



Comparing subtotal parathyroidectomy and total parathyroidectomy with autotransplantation in renal transplant recipients

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Background: Both subtotal parathyroidectomy (SPTX) and total parathyroidectomy with autotransplantation (TPTX + AT) are considered acceptable surgical approaches for renal patients. It is common that parathyroid surgery is performed in patients before they undergo kidney transplantation and there is currently no evidence considering the best surgical approach in this subset of patients.

Methods: Two cohorts were identified of consecutive patients who underwent parathyroidectomy for renal hyperparathyroidism by two surgeons at a single institution over equivalent time periods (SPTX and TPTX + AT). A retrospective chart review was performed to assess these techniques, including outcomes following kidney transplantation.

Results: There were 125 patients analysed, with 56 patients who underwent SPTX and 69 who underwent TPTX + AT. Both cohorts effectively reduced PTH post operatively. There were 22 patients in the SPTX cohort and 26 in the TPTX + AT cohort that subsequently received kidney transplants. There were no cases of recurrent hyperparathyroidism and one of hypoparathyroidism (4.5%) in the SPTX patients post-transplant. There was one case of recurrent hyperparathyroidism (3.8%) and four of persistent hypoparathyroidism (15.4%) in the TPTX + AT patients post-transplant.

Conclusions: Surgery for renal hyperparathyroidism requires a careful balance of the extent of parathyroid resection to prevent persistent/recurrent disease and avoid permanent hypoparathyroidism. SPTX may be a more appropriate option in kidney transplant candidates in order to minimise the risk of long-term hypoparathyroidism.

Keywords: Subtotal parathyroidectomy; total parathyroidectomy; renal transplant

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Introduction

Secondary hyperparathyroidism is a common complication in patients with chronic kidney disease due to abnormalities of calcium and phosphate homeostasis and altered vitamin

D metabolism, resulting in parathyroid gland hyperplasia (1-4). Despite advances in the medical management of hyperparathyroidism, it is not sufficient or tolerated in many patients and parathyroid surgery remains a common

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treatment option (1,3,5-8). However, although it has been long utilised in the management of these patients there is still no consensus regarding the best surgical approach, extent and timing for parathyroidectomy (5,7-11).

Both subtotal parathyroidectomy (SPTX) and total parathyroidectomy with autotransplantation (TPTX + AT) are considered acceptable surgical approaches for renal patients. Although long term and large randomised control trials are lacking, many studies have provided evidence that both approaches significantly reduce the parathyroid hormone (PTH) with no significant differences found between morbidity, mortality, symptomatic improvement, recurrence rate and reoperation rate (3,5,7,8,10). However, a few studies demonstrated a trend that TPTX + AT had a higher proportion of patients with permanent hypoparathyroidism, however not usually to a level of statistical significance (1,12,13).

Ultimately, normalising renal function by way of renal transplant is the ideal treatment in these patients, and is the only treatment option that addresses the underlying cause (5). However, although a successful kidney transplant corrects the majority of metabolic disturbances, persistent hyperparathyroidism is still often seen post-transplant, with some studies quoting occurrence in up to 80% of patients (9,14-16). This can result in hypercalcaemia, hypophosphataemia, elevated fibroblast growth factor 23 (FGF23) and nephrocalcinosis which are all associated with unfavourable graft and patient outcomes (9,14,17). It has also been shown that parathyroidectomy performed post kidney

transplant is associated with worse graft outcomes than pre-transplant parathyroidectomy due to the haemodynamic effects of PTH on renal function (5,18).

It is therefore common that parathyroid surgery is performed before patients undergo kidney transplantation. However not all patients will be suitable candidates and have access to transplantation. As such it is worth considering whether the subset of patients likely to undergo kidney transplantation might have different requirements from parathyroid surgery and should potentially be managed differently than those likely to remain on long term dialysis.

This study compares the efficacy of SPTX and TPTX + AT for renal related secondary hyperparathyroidism (rSHPT), specifically comparing outcomes in kidney transplant recipients. We present this article in accordance with the STROBE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/ggs-23-54/rc>).

Methods

Two cohorts were identified of consecutive patients who underwent different approaches of parathyroidectomy for rSHPT by two surgeons at a single institution (King's College Hospital) over equivalent time periods (SPTX 2008-2018 and TPTX + AT 2004-2014). A retrospective chart review was performed to analyse the relevant demographics and biochemical data, to assess these techniques in patients who later received a renal transplant and in those who continued long-term dialysis.

