue. According to the established Vienna criteria, intraoperative success was defined as a decay of greater than or equal to 50% from baseline (4).

The surgical strategy was divided into two categories: unilateral (UNE) and bilateral neck exploration (BNE). In the preoperative evaluation, if the pathologic gland was localized, unilateral PTx was performed; otherwise, bilateral exploration was performed. Three or three and a half gland excision was undertaken when parathyroid

hyperplasia was clinically diagnosed at operation.

The final diagnosis incorporated both histopathologic and iOPTh criteria: Single adenoma (SA) was defined as one histologically abnormal gland with a corresponding decrease in iOPTh after excision. Double adenoma (DA) refers to the presence of two glands that exhibit histological abnormalities with an appropriate iOPTh decrease after excision. Four-gland hyperplasia (HP) was defined as four histologically abnormal glands.

Post-operative PTH levels and serum calcium levels were measured on postoperative day one and at the first outpatient follow-up appointment, which typically occurred one month after surgery.

Long-term follow-up consisted of ionized calcium, PTH, and vitamin D levels obtained at 3, 6, and 12 months, and then annually.

Cure was defined as re-establishment of normal calcium homeostasis lasting a minimum of 6 months. PerPHPT was defined as ongoing hypercalcemia at any time within the 6 months after surgery. Records of patients not cured by initial surgery were reviewed to explore factors underlying failure to cure.

RESULTS

We included a total of 165 initial PTx. The mean age was 56 years [27-78] and 148 patients (89,7 %) were female. The incidence of family history of hyperparathyroidism or personal history of multiple endocrine neoplasia (MEN) was low: 2 patients.

On biochemical evaluation, the mean preoperative serum calcium was 118.36 mg/L (90-217 mg/L), and the mean preoperative PTH was 574,27 pg/mL (90-8890 pg/ml). Ten patients (6%) had normocalcemic PHPT.

All but one patient had US and MIBI. One or more enlarged glands were identified in 115 patients (70%) for US and 138 patients for MIBI (84%). Eighty-five patients (51,8 %) had lateralized and concordant imaging.

After comparing surgery, histopathological and biochemical data, the results were as follows: 90,3 % of patients (n=149) presented with a SA, 3,6 % had DA (n=6), and 4,8 % (n=8) had HP. Two patients (1,2 %) had parathyroid carcinoma (PC). The median biochemical follow-up time was 13,8 months [6-96].

The overall failure-to-cure rate was 6%. Of the 165 patients, 155 (94 %) underwent successful surgical treatment of PHPT at the initial operation. PerPHPT occurred in 10 patients. After re-exploring and treating most of these patients, the failure rate has been reduced to 2,4 % (2 patients).

Baseline factors including age, sex, preoperative laboratory values, and imaging did not differ significantly between cured and non-cured groups. In addition, the surgical approach did not impact the rate of perPHPT (Table 1).

Table 1. Demographics and clinical details of patients according to surgery outcome

	Cured (n=155)	Uncured (n=10)	P value
Age mean (SD)	55,81 (11,075)	55,88 (14,106)	p = 0,988
Gender female n (%)	138 (89)	10 (100)	p = 0,5
Calcium mg/l, mean (SD)	118,72 (17,048)	109,88 (7,338)	p = 0,15
PTH ng/L, mean (SD)	610,19 (1087,389)	312,88 (179,469)	p = 0,44
Alkaline phosphatase IU/L, mean (SD)	201,30 (176,801)	110,25 (39,542)	p = 0,31
Creatinine mg/l, mean (SD)	7,56 (2,412)	7,88 (1,356)	p = 0,71
Vitamin D (after correction) ng/ml, mean (SD)	31,82 (22,69)	39 (9)	p = 0,45
Localized PTH US (=115), n (%)	108 (94)	7 (6)	p = 0,27
Localized PTH MIBI (=138), n (%)	132 (96)	6 (4)	p = 0,055
Concordant/lateralized imaging (=85), n (%)	82 (96.5)	3 (3.5)	p = 0,41
Bilateral exploration, n (%)	36 (23.2)	5 (50)	p = 0,26
iOPHTH decrease, mean %	72.1	32	p < 0,001*

iOPHTH, Intraoperative Parathyroid Hormone; MIBI, Scintigraphy; PTH, Parathyroid Hormone; SD, Standard Deviation; US, Ultrasound.

