Outcomes of Limited Parathyroidectomy in Secondary Hyperparathyroidism

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ABSTRACT

Objective: To determine the outcomes of unintended limited parathyroidectomy (LPTX; three or less than three glands removed) in patients with secondary hyperparathyroidism (SHPT).

Study Design: Retrospective cohort study.

Place and Duration of Study: Jiangmen Central Hospital, China, from January 2012 and December 2019.

Methodology: The operative and biochemical outcomes of LPTX with total parathyroidectomy plus auto-transplantation (PTX+AT) among patients with SHPT were compared. Primary outcomes were persistence and time to recurrence. Secondary outcomes were all-cause death and levels of serum parathyroid hormone (PTH), calcium, alkaline phosphatase (ALP), and phosphate measured pre-surgery, on postoperative day 1 (POD1), and one-year post-PTX in patients cured after the initial surgery.

Results: Forty-three patients received LPTX, and 78 underwent PTX-AT. Persistent SHPT was more frequent in the LPTX group ($p = 0.001$). The area under the receiver operating characteristic curve was 0.89 for POD1 PTH ($p < 0.001$). The frequencies of SHPT recurrence and all-cause mortality were not significantly different. One-year postsurgery, PTH, calcium, ALP, and phosphate levels were significantly decreased in both groups, compared with the respective preoperative values ($p < 0.001$, each).

Conclusion: LPTX resulted in a higher proportion of persistent SHPT. However, more than half of the patients could be cured and achieved satisfactory outcomes. Cured patients who underwent LPTX can be identified according to PTH levels on POD1.

Key Words: *Limited parathyroidectomy, Secondary hyperparathyroidism, Recurrence, Persistence, All-cause death*.

How to cite this article: Li Y, Yuan L, Xu B. Outcomes of Limited Parathyroidectomy in Secondary Hyperparathyroidism. *J Coll Physicians Surg Pak* 2022; **32(11)**:1386-1391.

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a common and severe complication of chronic kidney disease (CKD) caused by a dysregulation of calcium and phosphate levels. This affliction is associated with increased mortality of CKD patients.[1] At present, the available therapies for SHPT include pharmacologic treatments and surgery. Although parathyroidectomy rates have decreased globally since the advent of cinacalcet, surgery remains the only curative treatment option for patients who do not respond to medical treatment and are intolerant to the adverse effects of medication.[2,3] In particular, a few studies reported that cinacalcet did not reduce the risk of all-cause and cardiovascular mortality in patients with SHPT.[4,5] In recent years, surgical therapy has now received renewed attention.[6]

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Received: June 16, 2022; Revised: September 30, 2022; Accepted: October 11, 2022
DOI: https://doi.org/10.29271/jcpsp.2022.11.1386

Currently, three surgical options are available: subtotal parathyroidectomy, total parathyroidectomy (PTX), and total parathyroidectomy with auto-transplantation (PTX+AT). These three surgical modalities can significantly improve the quality of life of hemodialysis patients with SHPT;[7] however, all surgical options require that surgeons detect all (generally, four) parathyroid glands. However, in some cases of parathyroidectomy, it is not possible to detect all four glands even after extensive neck exploration. Thus, in a proportion of patients, one or more glands remain after surgery. So far, the consequences for patients with three or less than three glands removed are unclear as no respective studies have been conducted.

To aim of this study was to compare limited parathyroidectomy (LPTX; *i.e.*, three or less than three glands removed) with PTX+AT regarding operative and biochemical outcomes in patients with SHPT.

METHODOLOGY

This study was registered in the Chinese Clinical trial registry, (ChiCTR2100044208). This retrospective study was conducted at Jiangmen Central Hospital after obtaining approval from the hospital's Ethics Committees. In Jiangmen Central Hospital, the indication for surgery of SHPT patients was PTH levels >10-fold

above the normal value, severe bone and joint pain, pruritus, or hypercalcemia and refractory to medical treatment, including paricalcitol and phosphate binders. Earlier surgery cases were excluded to avoid selection bias from less experienced surgeons who operated before 2012. All patients who underwent parathyroid surgery to treat SHPT between January 2012 and December 2019 were included in the study. None of the patients received cinacalcet.

