Original Article

Factors Determined Outcome of Parathyroidectomy in Patients Diagnosed with Primary Hyperparathyroidism

Imruetaicharoenchoke W, MD, PhD[1], Srisuworanan N, MD[2], Boonsripitayanon M, MD[1], Chuthapisith S, MD, PhD[1], Pisarnturakit P, MD[1]

[1] Division of Head, Neck and Breast, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2] Division of General Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: The aim of the present study was to determine the success rate of parathyroidectomy in primary hyperparathyroidism (pHPT) and the related causes for the persistence or recurrence of the disease after surgery.

Materials and Methods: A single center retrospective study of patients with primary hyperparathyroidism who underwent parathyroidectomy at the Department of Surgery, Faculty of Medicine Siriraj Hospital, during the period January 2007 to December 2015 was conducted.

Results: In total, 79 patients with a median follow-up period of 29 months (ranging from 6 to 110 months) were enrolled on the study. The success rate of parathyroidectomy was reported to be 90%, while 7% of the patients had persistent pHPT and 3% developed recurrent pHPT after surgery. The most common postoperative complications were transient symptomatic hypocalcemia (8%). There were no statistically significant related factors to the persistence or recurrence of the disease.

Conclusion: The high positive outcome of parathyroidectomy for pHPT patients in Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, shows it is safe and effective, with a success rate in 9-year experience of 90%. The authors believe that an improvement of pre-operative imaging for localization and the use of surgical adjuncts may help improve the outcome of the surgery in the future.

Keywords: Primary hyperparathyroidism, Persistent hyperparathyroidism, Recurrent hyperparathyroidism, Parathyroidectomy

J Med Assoc Thai 2020;103(Suppl.2): 32-6
Website: http://www.jmatonline.com

Primary hyperparathyroidism (pHPT) is an overproduction of parathyroid hormone (PTH) from abnormal parathyroid glands, which results in an elevated serum calcium level or hypercalcemia. Untreated hypercalcemia leads to the physiological alteration of multiple organ systems, including the renal, neurological, psychological, and skeletal systems. Currently, parathyroidectomy is the only definite and effective treatment for pHPT[1-4]. Curative parathyroidectomy has been demonstrated to have significant long-term advantages, even in asymptomatic patients[1].

In a high-volume endocrine center, the success rate of initial parathyroidectomy for primary hyperparathyroidism treatment was reported to be around 95%[1,5,6]. However, for some patients who fail to achieve normocalcemia within 6 months after the surgery, termed persistent hyperparathyroidism, or show a reoccurring increase in serum calcium or PTH levels, termed recurrent pHPT[7], the reoperation of parathyroidectomy might be required[8,9]. However, we have noticed that redoing parathyroidectomy is significantly associated with an increase in the morbidity rate due to a distorted anatomy and fibrosis in the tissue plane, also resulting in a consequential decrease in the quality of life of the patients, such as aspiration, hoarseness, or permanent hypocalcemia[8]. Therefore, to help achieve a sufficient success rate, the aim of the present study was to determine the outcome of parathyroidectomy for patients diagnosed with primary hyperparathyroidism in Siriraj Hospital and to ascertain the factors related to persistence or recurrence of the disease.

Correspondence to:

Pisarnturakit P.

Division of Head, Neck and Breast, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Phone: +66-2-4198016

E-mail: ppisarntu@gmail.com

Materials and Methods

This single-center retrospective trial enrolled patients with primary hyperparathyroidism, who had underwent parathyroidectomy from January 2007 to December 2015 at the Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok. Patients who had prior received parathyroid surgery from other hospitals or in a follow-up period of less than 6 months were excluded from the study.

All of the patients were evaluated by preoperative imaging to localize abnormal parathyroid glands. The most common imaging modality performed was Technetium (Tc-99m or 99mTc) parathyroid scintigraphy, including

How to cite this article: Imruetaicharoenchoke W, Srisuworanan N, Boonsripitayanon M, Chuthapisith S, Pisarnturakit P. Factors Determined Outcome of Parathyroidectomy in Patients Diagnosed with Primary Hyperparathyroidism. J Med Assoc Thai 2020;103(Suppl.2): 32-6.

99mTc sestamibi dual-phase parathyroid scintigraphy and 99mTc sestamibi/99mTc-pertechnetate subtraction scintigraphy. Some patients whose sestamibi scan showed no localization were considered for a second modality of imaging, including an ultrasound (US) or computerized tomography (CT) scan.