iOPHTH was documented for 62.4% (103/165) of all primary operations. Mean post-induction and post-excision PTH were 723,1 pg/mL (91-5400) and 155,8 pg/mL (17-1062), respectively. Mean post-excision PTH decrease was 66%, and PTH level decreased to a normal level in 34 patients. In 15 cases, post-excision iOPHTH levels fell by <50% from baseline levels.

Among patients receiving curative procedures (n=96), iOPHTH levels decreased by 50% or more in 88.5% of the cases (85/96), correctly predicting success (true positives), while in 11 cases (11.5%) the level fell by less than half (false negatives). Intra-operative PTH level was measured in 7/10 cases of surgical failure and was reduced by >50% in 3/7 cases, falsely suggesting operative success (false positives). Overall, the sensitivity and specificity of iOPHTH were 88.5% and 57.1%, respectively, with a Positive Predictive Value (PPV) of 96.59% and a Negative Predictive Value (NPV) of 26.67%.

The immediate post-surgery mean calcium level was 92,5 mg/L: postsurgical hypercalcemia was evident in 16 patients (9,7%) but only 10 presented perPHPT.

Analysis of patients in whom first surgery failed revealed that MGD accounted for 7/10 of perPHPT, and 5 of them were BNE. In one case (case 4, table 2), MGD was recognized preoperatively but the initial surgery was incomplete. Five other patients had failure due to a suspected or confirmed second adenoma. Another patient (case 5, table 2) did not undergo standard imaging and was operated on based on a CT scan suggesting a DA. The other cause of failure besides MGD was the inability

to detect a single adenoma. The use of iOPHTH or frozen section could have prevented two of these failures (case 1 and 2, table 2). The details of these patients are listed in Table 2.

DISCUSSION

When a parathyroidectomy is performed successfully, serum calcium levels typically return to the normal range, effectively addressing the metabolic issues associated with hypercalcemia. This normalization may also lessen symptoms and enhance quality of life (5). Despite a success rate exceeding 95% in experienced centers, the most common complication today remains surgical failure (6). Persistent primary hyperparathyroidism is defined as the persistence or reappearance of hypercalcemia within the first six months post-parathyroidectomy. This condition generally arises due to either a missed pathological parathyroid gland or an incomplete resection of hyperfunctional parathyroid tissue (7). Detailed causes of perPHPT after parathyroidectomy may include:

1/ Failure to detect a solitary adenoma due to surgical technical issues, often related to the surgeon's lack of experience (7), and in our cases, the absence of intraoperative tools. Missed solitary adenomas are common in low-volume centers, and these adenomas can be located in normal or ectopic positions (8). The incidence of ectopic glands can reach up to 16%, typically located in the neck (11.6%) or mediastinum (4.3%) and can cause perPHPT by missing a solitary adenoma (9). Supernumerary glands, although rare, can also contribute to perPHPT, especially in secondary or hereditary hyperparathyroidism. In a meta-analysis, it was found that 4.9% of healthy individuals and 6.3% of patients with hyperparathyroidism had five or more parathyroid glands (9).

We advocate the use of intraoperative aids since iOPHTH could have prevented two of our failures. In the presented series, the sensitivity of iOPHTH as an indicator of operative success was 88,5%. This compares with a 92% sensitivity reported by Westerdahl in a study of 269 PTx followed up for an average of 3.6 years (10). Other benefits of iOPHTH include cost benefits, avoidance of extensive dissection, and the correct and early identification of MGD (11).