Exclusion criteria were age <18 years, duration of dialysis <1 year, previous history of neck surgery, incomplete records, and primary hyperparathyroidism. A total of 161 patients with SHPT were originally scheduled to undergo PTX + AT. Patients were divided into two groups, according to the number of parathyroid glands removed after bilateral neck exploration, *i.e.*, an LPTX group (52; 32.3%) and a PTX+AT group (109; 67.7%). Patients in the PTX+AT group had four or more glands removed, whereas those in the LPTX group had three or fewer glands removed. Follow-up data were compiled using electronic medical records and telephone interviews.

The primary outcomes were persistence and time to recurrence. Persistent SHPT was defined as PTH levels remaining >five-fold higher than the upper limit of normal (ULN) within the first six months after surgery. Recurrent SHPT was presumed when PTH levels were > five-fold higher than the ULN after six months post-operation.[8] Accordingly, the cure was defined as PTH levels remaining below five-fold the ULN within the first six months after surgery. The secondary outcomes were the levels of intraoperative parathyroid hormone (ioPTH), all-cause death, and levels of serum PTH, calcium, alkaline phosphatase (ALP), and phosphate on postoperative day 1 (POD1), and one-year post-PTX in patients cured after initial surgery (PTX). Permanent hypocalcemia was defined as serum calcium levels below the reference value after one year. The reference ranges were 15–65 pg/mL for PTH, 2.00–2.60 mmol/L for calcium, 0.75–1.50 mmol/L for phosphate, and 30–110 U/L for ALP.

Statistical analyses were performed using IBM SPSS Statistical Software (IBM SPSS Statistics version 22.0, IBM SPSS, USA). Normality was assessed using a Shapiro-Wilk normality test. Continuous data are expressed as means ± standard deviation when the data followed normal distribution; otherwise, they are expressed as medians (interquartile range). Count data are expressed as n (%). Where appropriate, differences among cohorts were tested using a χ^2 test, two-sample t-test, or Mann-Whitney U-test. Recurrence rates were estimated using the Kaplan–Meier method and are shown as recurrence curves. Receiver operating characteristic (ROC) curve analysis was performed to assess threshold values for PTH relative to persistence. Statistical significance was reported at $p < 0.05$. The validation sample size was calculated as previously described,[6] indicating that at least 23 patients in the LPTX group and 45 in the PTX+AT were required to obtain a power of at least 80% for identifying a hazard ratio (HR) >2.0 for recurrence, a one-sided effect, and a type I error rate of 5%.

RESULTS

A total of 121 patients were included, of which 44 underwent LPTX, and 77 underwent PTX+AT. The patient population was grouped as summarised in Figure 1. One patient in the LPTX group and three in the PTX+AT group underwent thyroid lobectomy for thyroid cancer. Thymectomy was not performed in either group.

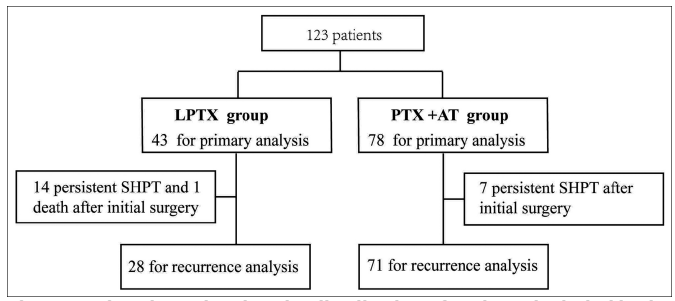

Figure 1: Flowchart showing the distribution of patients included in the study.

The baseline characteristics of the patients are shown in Tables I and II; no significant differences in age, gender distribution, and other factors occurred between the two groups, except for the number of parathyroid glands identified by ultrasound and the ratio of patients with thyroid nodules. In the LPTX group, the median number of glands identified by ultrasound scan per patient was two, and it was three in the PTX+AT group ($p = 0.04$). Furthermore, 61.3% (27/44) of patients in the LPTX group had concurrent thyroid nodules, and this proportion was 39.0% (30/77) in the PTX+AT group ($p = 0.02$). Tc-99m sestamibi (MIBI) scintigraphy was performed in 45 patients; however, no ectopic parathyroid glands were located. The average number of glands per case was 1.4 in these patients. Only one patient (with persistent SHPT) underwent renal transplantation.