SPTX was defined as an identification of all four glands, leaving a well vascularised remnant the size of a normal parathyroid, and including a cervical thymectomy. TPTX + AT was defined as identification and removal of all four glands, and including a cervical thymectomy, with a portion of one parathyroid being diced and reimplanted into muscle, typically in the forearm. Patients who were undergoing reoperative parathyroid surgery and patients who had no follow-up beyond their surgical admission were excluded. Groups were analysed based on the intention to treat principles. There should be no selection bias as the surgical approach was based on individual surgeon preference, not patient factors.

PTH values were reported in ng/L, with a normal reference range of the assay being 10-70 ng/L. Corrected calcium values were reported in mmol/L with a normal reference range of 2.15-2.60 mmol/L.

Persistent hyperparathyroidism was assumed if PTH

Highlight box

Key findings

- SPTX may be a safer and more appropriate option in kidney transplant candidates as it could minimise the period of hypocalcaemia and risk of long-term hypoparathyroidism.

What is known and what is new?

- Surgery for rSHPT requires a careful balance of the extent of parathyroid resection to prevent persistent or recurrent disease and avoid of postoperative permanent hypoparathyroidism.
- Both SPTX and TPTX + AT are acceptable and can effectively reduce PTH postoperatively with low risk of recurrence.
- There is a trend that the rate of persistent hypoparathyroidism is higher in TPTX + AT.

What is the implication, and what should change now?

- Whether or not a patient is likely to subsequently receive a kidney transplant should be taken into consideration when deciding the surgical approach for parathyroidectomy.

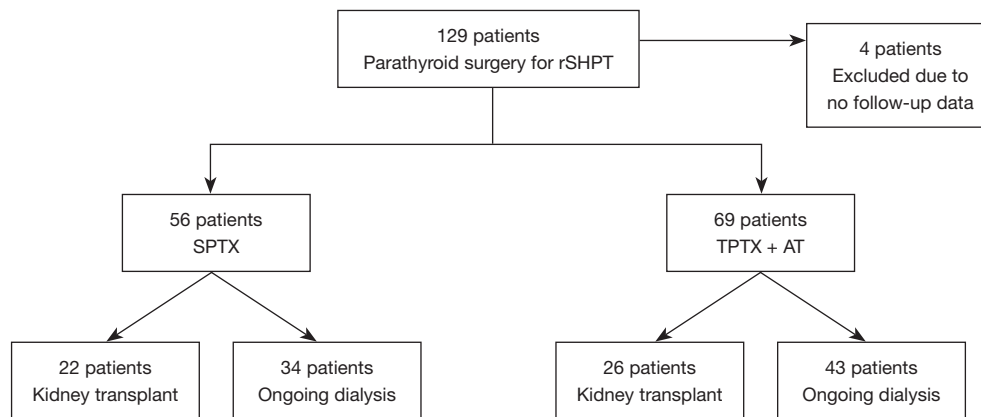


Figure 1 Flow chart of patients included in this study. rSHPT, renal related secondary hyperparathyroidism; SPTX, subtotal parathyroidectomy; TPTX + AT, total parathyroidectomy with autotransplantation.

level remained above five times the upper limit of normal within the first six months after surgery. Recurrent hyperparathyroidism was defined as a PTH level rising above five times the upper limit of normal after six months post-surgery. Permanent hypoparathyroidism was defined as persistently low or undetectable concentrations of PTH more than twelve months after surgery, making the patients dependent on calcium replacement for life.

Statistical analysis

Baseline characteristics were analysed with descriptive methods. The description of continuous variables included the mean \pm standard deviation. The description of categorical variables included relative frequencies. Statistical analysis where appropriate was performed by Chi Squared test and Fisher's Exact test. A P value of 0.05 or less was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was a retrospective clinical audit therefore exempt from ethics approval as per the NHS Health Research Authority. The individual consent for this retrospective analysis was waived.

Results

A total of 129 patients underwent parathyroid surgery for rSHPT during this time, while four patients with no follow-

up data beyond their surgical admission were excluded from analysis. Therefore, there were 125 patients evaluated, with 56 patients who underwent SPTX and 69 who underwent TPTX + AT (see *Figure 1*).

Patient demographics and baseline data of patients who underwent SPTX compared to TPTX + AT are depicted in *Table 1*. There were no statistical differences between the groups.