All of the operations were carried out by the standard bilateral neck exploration technique. However, an intra-operative frozen section of parathyroid glands was applied depending on the surgeon's preference, but was not routinely performed.

Postoperative serum calcium was regularly obtained within 24 hours after the surgery. Follow-up blood chemistry analyses, consisting of serum calcium and serum parathyroid hormone (PTH), were also obtained at the first postoperative visit around 1 to 2 weeks from the operation, at 6 months, and then annually. The normal level of serum calcium and PTH were 8.6 to 10.0 mg/dl and 15.00 to 65.00 pg/ml, respectively. Oral calcium supplementation was given to the patients who developed hypocalcemia.

The primary outcome of the present study was to determine the outcome of parathyroidectomy in primary hyperparathyroidism. The secondary outcome was additionally to evaluate the related factors involved in persistence or recurrence of the disease after surgery and postoperative complications.

Regarding the definitions of success and failure, successful parathyroidectomy is the reestablishment of normal calcium homeostasis lasting at least 6 months after surgery, while the failure of parathyroidectomy includes persistent or recurrent hyperparathyroidism. Persistent pHPT is defined as a failure to achieve normocalcemia within 6 months of parathyroidectomy, while recurrent pHPT is determined by the reappearance of high levels of serum calcium and parathyroid hormone after a period of normocalcemic interval at more than 6 months after parathyroidectomy[1].

Statistical analysis

The demographic data, from the group with successful surgery, were compared with the group with failed parathyroidectomy using an independent t-test, Mann-Whitney U test, and 2-tailed Fisher exact test. The statistical analysis was performed using SPSS software version 18.

Results

In total, 79 patients diagnosed with primary hyperparathyroidism who underwent parathyroidectomy in Faculty of Medicine Siriraj Hospital between 2007 and 2015 were included in the present study. The median follow-up period was 29 months (ranging from 6 to 110 months). The success rate of parathyroidectomy was 90%, with persistence and recurrence rates of 7% and 3%, respectively (Figure 1). The most common postoperative complications were transient symptomatic hypocalcemia (8%).

The demographic data of all the patients are summarized in Table 1. There was no statistically significant difference in age, sex, and pre-operative biochemistry between

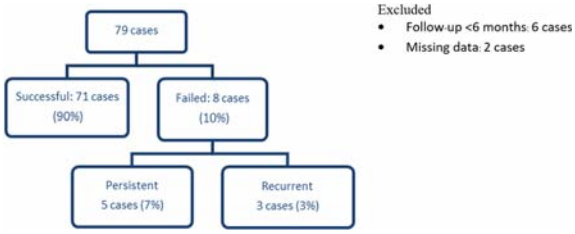

Figure 1. The result of parathyroidectomy in patients with primary hyperparathyroidism who underwent surgery from 2007 to 2015 at the Department of Surgery, Faculty of Medicine, Siriraj Hospital.

the group of successful and failed parathyroidectomy patients. Postoperative serum calcium in the patients whose treatment had failed was significantly higher compared with those who underwent successful parathyroidectomy (10.5±1.06 vs. 9.6±1.14, p = 0.043). There was also a statistically significant increase in postoperative serum PTH in the failure group (171 vs. 16, p<0.01).

The factors of multiple gland disease and ectopic parathyroid position, which were identified to be the major causes of failure for parathyroidectomy in the literature review, showed no significant difference between the two groups. Although the number of patients with ectopic gland disease was noticeably higher in the failure group (50% vs. 1%, p = 0.193), this was not a statistically significant pertinent factor for the failure of surgery demonstrated in these data analyses.

Discussion

Parathyroidectomy is usually considered to be an efficient procedure for the curative treatment of primary hyperparathyroidism. In an experienced center, the success rate may approach 95%[1,5,6]. The failure of surgery occurs only rarely, but may considerably result in a persistence or recurrence of the disease and lead to more inevitable postoperative complications, including transient (around 12% of cases) or permanent recurrent laryngeal nerve injury (7%) and permanent hypocalcemia (14%), which can significantly affect patients' quality of life[8,10].