2/ Incomplete resection of MGD is a significant cause of perPHPT, especially in high-volume centers (8). In a recent study of 3,779 subjects (8), MGD was identified in up to 15% of patients with PHPT. Among those with MGD, 12% had double adenomas, while the remainder presented with four-gland hyperplasia. In our study, we observed a rate of 3,6% for DA and 4,8% for HP, which falls within the reported range of rates (2,12). Inadequate resection in patients with DA often leads to perPHPT. This is typically due to prematurely ending the surgical exploration, as the condition is initially assessed as a SA during the preoperative phase. Because there is also a risk of recurrent disease in DA, some authors suggest that DA might indicate asymmetric or asynchronous HP (13).

Table 2. Characteristics of patients where initial surgery failed to cure primary hyperparathyroidism

No.	Age	Ca/PTH	US	MIBI	Dual imaging results	First surgery	iOPTH (decrease %)	Imaging after surgery	Redo surgery	Failure cause
1	61	108/127	Lateralized to right side	Negative	Discordant	UNE: lymph node excised	Not done	Spect CT: right lesion	UNE: excision of inferior right gland - Cured	inability to identify SA – lack of intra-operative tools
2	50	115/325	Lateralized to right side	Lateralized to right side	Lateralized side and concordant	UNE: excision of thymic tissue	Not done	MIBI : inferior right	Negative UNE – Right lobectomy: intra-thyroidal gland (iOPTH: 69%) - Cured	inability to identify SA - lack of intra-operative tools
3	46	107/301	Lateralized to right side	Lateralized to right side	Lateralized side and concordant	UNE: excision of inferior right gland (iOPTH increase) -- Negative BNE: glands were considered normal	increase	SPECT ectopic gland	CT: Excision of ectopic retro tracheal right gland - Cured	inability to identify SA - Ectopic adenoma
4	69	112/1500	Negative	3 glands	Discordant	BNE: identification of 3 glands (excision of two and a half gland)	Not done	MIBI: Negative	Lost to follow up	MGD -inability to identify gland in HP
5	73	119/290	Not performed	Not performed CT scan: Dual bilateral	--	BNE: excision of 2 inferior glands / other glands were assessed as normal	increase	SPECT superior left lesion	CT: UNE: Excision of superior left gland (iOPTH decrease 80%) - Cured	MGD - HP
6	39	107-172	Lateralized to right side (dual)	Lateralized to right side (single)	Lateralized	UNE: 2 right glands seen, excision of inferior right (enlarged)	67%	SPECT left lesion	CT: UNE: Excision of left inferior gland - Cured	MGD -Missed second adenoma
7	70	120-702	Lateralized to right side	Negative	Discordant	BNE: excision of right adenoma	52%	SPECT left lesion	CT: UNE: excision of left inferior adenoma - Cured	MGD -Missed second adenoma
8	39	100/198	Lateralized to left side	Lateralized to left side	Lateralized and concordant	UNE: excision left inferior adenoma	40%	US + MIBI : negative	BNE: excision of enlarged right inferior gland - Cured	MGD- Missed second adenoma
9	69	103-388	Dual bilateral	Lateralized to right side	Discordant	BNE: excision of right inferior adenoma / left adenoma not found – left lobectomy	25%	Not done	observed over a 12-month period and did not meet the requirements for reoperation.	MGD -Probable missed second adenoma
10	50	124/819	Negative	Negative	-	BNE: 4 glands seen: excision of an enlarged right gland (histology: adenoma) – a second suspect gland was left in place	55%	--	Lost to follow up	MGD - Probable missed second adenoma

BNE, Bilateral Neck Exploration; Ca/PTH, Calcium / Parathyroid Hormone; HP, Hyperplasia; iOPTH, Intraoperative Parathyroid Hormone; MIBI, Scintigraphy; MGD, Multiglandular Disease; No, Number; SA, Single Adenoma; SPECT CT, Computed Tomography; UNE, Unilateral Neck Exploration; US, Ultrasound.

Differentiating between DA and asymmetric HP is crucial for patient management.