The persistent disease was observed in 23 (19.0%) patients. The prevalence of persistent disease was higher in the LPTX group (36.3%; 16/44) than in the PTX+AT group (9.1%; 7/77; $p < 0.001$). Among them, one patient underwent cervical reoperation, one patient of the LPTX group underwent microwave ablation for the fourth gland, and one patient of the PTX+AT group underwent reoperation. The other patients were treated pharmacologically, with the vast majority receiving cinacalcet.

A markedly higher proportion (20/28; 71.4%) of female patients showed cured SHPT ($p = 0.01$). Additionally, the POD1 PTH level, but not that of ioPTH, was distinctively different. ROC curve data of POD1 PTH revealed a strong predictive power to distinguish cured SHPT from persistent SHPT (AUC: 0.89, 95% CI: 0.78–1, $p < 0.001$; Figure 1). The maximum Youden Index (Youden Index = Sensitivity + Specificity -1) was 0.705, with a cutoff of 121.3 pg/mL, the sensitivity of 81.3%, and specificity of 89.3%.

One patient had bilateral recurrent laryngeal nerve paresis and died of pneumonia during hospitalisation. After excluding persistent cases and deaths, 99 patients were included in recurrence analyses, *i.e.*, 28 (28.2%) in the LPTX group and 71 (71.7%) in the PTX+AT group.

Table I: Preoperative characteristics and clinical outcomes in overall patients and patients after LPTX.

	Overall patients			Patients after LPTX.		
Characteristic	**LPTX (n=44)**	**PTX+AT (n=77)**	***p*-value**	**Cured (n=28)**	**Persistence (n=16)**	***p*-value**
Age[#] (years)	48.16±9.63	45.58±11.31	0.21	47.8 ± 10.6	48.9 ± 8.0	0.71
Gender*						
Male; n (%)	19 (43.2%)	32 (41.6%)	0.86	8 (28.6%)	11 (68.7%)	0.01
Female; n (%)	25 (56.8%)	45 (58.4%)		20 (71.4%)	5 (31.3%)	
Duration of dialysis[&]; years	5.5 (5)	5 (3)	0.82	6 (5)	5 (5)	0.45
Number of glands under ultrasound[&]	2 (1)	3 (2)	0.03	2 (1)	2.5 (2)	0.3
Concomitant thyroid nodules[*]; n (%)	27 (61.3%)	30 (39.0%)	0.02	17 (60.7%)	10 (62.5%)	0.91
Peresistent SHPT; n (%)	16 (36.3%)	7 (9.1%)	<0.001	NA	NA	
Baseline PTH[&]; pg/mL	1549.6 (667.5)	1522.8 (636.5)	0.87	1549.6 (667.5)	1698.8 (725.1)	0.58
Baseline Calcium[&]; mmol/L	2.47 ± 0.20	2.49 ± 0.25	0.59	2.51 (0.27)	2.42 (0.20)	0.15
Baseline ALP[&]; U/L	187.0 (299.25)	211.0 (168.0)	0.91	186.0 (178.5)	199.0 (383.75)	0.61
Baseline Phosphate[#]; mmol/L	2.58 ± 0.49	2.67 ± 0.51	0.33	2.60 ± 0.47	2.53 ± 0.55	0.66
IOPTH[&]; pg/mL	313.2 (293.7)	258.9 (202.0)	0.07	364.6 (217.58)	449.66 (239.28)	0.08
PTH POD1[&]; pg/mL	33.9 (183.0)	17.6 (22.5)	<0.001	17.5 (30.35)	336.7 (631.25)	<0.001

*NA: Not applicable. #: Data given as mean ± standard deviation; independent samples t-test was applied. *:Data given as n (%); Pearson Chi-square test was applied. and : Data given as median (interquartile range) ; Mann-Whitney U-test was applied.*

Table II: Preoperative characteristics and clinical outcomes in patients cured after LPTX or PTX+AT.