As reported in a previous study and according to our literature review, the pre-operative localization technique used to identify the abnormal parathyroid glands causing primary hyperparathyroidism is one of the most important factors related to the success rate of parathyroidectomy in pHPT patients[1]. In addition, parathyroid scans, including 99mTc sestamibi dual-phase parathyroid scintigraphy and 99mTc sestamibi/99mTc-pertechnetate subtraction scintigraphy, are the most relevant and cost-effective tools to locate gland disease. These imagings provide high sensitivity and a high positive predictive value of approximately 85-90% and 95%, respectively, especially for patients whose histology shows a single parathyroid adenoma[1,7,8,11,12]. Nevertheless, the identification rate decreases to around

Table 1. Demographic data

	Success (n = 71)	Failure (n = 8)	*p*-value
Age (median, range)	61 (16 to 87)	62 (43 to 72)	0.745
Gender (%)			
Female	55 (78%)	4 (50%)	0.107
Male	16 (23%)	4 (50%)	
Preoperative biochemistry			
Calcium (mean ± SD)	11.0±0.92	11.6±0.86	0.097
PTH (median, range)	194 (72 to 4,255)	1,293 (72 to 2,065)	0.077
Phosphorus (mean ± SD)	2.4±0.55	2.4±0.65	0.966
Alkaline phosphatase (mean ± SD)	259±469	308±336	0.779
Postoperative biochemistry			
Calcium (mean ± SD)	9.6±1.14	10.5±1.061	0.043
PTH (median, range)	16 (2 to 171)	71 (28 to 1,501)	<0.001
Histopathology			
Adenoma	45 (63%)	5 (63%)	0.362
Hyperplasia	24 (34%)	2 (25%)	
Carcinoma	2 (3%)	1 (13%)	
Disease gland			
Single	64 (90%)	5 (83%)	0.494
Multiple	7 (10%)	1 (17%)	
Location			
Eutopic	70 (99%)	4 (50%)	0.193
Ectopic	1 (1%)	4 (50%)	

Table 2. Persistent and recurrent case

Gender	Age	Histopathology	No. of disease gland	Cause
1) Male	69	Adenoma	1	Ectopic gland - intrathyroid
2) Male	62	Adenoma	2	Ectopic gland - mediastinum
3) Male	51	Hyperplasia	1	No reoperation
4) Female	62	Adenoma	1	Ectopic gland - carotid sheath
5) Female	72	Hyperplasia	1	Missing eutopic gland
6) Female	47	Adenoma	2	Ectopic gland - intrathyroid
7) Female	71	Adenoma	2	Missing eutopic gland
8) Male	43	Carcinoma	1	Recurrent carcinoma

41 to 62% in the case of hyperplastic glands or multiple parathyroid adenomas[8,10,11,13-16], where a combination of scintigraphy and ultrasound or single photon emission computed tomography (SPECT) applied to locate the glands can significantly achieve more successful operations, with 94% sensitivity[1,11,14,16,17]. As the incidence of multiple gland disease is approximately 3 to 15% leading to a failure of parathyroidectomy[1,9,10,15,18], the standard bilateral neck exploration is considered one of the best strategies to increase the successful operation rate in this circumstance[1,19-22].

Furthermore, the ectopic parathyroid locations, including the superior and inferior glands, are the other factors related to the significantly higher failure of parathyroidectomy in pHPT patients. The incidence of the abnormal gland position is approximately 16 to 44% in this group of patients, as reviewed in multiple studies[8,10,23,24]. The integration of more than one imaging, such as SPECT, combined with parathyroid scintigraphy or the use of intra-operative parathyroid hormone assays may reduce the rate of unsuccessful operation in these patients[1,15,16,25].

In the present study, the results of the related factors for the failure of surgery may have shown no statistical significance due to the small sample size of the failure group compared to the successful parathyroidectomy group (8 vs. 71 cases). However, there was a clear trend of ectopic gland disease in the group of failed parathyroidectomy cases (50% vs. 1%, $p = 0.193$), where the common sites of the ectopic glands were the intrathyroid, carotid sheath, and mediastinum (Table 2).

Despite pre-operative imaging and standard bilateral neck exploration, identifying the location of the ectopic gland is somewhat difficult, even with experience hands. Therefore, the improvement of localization in pre-operative imaging and the use of a surgical adjunct, such as an intra-operative parathyroid hormone assay, may help to improve the outcome of parathyroidectomy in the future.

Conclusion

The outcome of parathyroidectomy for patients with primary hyperparathyroidism in a 9-year experience of Faculty of Medicine Siriraj Hospital from January 2007 to December 2015 was reported to be a success rate of 90%. It is thus considered to be a safe and effective procedure. The authors believe that further study to improve the modality of pre-operative imaging and the use of adjunct tools may help improve the outcome of the surgery in the future.