Patients with genuine DA can be effectively cured by removing both abnormal glands, whereas those with asymmetric HP remain at elevated risk of persistence or recurrence. Several recent studies have focused on this subject; however, data is limited and current criteria for the diagnosis of DA are insufficient to separate true DA from asymmetric HP (12). Overall, MGD is linked to a higher risk of intraoperative failure, persistent hyperparathyroidism, and recurrent disease (2).

3/ Additionally, parathyroid cancer, although rare, can lead to perPHPT if not completely resected, with persistent disease suggesting residual or metastatic

involvement (14). The gold standard for PC is “en bloc” resection, which involves removing the parathyroid lesion along with surrounding fat tissue, the ipsilateral thyroid lobe, and possibly the recurrent laryngeal nerve and ipsilateral central neck compartment lymph nodes (15). Studies show this technique yields better outcomes than local excision by reducing R1 margins and the risk of locoregional recurrence or residual disease (16).

The failure rate in the current observational study is 6% which is similar to other published results (17), but we did not find any predictive factors apart from the established iOPTH. In a multivariate analysis of 2,239 patients treated for PHPT, independent risk factors for perPHPT were identified. These included age >70 years,

low volume centers, failure to locate enlarged glands on US or MIBI, higher preoperative calcium levels, lower preoperative parathyroid hormone levels, failure to meet iOPHT criteria, and lower weight of excised glands (18). These risk factors ultimately align with the predictive MGD factors (19,20), which remains the most critical factor in perPHPT and can further guide surgical decision-making in parathyroidectomy. Normocalcemic hyperparathyroidism was also found to be associated with a higher incidence of perPHPT due to a higher incidence of MGD (21).

- Imaging is crucial for exploring PHPT, and all patients should undergo preoperative combined imaging with high-definition ultrasound and Technetium (99m Tc) sestamibi scintigraphy (17,22). This approach aims to minimize the risk of missing adenomas, especially in cases of MGD or ectopic adenomas. While lateralized and concordant imaging has shown high accuracy (95-100%) for single adenomas (23), the sensitivity for MGD is significantly lower, with rates dropping to less than 50% (24). Negative preoperative studies are strong indicators of MGD (25), and neglecting standard imaging may lead to missed diagnoses, as demonstrated in one patient who underwent surgery based on a CT scan without prior imaging.

- Achievement of iOPHT criteria is also a known predictor of operative success, though the final target iOPHT level is not universally agreed upon. Existing research suggests that a drop of 50% is insufficient to demonstrate intraoperative cure in both DA and HP. In their study of iOPHT monitoring which included 271 patients with MGD, Richards et al. (26) demonstrated that using only the criterion of a 50% decrease in iOPHT would lead to perPHPT in more than 20% of patients with MGD. Similar results were found for DA by Goodsell et al. (12). This raises the question of adopting stricter iOPHT criteria when MGD is suspected, such as the Rome or Halle protocols, which require iOPHT normalization and reportedly enhance intraoperative sensitivity for detecting MGD (27,28). In contrast, the more balanced Miami and Vienna criteria may be better suited for straightforward cases without MGD suspicion (27). Foley et al. (29) used ROC analysis to determine that a 72% decrease in iOPHT (using the Vienna criteria) was optimal for identifying MGD, though this threshold had low sensitivity and specificity. Ultimately, a unanimous threshold or criterion is lacking, and sound clinical judgment remains vital. While iOPHT is more sensitive than localization studies (28), further research is needed to investigate the kinetic variations in iOPHT between SA and MGD, and to establish more effective criteria for identifying MGD. Moreover, combining iOPHT with preoperative imaging has proven to be the most reliable method for predicting MGD (30).

- In conjunction with these methods, researchers have developed preoperative scoring systems to predict MGD and guide surgical decisions. The CaPTHUS score (31) and Wisconsin index (32) are the most commonly used tools, combining biochemical markers and imaging results to assess the likelihood of MGD. Studies confirm these scores perform well, but thresholds do not fully

rule out MGD (33). Additional scoring models, such as the 4D-CT MGD score (34), incorporate imaging data and biochemical markers, enhancing specificity. Emerging machine learning techniques, also known as artificial intelligence, have demonstrated significant potential (35), with models such as RandomTree achieving high accuracy and JRip optimizing predictive value (36). These advancements provide innovative approaches for identifying MGD when traditional methods yield inconclusive results.