Characteristic	**LPTX (n=28)**	**PTX+AT (n=71)**	**p-value**
Age[#] (years)	47.75 ± 10.57	45.56 ± 11.40	0.38
Gender*			
Male; n (%)	8 (28.6%)	31 (43.7%)	0.17
Female; n (%)	20 (71.4%)	40 (56.3%)	
Duration of dialysis[&]; years	6 (5)	5 (3)	0.48
Follow-up[&]; months	29 (25.75)	29 (33.27)	0.12
Number of glands under ultrasound&	2 (1)	3 (2)	0.02
Concomitant thyroid nodules*; n (%)	16 (57.1%)	23 (32.4%)	0.02
Recurrence*; n (%)	11 (39.3%)	24 (33.8%)	0.61
Hypercalcemia before surgery*; n (%)	7 (25.0%)	20 (28.2%)	0.75
Death*; n (%)	3 (10.7%)	6 (8.5%)	0.71[a]
Baseline PTH[&]; pg/mL	1549.6 (667.5)	1503.3 (647.3)	0.99
Baseline Calcium[#]; mmol/L	2.51 ± 0.20	2.49 ± 0.25	0.79
Baseline ALP[&]; U/L	186.0 ± 178.5	204.0 ± 161.0	0.91
Baseline Phosphate[#]; mmol/L	2.60 ± 0.47	2.70 ± 0.49	0.37
PTH POD1[&]; pg/mL	18.65 (39.63)	13.4 (18.3)	0.03
Calcium POD1[&]; mmol/L	1.96 (0.41)	1.87 (0.43)	0.13
PTH 1-year[#]; pg/mL	62.6 (126.85)	36.7 (101.0)	0.08
Calcium 1-year[#]; mmol/L	2.18 ± 0.33	1.95 ± 0.34	0.004
Permanent hypocalcemia 1-year*; n (%)	6 (21.4%)	44 (62.0%)	< 0.001
ALP 1-year[&]; U/L	80.5 (19.5)	70 (43)	0.44
Phosphate 1-year[#]; mmol/L	1.77 ± 0.61	1.84 ± 0.66	0.63

*#: Data given as mean ± standard deviation; independent samples t-test was applied. *:Data given as n (%); Pearson Chi-square test was applied. &: Data given as median (interquartile range) ; Mann-Whitney U-test was applied. a: Fisher Exact Test.*

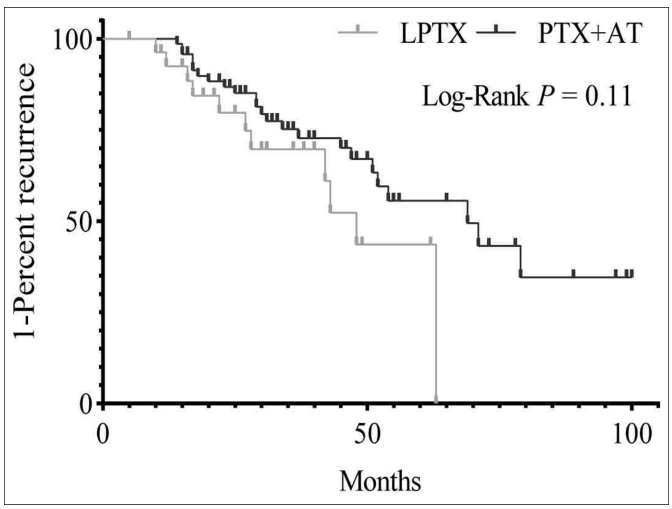

Figure 2: Analysis of the Kaplan–Meier survival curve for recurrence.

There were no differences in the follow-up period between the groups (29 months for LPTX and 33 months for PTX+AT, p = 0.12). The number of parathyroid glands was significantly higher in PTX+AT group (p = 0.02).

A total of 35 recurrences were observed, *i.e.*, 11 (39.3%) in the LPTX group and 24 (33.8%) in the PTX+AT group. The median time to recurrence was 48 months in the LPTX group and 69 months in the PTX+AT group. Recurrence rates did not differ significantly between the two groups (p = 0.61). A Kaplan–Meier survival analysis indicated no significant difference in recurrence between the groups (p = 0.12; Figure 2).