Four parathyroid glands were documented on final histology in 84% of patients. The average PTH preoperatively compared to postoperatively between the surgical approaches is demonstrated in *Figure 2A,2B*.

The rate of persistent rSHPT, recurrent hyperparathyroidism and permanent hypoparathyroidism across the two surgical approaches is shown in *Table 2*. The median duration of follow-up data able to be obtained was over five years [63 months, interquartile range (IQR), 34–105].

There were 22 patients in the SPTX group and 26 in the TPTX + AT group that subsequently received kidney transplants. The average time from parathyroid surgery to kidney transplant was 17 months in the SPTX group and 32 months in the TPTX + AT group. The rate of recurrent SHPT and permanent hypoparathyroidism in these subset of patients are shown in *Table 3*.

Discussion

Surgery for rSHPT requires a careful balance of the extent of parathyroid resection. The goal is to prevent persistent or recurrent disease and avoid of postoperative permanent hypoparathyroidism (5,13,19).

Table 1 Patient demographics and baseline biochemistry

Variable	SPTX (n=56)	TPTX + AT (n=69)	P value
Age (years), mean ± SD	48.6±12.6	47.0±11.4	0.231
Sex (male/female)	30/26	39/30	0.741
PTH (ng/L), mean ± SD	1,615±372	1,473±459	0.056
Calcium (mmol/L), mean ± SD	2.36±0.23	2.33±0.27	0.295
Phosphate (mmol/L), mean ± SD	1.59±0.55	1.55±0.61	0.416
ALP (IU/L), mean ± SD	220±177	237±188	0.325
Preoperative cinacalcet (yes), n (%)	13 (23.2)	6 (8.7)	0.051

SPTX, subtotal parathyroidectomy; TPTX + AT, total parathyroidectomy with autotransplantation; SD, standard deviation; PTH, parathyroid hormone; ALP, alkaline phosphatase.

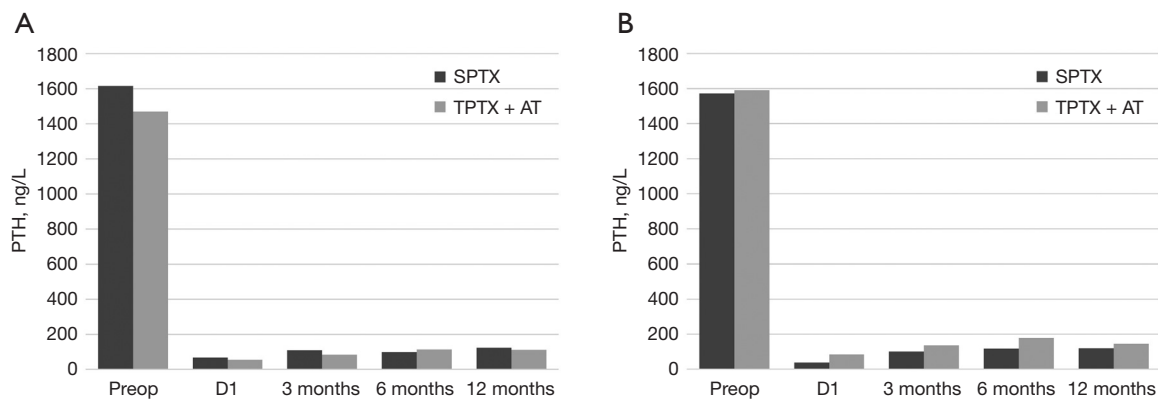


Figure 2 Serial PTH values over time for (A) all patients and (B) patients in the kidney transplant group. SPTX, subtotal parathyroidectomy; TPTX + AT, total parathyroidectomy with autotransplantation; PTH, parathyroid hormone; Preop, preoperatively; D1, day one postoperatively.

Table 2 Parathyroid status post parathyroidectomy

Status	SPTX, n (%)	TPTX + AT, n (%)	P value
Persistent rSHPT	1 (1.8)	3 (4.3)	0.655
Recurrent rSHPT	5 (8.9)	5 (7.2)	0.119
Hypoparathyroidism	3 (5.4)	10 (13.5)	0.096

SPTX, subtotal parathyroidectomy; TPTX + AT, total parathyroidectomy with autotransplantation; rSHPT, renal related secondary hyperparathyroidism.