After curative parathyroidectomy, normocalcemia is achieved in the majority of patients within 48–72 hours postoperatively. Approximately 10% of patients may experience delayed normalization of calcium levels, which typically resolves within 1–2 weeks (37). This early transient persistent hypercalcemia is not predictive of perPHPT and should not be mistaken for persistent disease. Evaluating these patients postoperatively requires time, especially for those with an adequate decline in PTH levels, and early reintervention should be avoided in these cases. Secondary surgery should be delayed until at least 3 months postoperatively, as the surgical field is significantly affected by inflammatory scarring from the initial surgery for several months (38). Surgical indications for perPHPT are similar to those for PHPT and are recommended when patients meet the established guidelines for surgery, provided there are no contraindications (39). However, deciding if and when to operate is complex, as it requires balancing a decreased cure rate with the increased risk of complications such as vocal cord paralysis, permanent hypoparathyroidism as well as tracheal and cervical esophageal injury (40). Parathyroid reoperations should involve a multidisciplinary team discussion and should be conducted by experienced surgeons (those who perform at least 50 parathyroidectomies per year are considered by most endocrine surgeons to be experienced (39)). A targeted operation is also imperative for surgical success in re-operative surgery; thus, having specific imaged glands is essential. First-line imaging modalities include ultrasound and scintigraphy, followed by advanced techniques such as four-dimensional (4-D) CT, dynamic 4D-MRI, and positron emission tomography (PET) or PET/CT with 18F-fluorocholine (7,40). These imaging techniques are crucial for accurately locating the parathyroid glands and planning the surgical approach. This study was limited by its small sample size and its retrospective nature, which inherently comes with associated challenges. Some patient data were missing due to unavailable medical records. The use of preoperative imaging and intraoperative tools was variable. Given the retrospective design and limited access to patient records, distinguishing between SA and MGD relied on reviewers' judgment based on clinical and histopathological records.

CONCLUSION

In conclusion, our study highlights the essential role of multiglandular disease as a major contributor to

persistent primary hyperparathyroidism and stresses the importance of identifying risk factors associated with MGD. Both imaging and iOPTh measurements are crucial in this context, though iOPTh offers greater sensitivity, and the optimal final value of iOPTh remains a topic of discussion. Ultimately, combining these methods, particularly using scoring systems, can aid in minimizing therapeutic failures.

Abbreviations - Corresponding Terms:

BNE: Bilateral Neck Exploration
Ca: Calcium
CT: Computed Tomography
DA: Double Adenoma
HP: Hyperplasia
iOPTh: Intraoperative Parathyroid Hormone
MGD: Multi-Glandular Disease
MIBI: Technetium (99m Tc) Sestamibi Scintigraphy
PC: Parathyroid Carcinoma
perPHPT: Persistent Primary Hyperparathyroidism
PHPT: Primary Hyperparathyroidism
PTH: Parathyroid Hormone
PTx: Parathyroidectomy
SA: Single Adenoma
UNE: Unilateral Neck Exploration
US: Ultrasonography