What is already known on this topic?

The success rate of parathyroidectomy in primary hyperparathyroidism patients was reported to be around 95% in the high volume centers, depending on surgeon's experience.

What this study adds?

Ectopic glands were strongly associated with failed parathyroidectomies in primary hyperparathyroidism treatment.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. 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 Surg 2016;151: 959-68.
2. Wang TS, Pasieka JL, Carty SE. Techniques of parathyroid exploration at North American endocrine surgery fellowship programs: what the next generation is being taught. Am J Surg 2014;207:527-32.
3. Callender GG, Udelsman R. Surgery for primary hyperparathyroidism. Cancer 2014;120:3602-16.
4. Mack LA, Pasieka JL. Asymptomatic primary hyperparathyroidism: a surgical perspective. Surg Clin North Am 2004;84:803-16.
5. Akerstrom G, Malmaeus J, Bergstrom R. Surgical anatomy of human parathyroid glands. Surgery 1984;95:14-21.
6. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. Ann Surg 2002;236:543-51.
7. Lai V, Yen TW, 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 2016;23:2310-4.
8. Nawrot I, Chudzinski W, Ciacka T, Barczynski M, Szmidt J. Reoperations for persistent or recurrent primary hyperparathyroidism: results of a retrospective cohort study at a tertiary referral center. Med Sci Monit 2014;20:1604-12.
9. Gough I. Reoperative parathyroid surgery: the importance of ectopic location and multigland disease. ANZ J Surg 2006;76:1048-50.
10. Catalfamo A, Fama F, Pergolizzi FP, Bartolo V, Rizzo AG, Marullo M, et al. Management of undetectable and lost parathyroid adenoma. Ann Thyroid 2018;3:1-12.
11. Lumachi F, Ermani M, Basso S, Zucchetta P, Borsato N, Favia G. Localization of parathyroid tumours in the minimally invasive era: which technique should be chosen? Population-based analysis of 253 patients undergoing parathyroidectomy and factors affecting parathyroid gland detection. Endocr Relat Cancer 2001;8:63-9.
12. Nichols KJ, Tomas MB, Tronco GG, Rini JN, Kunjummen BD, Heller KS, et al. Preoperative parathyroid scintigraphic lesion localization: accuracy of various types of readings. Radiology 2008;248:221-32.
13. Mihai R, Simon D, Hellman P. Imaging for primary hyperparathyroidism—an evidence-based analysis. Langenbecks Arch Surg 2009;394:765-84.
14. Solorzano CC, Carneiro-Pla D. Minimizing cost and maximizing success in the preoperative localization strategy for primary hyperparathyroidism. Surg Clin North Am 2014;94:587-605.
15. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg 2005;132:359-72.
16. Fraker DL, Harsono H, Lewis R. Minimally invasive parathyroidectomy: benefits and requirements of localization, diagnosis, and intraoperative PTH monitoring. long-term results. World J Surg 2009;33: 2256-65.
17. Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. Would scan, but which scan? A cost-utility analysis to optimize preoperative imaging for primary hyperparathyroidism. Surgery 2011;150:1286-94.
18. Alhefdhi A, Schneider DF, Sippel R, Chen H. Recurrent and persistence primary hyperparathyroidism occurs more frequently in patients with double adenomas. J Surg Res 2014;190:198-202.
19. Abdulla AG, Ituarte PH, Harari A, Wu JX, Yeh MW. Trends in the frequency and quality of parathyroid surgery: analysis of 17,082 cases over 10 years. Ann Surg 2015;261:746-50.
20. Allendorf J, DiGorgi M, Spanknebel K, Inabnet W, Chabot J, Logerfo P. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. World J Surg 2007;31:2075-80.
21. Miller P, Kindred A, Kosoy D, Davidson D, Lang H, Waxman K, et al. Preoperative sestamibi localization combined with intraoperative parathyroid hormone assay predicts successful focused unilateral neck exploration during surgery for primary hyperparathyroidism. Am Surg 2003;69:82-5.

22. Kountakis SE, Maillard AJ. Parathyroid adenomas: is bilateral neck exploration necessary? Am J Otolaryngol 1999;20:396-9.
23. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. Am J Surg 2006;191:418-23.
24. Karakas E, Schneider R, Rothmund M, Bartsch DK, Schlosser K. Initial surgery for benign primary hyperparathyroidism: an analysis of 1,300 patients in a teaching hospital. World J Surg 2014;38:2011-8.
25. Bergenfelz AO, Wallin G, Jansson S, Eriksson H, Martensson H, Christiansen P, et al. Results of surgery for sporadic primary hyperparathyroidism in patients with preoperatively negative sestamibi scintigraphy and ultrasound. Langenbecks Arch Surg 2011;396:83-90.