Table 3 Parathyroid status post parathyroidectomy and subsequent renal transplant

Status	SPTX, n (%)	TPTX + AT, n (%)	P value
Recurrent rSHPT	0 (0)	1 (3.8)	1
Hypoparathyroidism	1 (4.5)	4 (15.4)	0.357

SPTX, subtotal parathyroidectomy; TPTX + AT, total parathyroidectomy with autotransplantation; rSHPT, renal related secondary hyperparathyroidism.

This study supports that both SPTX and TPTX + AT can effectively reduce PTH postoperatively. Recurrence rates over time were low in both groups (SPTX 8.9% and TPTX + AT 7.2%), which is consistent with other studies including meta-analysis calculating recurrence rates of 9.2%

for SPTX and 7.1% for TPTX + AT (4,10,13,19-21). One of the perceived benefits of TPTX + AT is that a recurrence may be easier to deal with if the autotransplanted tissue is the culprit, as reoperations in the forearm may be considered easier, however cervical reoperations may still be

necessary (4,21).

Although not reaching statistical significance due to the sample size, there was a trend that the rate of persistent hypoparathyroidism was higher in the TPTX + AT group (13.5% *vs.* 5.4%), including in the subset of patients who subsequently underwent successful kidney transplantation (15.4% *vs.* 4.5%). Other studies have also shown that TPTX + AT is related with more cases of severe hypoparathyroidism, and a higher need for calcium and vitamin D analogues (10,13,19,22).

Autotransplanted parathyroid tissue will not become functional until it has undergone neovascularisation, so transient hypoparathyroidism is more common and pronounced following TPTX + AT than SPTX (1,7). Parathyroid autotransplantation can also fail and result in long term hypoparathyroidism.

In patients who remain on dialysis long-term (non-transplanted patients or failed transplant patients), there is a higher incidence of recurrence of rSHPT, consistent with the fact that the underlying cause persists (7,18,19). The surgical strategy could therefore attempt to be more aggressive with regards to the extent of resection, due to the higher risk of recurrence.

Conversely, patients who undergo successful kidney transplantation will no longer have the same pathological drive to stimulate parathyroid cell hyperplasia. Therefore, it is less likely to recur, and they may also be less likely to recover from hypoparathyroidism in the long-term. Furthermore, it's been shown that in the presence of good renal function following transplantation, remaining hyperplastic parathyroid glands undergo apoptotic changes and lead to an overall reduction in parathyroid cell mass (5,17,23,24). Therefore, a less aggressive parathyroid resection would be suitable as they're likely to see ongoing improvement post-transplant. Additionally, after successful kidney transplantation, the reverses of the acidosis symptoms of hypocalcaemia can be exaggerated (5). As such, this papers authors would argue SPTX may be a safer and more appropriate option in these patients as it could minimise the period of hypocalcaemia and risk of long-term hypoparathyroidism.

There have been a number of studies considering timing of parathyroidectomy pre- and post-kidney transplant (15,25,26). There seems to be a benefit to pre-transplant parathyroidectomy to minimise the haemodynamic effects of sudden PTH drop on graft function, therefore, decreasing the risk of graft failure, although specific criteria for the indications for parathyroidectomy and evidence on

exact timing in transplant candidates is limited (9,11,18). This is the first study specifically considering the outcome of different parathyroidectomy approaches in patients who subsequently undergo successful transplantation.

We acknowledge that this study is limited by the fact that it is a retrospective review. It is also a small sample size for statistical analysis, however, small sample size is common in many studies on this issue due to the subspeciality nature of these procedures. Further studies with a larger sample size would be beneficial to be able to gain more evidence on the appropriate parathyroid surgical approach for transplant candidates.

Conclusions

The management of rSHPT is complex and benefits from multidisciplinary cooperation (18). Current evidence suggests parathyroidectomy when required should ideally be performed prior to kidney transplantation to prevent persistent hyperparathyroidism post-transplant and improve graft outcomes. SPTX and TPTX + AT are both effective treatment options and currently the choice depends predominately on surgeon preference. But this study would advocate that the likelihood of the patient subsequently receiving a kidney transplant should be taken into consideration when deciding the surgical approach.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-23-54/rc>

Data Sharing Statement: Available at <https://gs.amegroups.com/article/view/10.21037/gS-23-54/dss>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gS-23-54/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was a retrospective clinical audit therefore exempt from ethics approval as per the NHS Health Research Authority. The individual consent for this retrospective analysis was waived.

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