REFERENCES

- Caldwell M, Laux J, Clark M, Kim L, Rubin J. Persistently Elevated PTH After Parathyroidectomy at One Year: Experience in a Tertiary Referral Center. *J Clin Endocrinol Metab.* 2019 Oct 1;104(10):4473-4480. doi: 10.1210/jc.2019-00705. PMID: 31188435; PMCID: PMC6736213.
- Mazotas IG, Yen TWF, Doffek K, Shaker JL, Carr AA, Evans DB, Wang TS. Persistent/Recurrent Primary Hyperparathyroidism: Does the Number of Abnormal Glands Play a Role? *J Surg Res.* 2020 Feb;246:335-341. doi: 10.1016/j.jss.2019.08.007. Epub 2019 Oct 18. PMID: 31635835.
- Udelsman R. Approach to the patient with persistent or recurrent primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2011 Oct;96(10):2950-8. doi: 10.1210/jc.2011-1010. PMID: 21976743.
- Riss P, Kaczirek K, Heinz G, Bieglmayer C, Niederle B. A "defined baseline" in PTH monitoring increases surgical success in patients with multiple gland disease. *Surgery.* sept 2007;142(3):398-404.
- Mack LA, Pasiaka JL. Asymptomatic primary hyperparathyroidism: a surgical perspective. *Surg Clin North Am.* juin 2004;84(3):803-16.
- Elaraj D, Sturgeon C. Operative treatment of primary hyperparathyroidism: balancing cost-effectiveness with successful outcomes. *Surg Clin North Am.* juin 2014;94(3):607-23.
- Uludag M, Unlu MT, Kostek M, Caliskan O, Aygun N, Isgor A. Persistent and Recurrent Primary Hyperparathyroidism: Etiological Factors and Pre-Operative Evaluation. *Sisli Etfal Hastan Tip Bul.* 21 mars 2023;57(1):1-17.
- Chen H, Wang TS, Yen TWF, Doffek K, Krzywda E, Schaefer S, et al. Operative failures after parathyroidectomy for hyperparathyroidism: the influence of surgical volume. *Ann Surg.* oct 2010;252(4):691-5.
- Taterra D, Wong LM, Vikse J, Sanna B, Pękala P, Walocha J, et al. The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. *Langenbecks Arch Surg.* 2019;404(1):63-70.
- Westerdahl J, Bergenfelz A. Parathyroid surgical failures with sufficient decline of intraoperative parathyroid hormone levels: unobserved multiple endocrine neoplasia as an explanation. *Arch Surg.* juin 2006;141(6):589-94.
- Bagul A, Patel HP, Chadwick D, Harrison BJ, Balasubramanian SP. Primary hyperparathyroidism: an analysis of failure of parathyroidectomy. *World J Surg.* mars 2014;38(3):534-41.
- Goodsell KE, Ermer JP, Zaheer S, Kelz RR, Fraker DL, Wachtel H. Double adenoma as a cause of primary hyperparathyroidism: Asymmetric hyperplasia or a distinct pathologic entity? *Am J Surg.* sept 2021;222(3):483-9.
- Alhefthi A, Schneider DF, Sippel R, Chen H. Recurrent and persistence primary hyperparathyroidism occurs more frequently in patients with double adenomas. *J Surg Res.* juill 2014;190(1):198-202.
- Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. *Curr Treat Options Oncol.* mars 2012;13(1):11-23.
- Iihara M, Okamoto T, Suzuki R, Kawamata A, Nishikawa T, Kobayashi M, et al. Functional parathyroid carcinoma: Long-term treatment outcome and risk factor analysis. *Surgery.* déc 2007;142(6):936-43; discussion 943.e1.