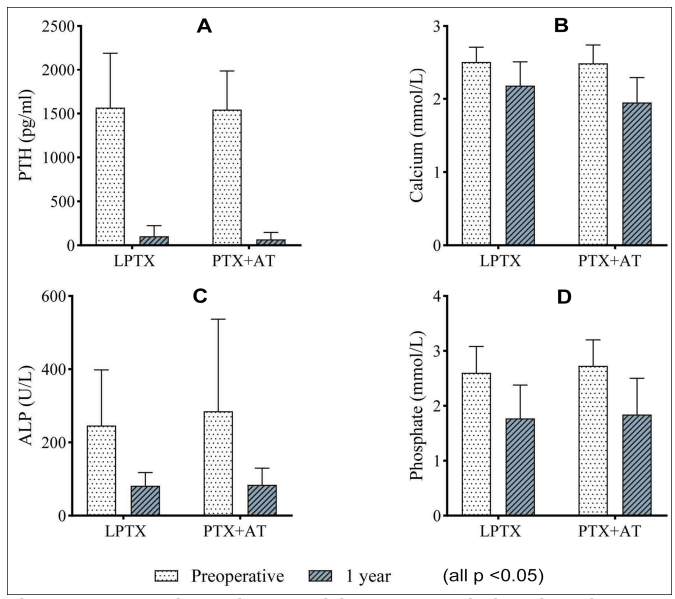

Figure 3: Comparison of PTH, Calcium, ALP, and Phosphate between preoperative and 1-year after surgery in cured patients of LPTX or PTX+AT groups. (A. PTH; B. Calcium; C. ALP; D. Phosphate).

In the LPTX group, transient hypocalcemia occurred in 17 (60.7%) patients and 6 patients developed permanent hypocalcemia (21.4%). In the PTX+AT group, temporary hypocalcemia occurred in 56 patients (78.9%), and 44 patients (62.0%) experienced permanent hypocalcemia. Permanent hypocalcemia was more common in the PTX+AT group (p <0.001).

In patients cured after initial surgery, no difference in serum PTH, calcium, ALP, and phosphate levels at baseline

occurred between the LPTX and PTX+AT groups. One year after surgery, PTH, calcium, ALP, and phosphate levels decreased significantly in both groups, compared with preoperative levels ($p < 0.001$, each; Figure 3). On POD1, serum PTH levels were significantly lower in the PTX+AT group ($p = 0.03$). One year after surgery, calcium levels were still lower in the PTX+AT group (markedly below the lower limit of normal; $p = 0.004$), whereas PTH, ALP, and phosphate levels were comparable in both groups.

During follow-up, three patients died in the LPTX group, and six died in the PTX+AT group. In the LPTX group, three patients died before the recurrence of SHPT (one from endometrial cancer, one from peritoneal infection, and one from heart failure). In the PTX+AT group, one patient died of cerebrovascular disease with severe recurrent SHPT. The other five died when SHPT was under control (two died of infection, one of bladder cancer, one of severe head injury, and one of unexplained cardiac arrest during hemodialysis). A Kaplan–Meier survival analysis indicated no significant difference in all-cause mortality between the two groups ($p = 0.534$).

DISCUSSION

Insufficient parathyroidectomy is unavoidable.[5,8-10] We aimed to provide useful insights into the basis for treatment decisions after LPTX by describing the biochemical and operative outcomes of LPTX. This study demonstrated that LPTX resulted in a higher proportion of persistent SHPT. However, 50% of patients with SHPT in our LPTX group could also be 'cured' (defined as PTH levels remaining below five times the ULN during follow-up). Furthermore, we found that the 'cured' patients in the LPTX group could also achieve satisfactory outcomes. Except for serum calcium, the other parameters including serum PTH, ALP, and phosphate were similar one year after surgery between the two 'cured' (PTX and LPTX) groups. Mortality rates did not differ significantly between the two groups.

Compared with PTX, persistent SHPT was substantially more frequent after LPTX. Previous studies showed that persistence rates among LPTX patients were 50%–75%.[10,11] Identifying patients prone to persistent SHPT remains a difficult task for surgeons, and routine preoperative MIBI scans cannot effectively detect ectopic glands in patients with SHPT.[12] This study supports the above findings that preoperative MIBI is of limited use for locating glands during SHPT.