ผลของการผ่าตัดและปัจจัยที่เกี่ยวข้องกับความสำเร็จของการผ่าตัดต่อมพาราไธรอยด์ในผู้ป่วยที่มีภาวะต่อมพาราไธรอยด์ทำงานสูงผิดปกติแบบปฐมภูมิ

วราภรณ์ อิ่มฤทัยเจริญโชค, ณิชา ศรีสุวรนันท์, มงคล บุญศรีพิทยานนท์, สืบวงศ์ จุฑาภิสิทธิ์, พงษ์เทพ พิศาลธุรกิจ

วัตถุประสงค์: เพื่อศึกษาผลของการรักษา และปัจจัยที่ส่งผลต่อความสำเร็จในการผ่าตัดต่อมพาราไธรอยด์ในผู้ป่วยที่มีภาวะต่อมพาราไธรอยด์ทำงานสูงผิดปกติแบบปฐมภูมิ

วัสดุและวิธีการ: เป็นการศึกษาที่เก็บข้อมูลผู้ป่วยที่ได้รับการวินิจฉัยเป็นภาวะต่อมพาราไธรอยด์ทำงานสูงผิดปกติแบบปฐมภูมิ และได้รับการรักษาด้วยการผ่าตัดต่อมพาราไธรอยด์ที่มีพยาธิสภาพออก โดยผู้ป่วยทั้งหมดได้รับการผ่าตัดที่ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ช่วงระหว่างเดือนมกราคม พ.ศ. 2550 ถึง เดือนธันวาคม พ.ศ. 2558

ผลการศึกษา: ผู้ป่วยทั้งหมด 79 คนที่อยู่ในการศึกษานี้ มีระยะเวลาเฉลี่ยในการตรวจติดตามผู้ป่วยหลังผ่าตัดประมาณ 29 เดือน (6 ถึง 110 เดือน) ผู้ป่วยส่วนใหญ่ 90% หายจากภาวะต่อมพาราไธรอยด์ทำงานสูงผิดปกติด้วยการผ่าตัดรักษาต่อมที่มีพยาธิสภาพออกโดยที่ 7% ของผู้ป่วยยังคงมีระดับของพาราไธรอยด์ฮอร์โมนที่สูงตามหลังการผ่าตัดตลอด (persistence) และ 3% มีระดับของพาราไธรอยด์ฮอร์โมนที่ต่ำลงไปชั่วคราวตามหลังการผ่าตัดและกลับมาสูงขึ้นใหม่ในระยะเวลาประมาณ 6 เดือน (recurrence) ภาวะแทรกซ้อนที่พบได้บ่อยที่สุดคือการที่ผู้ป่วยมีระดับแคลเซียมต่ำกว่าปกติชั่วคราวตามหลังการผ่าตัด (8%) นอกจากนี้ยังพบว่าไม่มีปัจจัยใดที่ส่งผลต่อการเกิดภาวะ persistent หรือ recurrent hyperparathyroidism อย่างมีนัยสำคัญทางสถิติ แต่อย่างไรก็ตามในการศึกษานี้พบว่าผู้ป่วยที่มีต่อมพาราไธรอยด์อยู่ในตำแหน่งที่ผิดปกติ (ectopic glands) เป็นปัจจัยหนึ่งที่มีแนวโน้มทำให้เกิดความล้มเหลวในการผ่าตัดรักษาภาวะต่อมพาราไธรอยด์ทำงานสูงผิดปกติแบบปฐมภูมิได้

สรุป: การผ่าตัดต่อมพาราไธรอยด์เป็นการรักษาภาวะต่อมพาราไธรอยด์ทำงานสูงผิดปกติแบบปฐมภูมิที่ประสบความสำเร็จสูงและปลอดภัย และการส่งตรวจทางรังสีเพิ่มเติมด้วยวิธีการต่าง ๆ ก่อนการผ่าตัดเพื่อระบุตำแหน่งของต่อมพาราไธรอยด์ที่มีพยาธิสภาพ (Preoperative parathyroid localization) เป็นแนวทางที่สามารถเพิ่มประสิทธิภาพในการผ่าตัดให้ได้ผลดียิ่งขึ้นได้