- Roser P, Leca BM, Coelho C, Schulte KM, Gilbert J, Drakou EE, Kosmas C, Ling Chuah L, Wassati H, Miras AD, Crane J, Aylwin SJB, Grossman AB, Dimitriadis GK. Diagnosis and management of parathyroid carcinoma: a state-of-the-art review. *Endocr Relat Cancer.* 2023 Mar 22;30(4):e220287. doi: 10.1530/ERC-22-0287. PMID: 36621911.
- Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surgery.* 1 oct 2016;151(10):959-68.
- Cron DC, Kapeles SR, Andraska EA, Kwon ST, Kirk PS, McNeish BL, Lee CS, Hughes DT. Predictors of operative failure in parathyroidectomy for primary hyperparathyroidism. *Am J Surg.* 2017 Sep;214(3):509-514. doi: 10.1016/j.amjsurg.2017.01.012. Epub 2017 Jan 10. PMID: 28108069.
- Thier M, Daudi S, Bergenfelz A, Almquist M. Predictors of multiglandular disease in primary hyperparathyroidism. *Langenbecks Arch Surg.* 2018 Feb;403(1):103-109. doi: 10.1007/s00423-017-1647-9. Epub 2018 Jan 2. PMID: 29294178; PMCID: PMC5805794.
- Shah US, McCoy KL, Kelley ML, Carty SE, Yip L. How and when is multiglandular disease diagnosed in sporadic primary hyperparathyroidism? *Surgery.* 2022 Jan;171(1):35-39. doi: 10.1016/j.surg.2021.09.018. PMID: 34924180.
- Trébouet E, Bannani S, Wargny M, Leux C, Caillard C, Kraeber-Bodéré F, et al. Mild sporadic primary hyperparathyroidism: high rate of multiglandular disease is associated with lower surgical cure rate. *Langenbecks Arch Surg.* juin 2019;404(4):431-8.
- Kuzminski SJ, Sosa JA, Hoang JK. Update in Parathyroid Imaging. *Magn Reson Imaging Clin N Am.* févr 2018;26(1):151-66.
- Broome DT, Naples R, Bailey R, Tekin Z, Hamidi M, Bena JF, Morrison SL, Berber E, Siperstein AE, Scharpf J, Skugor M. Use of Preoperative Imaging in Primary Hyperparathyroidism. *J Clin Endocrinol Metab.* 2021 Jan 1;106(1):e328-e337. doi: 10.1210/clinem/dgaa779. PMID: 33119066.24. Merlino JJ, Ko K, Minotti A, McHenry CR. The false negative technetium-99m-sestamibi scan in patients with primary hyperparathyroidism: correlation with clinical factors and operative findings. *Am Surg.* mars 2003;69(3):225-9; discussion 229-230.
- Thier M, Daudi S, Bergenfelz A, Almquist M. Predictors of multiglandular disease in primary hyperparathyroidism. *Langenbecks Arch Surg.* 2018 Feb;403(1):103-109. doi: 10.1007/s00423-017-1647-9. Epub 2018 Jan 2. PMID: 29294178; PMCID: PMC5805794.
- Richards ML, Thompson GB, Farley DR, Grant CS. An optimal algorithm for intraoperative parathyroid hormone monitoring. *Arch Surg.* mars 2011;146(3):280-5.
- Barczynski M, Konturek A, Hubalewska-Dydejczyk A, Cichon S, Nowak W. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. *Langenbecks Arch Surg.* 2009 Sep;394(5):843-9. doi: 10.1007/s00423-009-0510-z. Epub 2009 Jun 16. PMID: 19529957.
- Yang L, Jing X, Pang H, Guan L, Li M. Primary hyperparathyroidism: predictors of sporadic multi-gland disease. *Endocr Connect.* 2024 Apr 4;13(5):e230492. doi: 10.1530/EC-23-0492. PMID: 38513354; PMCID: PMC11046330.
- Foley CS, Moore EC, Milas M, Berber E, Shin J, Siperstein