Moreover, the usefulness of the classic Miami criterion (*i.e.*, testing positive for the persistence of SHPT if maintaining ioPTH at 10 min >50%) was limited for delayed PTH clearance in dialysis patients because of impaired renal functioning.[13-16] The ioPTH values did not significantly differ between cured patients and persistent patients in the LPTX group. PTH levels on POD1 may be a key diagnostic tool for differentiating persistent SHPT, according to the results of this study. This may help identify persistent SHPT for further exploration of remnant glands.

The presently reported patient population included a higher proportion of LPTX. Other than selection bias, the omission of thymectomy may be a further important reason. Nevertheless, some LPTX patients had an unexpectedly low level of postoperative PTH for a very long time. This may be because some people congenitally have fewer glands. Autopsy examinations found that the proportion of cases with fewer than four parathyroid glands is 3.6%–19%.[11] As an alternative explanation, the blood supply to the remnant gland may have been unintentionally interrupted during exploration. When persistent cases were removed, the recurrence rates between the LPTX and PTX+AT groups were similar. However, the authors noticed that the median time to recurrence in the LPTX group was 21 months shorter than that in the PTX-AT group. Therefore, negative results should be interpreted with caution. First, we used an HR of 2 to calculate the required sample size, according to a large real-world study. The different definitions of recurrent SHPT and HR sets would affect the minimum calculated sample size, thus the authors could not exclude type II errors. Second, the follow-up period in the real-world study was 2.5-fold longer than that in the current study. The recurrence rate between the two cured groups was similar during the short follow-up period. This lack of difference in recurrence rates was likely due to the short postoperative follow-up period.

Parathyroidectomy could decrease all-cause and cardiovascular mortality in CKD patients with sHPT, compared with medical treatments.[17,18] There was no difference in mortality among the different surgical options. Some studies have suggested that hyperphosphatemia was associated with an increased risk of all-cause mortality.[19] All-cause mortality rates were similar between the two cured groups in this study. This may be because serum ALP was not different between the two groups in the follow-up.

LPTX patients with persistent SHPT should undergo reoperation; however, most of these patients included in the present study did not undergo reoperation. As this was an observational retrospective study, the underlying reasons were unclear. After a review of the medical records, the authors speculate that there may have been several reasons. First, remnant glands detected through ultrasonography and MIBI scans could not be performed in some patients during the immediate postoperative period. Second, as reported previously,[10] some patients experienced improved clinical symptoms despite LPTX rather than PTX. Finally, and most importantly, many patients switched to drug therapy, especially when cinacalcet was first introduced on the Chinese market in 2014. The results of a pan-European, multi-centre study supported the successful use of cinacalcet in patients with persistent SHPT after PTX.[20]

The current study has some limitations. First, this was a retrospective single-centre study, with inherent limitations associated with retrospective analyses, and surgeon and patient selection bias could not be avoided. Second, patients lost to follow-up were removed from recurrence analyses, which may also have introduced bias. Third, although the minimum required sample size was used, the results should be verified through more studies with a larger sample sizes. Long-term follow-up is necessary to evaluate the long-term outcomes of LPTX. Moreover, patients with incomplete records were excluded from analyses, which may have biased the results. However, LPTX was revealed to be a treatment with acceptably low risk for some patients with SHPT. For ethical reasons, randomised controlled trials in this field should be precluded. A prospective study with a larger sample size is necessary to confirm these findings.

CONCLUSION

LPTX leads to a higher rate of persistent SHPT. Some of these patients could achieve an ideal therapeutic effect. LPTX did not indicate complete surgical failure. The POD1 PTH level is a useful way to screen out cured SHPT after LPTX.

ETHICAL APPROVAL:
The study was approved by the Ethics Committee of Jiangmen Central Hospital (No. [2021]02) and registered on ChiCTR2100044208.

PATIENTS' CONSENT:
Written informed consent were obtained from all the patients.

COMPETING INTEREST:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORS' CONTRIBUTION:
YL: Writing-original draft preparation, conceptualisation, and methodology.
LY: Data curation, visualisation, and investigation.
BX: Supervision, writing, reviewing, and editing.
All the authors have approved the final version of the manuscript to be published.

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