- AE. RECEIVER OPERATING CHARACTERISTIC ANALYSIS OF INTRAOPERATIVE PARATHYROID HORMONE MONITORING TO DETERMINE OPTIMUM SENSITIVITY AND SPECIFICITY: ANALYSIS OF 896 CASES. *Endocr Pract.* nov 2019;25(11):1117-26.
29. Aygün N, Uludağ M. Intraoperative Adjunct Methods for Localization in Primary Hyperparathyroidism. *Sisli Etfal Hastan Tip Bul.* 2019 Jul 11;53(2):84-95. doi: 10.14744/SEMB.2019.37542. PMID: 32377064; PMCID: PMC7199831.
 30. Kebebew E Hwang J Reiff E Duh QY & Clark OH. Predictors of single-gland vs multigland parathyroid disease in primary hyperparathyroidism: a simple and accurate scoring model. *Archives of Surgery* 2006141777–782. (10.1001/archsurg.141.8.777).
 31. Mazeh H Chen H Levenson G & Sippel RS. Creation of a “Wisconsin index” nomogram to predict the likelihood of additional hyperfunctioning parathyroid glands during parathyroidectomy. *Annals of Surgery* 2013257138–141. (10.1097/SLA.0b013e31825ffbe1).
 32. De Pasquale L, Lori E, Bulfamante AM, Felisati G, Castellani L, Saibene AM. Evaluation of Wisconsin and CaPTHUS Indices Usefulness for Predicting Monoglandular and Multiglandular Disease in Patients with Primary Hyperparathyroidism through the Analysis of a Single-Center Experience. *Int J Endocrinol.* 2021 Oct 11;2021:2040284. doi: 10.1155/2021/2040284. PMID: 34671396; PMCID: PMC8523259.
 33. Sepahdari AR, Bahl M, Harari A, Kim HJ, Yeh MW, Hoang JK. Predictors of Multigland Disease in Primary Hyperparathyroidism: A Scoring System with 4D-CT Imaging and Biochemical Markers. *AJNR Am J Neuroradiol.* 2015 May;36(5):987-92. doi: 10.3174/ajnr.A4213. Epub 2015 Jan 2. PMID: 25556203; PMCID: PMC7990586.
 34. Sandqvist P, Sundin A, Nilsson IL, Grybäck P, Sanchez-Crespo A. Primary hyperparathyroidism, a machine learning approach to identify multiglandular disease in patients with a single adenoma found at preoperative Sestamibi-SPECT/CT. *Eur J Endocrinol.* 2022 Jun 24;187(2):257-263. doi: 10.1530/EJE-22-0206. PMID: 35666799.
 35. Apostolopoulos ID, Papathanasiou ND, Apostolopoulos DJ. A Deep Learning Methodology for the Detection of Abnormal Parathyroid Glands via Scintigraphy with 99mTc-Sestamibi. *Diseases.* 2022 Aug 23;10(3):56. doi: 10.3390/diseases10030056. PMID: 36135211; PMCID: PMC9497534.
 36. Lai V, Yen TWF, Doffek K, Carr AA, Carroll TB, Fareau GG, et al. Delayed Calcium Normalization After Presumed Curative Parathyroidectomy is Not Associated with the Development of Persistent or Recurrent Primary Hyperparathyroidism. *Ann Surg Oncol.* juill 2016;23(7):2310-4.
 37. Weber T, Dotzenrath C, Dralle H, Niederle B, Riss P, Holzer K, et al. Management of primary and renal hyperparathyroidism: guidelines from the German Association of Endocrine Surgeons (CAEK). *Langenbecks Arch Surg.* mai 2021;406(3):571-85.
 38. Bilezikian JP, Khan AA, Silverberg SJ, Fuleihan GE, Marcocci C, Minisola S, Perrier N, Sitges-Serra A, Thakker RV, Guyatt G, Mannstadt M, Potts JT, Clarke BL, Brandi ML; International Workshop on Primary Hyperparathyroidism. Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. *J Bone Miner Res.* 2022 Nov;37(11):2293-2314. doi: 10.1002/jbmr.4677. Epub 2022 Oct 17. PMID: 36245251.
 39. Stack BC Jr, Tolley NS, Bartel TB, Bilezikian JP, Bodenner D, Camacho P, Cox JPD, Dralle H, Jackson JE, Morris JC 3rd, Orloff LA, Palazzo F, Ridge JA, Scott-Coombes D, Steward DL, Terris DJ, Thompson G, Randolph GW. AHS Series: Do you know your guidelines? Optimizing outcomes in reoperative parathyroid surgery: Definitive multidisciplinary joint consensus guidelines of the American Head and Neck Society and the British Association of Endocrine and Thyroid Surgeons. *Head Neck.* 2018 Aug;40(8):1617-1629. doi: 10.1002/hed.25023. Epub 2018 Aug 2. PMID: 30070413.