Langenbeck's Archives of Surgery (2019) 404:669–679
https://doi.org/10.1007/s00423-019-01809-7

SYSTEMATIC REVIEWS AND META-ANALYSIS

Subtotal parathyroidectomy versus total parathyroidectomy with autotransplantation for secondary hyperparathyroidism: an updated systematic review and meta-analysis

Qianqian Yuan[1] · Yiqin Liao[1] · Rui Zhou[1] · Jiuyang Liu[1] · Jianing Tang[1] · Gaosong Wu[1]

Received: 16 April 2019 / Accepted: 23 July 2019 / Published online: 3 August 2019

Abstract

Purpose The optimal surgical approach of parathyroidectomy for patients with secondary hyperparathyroidism (SHPT) has been controversial. The updated meta-analysis aimed to compare the effectiveness of subtotal parathyroidectomy (SPTX) versus total parathyroidectomy with autotransplantation (TPTX + AT).

Methods A thorough systematic search was performed on the databases of PubMed, EMBASE, and Cochrane library to identify eligible studies. Data were extracted and pooled into a meta-analysis. The primary outcomes were the symptomatic improvement, radiological changes, hypocalcemia rate, the requirement for vitamin D analogues, time to recurrence, recurrence, persistence, and reoperation rates of SPTX versus TPTX + AT.

Results A total of 18 studies with 3656 patients (1864 patients in SPTX and 1792 patients in TPTX + AT group) were included, and 15 studies were included in quantitative synthesis. No significant difference was observed in symptomatic improvement (93.3%, 89.0%; $P = 0.99$), radiological changes (85.4%, 85.3%; $P = 0.91$), hypocalcemia rate (16.6%, 18.1%; $P = 0.29$), persistence rate (6.1%, 2.0%; $P = 0.16$), time to recurrence (mean difference 1.46; $P = 0.87$), recurrence rate (9.2%, 7.1%; $P = 0.76$), and reoperation rate (5.3%, 5.8%; $P = 0.66$) between SPTX and TPTX + AT groups. Longer operative time (150 vs. 120 min), prolonged in-hospital stay (5.0 vs. 4.1 days), lower 1-month serum calcium level, and higher requirement for vitamin D analogues at 12 months were significantly observed in patients who underwent TPTX + AT compared to SPTX.

Conclusions The two surgical approaches were both effective at controlling SHPT in clinical and laboratory terms. However, most of the data shown were not statistically significant. It was acceptable that surgeons chose either SPTX or TPTX + AT for SHPT.

Keywords Secondary hyperparathyroidism · Parathyroidectomy · End-stage renal disease · Meta-analysis

Introduction

Secondary hyperparathyroidism (SHPT) is a primary cause of morbidity, such as cardiovascular mortality, ectopic calcifications, renal osteodystrophy, insomnia, and depression for patients with end-stage renal disease (ESRD) [1]. Surgical treatment for SHPT is indicated when medical treatment is ineffective [2]. The demand for parathyroidectomy increases with the time on dialysis and prolonged survival of patients with ESRD, for which the surgical options are subtotal or total parathyroidectomy with autotransplantation [2, 3]. Although proof of autografted normal parathyroid gland function is controversial, parathyroid autotransplantation of hyperplastic parathyroid tissue in patients with SHPT does function well [4, 5].

When total parathyroidectomy with autotransplantation (TPTX + AT) is performed, a fragment of parathyroid tissue is placed into the forearm, sternocleidomastoid muscle, presternal region, infraclavicular region, or lower extremities, and it has a slightly lower risk for recurrent hyperparathyroidism [6]. When subtotal parathyroidectomy (SPTX) is done, a remnant parathyroid tissue with its original blood supply is

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00423-019-01809-7) contains supplementary material, which is available to authorized users.

✉ Gaosong Wu
wugaosong@whu.edu.cn

[1] Department of Thyroid and Breast Surgery, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, Hubei, People's Republic of China

preserved in situ, and it has a lower risk of postoperative permanent hypocalcemia [7, 8]. The surgical approach in SHPT should focus on a balance between the prevention of persistent/recurrent hyperparathyroidism and avoidance of postoperative permanent hypocalcemia.

Optimal surgical approach of parathyroidectomy for SHPT patients have been explored for decade years [9]. A meta-analysis concluded that there were no real differences in clinical symptomatic improvement, imaging examination improvement, recurrence, and reoperation rate between patients who underwent TPTX + AT and those who underwent SPTX [10]. In spite of this evidence, still, the surgical strategy continued to be controversial and depended on the surgeons' preference [6]. No meta-analysis concentrated on the detailed surgical procedure, the operative time, in-hospital stay, hypocalcemia rate and the requirement for calcium and vitamin D analogues, and time to recurrence, which were significantly important for patients' postoperative quality of life. And summarizing the quality of remnant or autotransplant parathyroid tissue in parathyroidectomy would provide detailed surgical procedure for references. The aim of our research was to evaluate the symptomatic improvement, radiological changes, hypocalcemia rate, the requirement for calcium and vitamin D analogues, time to recurrence, persistence, recurrence, and reoperation rates of SPTX versus TPTX + AT.

Materials and methods

Study protocol and registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1). The protocol for this study had been registered on PROSPERO, and the registration number was CRD42019120022.

Search strategy

A systematic search of literature up to November 2018 was conducted on the electronic databases, PubMed, EMBASE, and Cochrane library to identify studies eligible for inclusion. The search strings used for the literature searching were combined using the terms "subtotal parathyroidectomy," "near-total parathyroidectomy," "parathyroidectomy," "secondary parathyroidectomy," and the Boolean "OR" or "AND." Only articles in English were included.

Selection criteria

Two independent investigators retrieved study titles and abstracts using the search strategy. Results from all searches were merged, and duplicates were removed. The inclusion criteria were articles published in English that compared SPTX with TPTX + AT in patients with ESRD and SHPT. Articles were excluded if they met any one of the following exclusion criteria: patients with primary or tertiary hyperparathyroidism and patients with minimally invasive parathyroidectomy (open unilateral parathyroidectomy, open focused parathyroidectomy, endoscopic unilateral parathyroidectomy). And conference abstracts, case reports, letters to editors, and studies with incomplete or irrelevant data were excluded. Full texts of articles that remained were obtained and evaluated; those not meeting the inclusion criteria were discarded. Any disagreements between investigators arising during the eligibility assessment were settled through a discussion. Furthermore, the reference list of the included articles was reviewed to identify more relevant articles meeting the inclusion criteria.

Data extraction and quality assessment

Both the two investigators extracted results independently from each article that fulfilled the inclusion criteria based on a standardized data extraction template. Any discrepancies were recognized. Recorded data included were study characteristics (first author, year, country, study design, age, sample size, the quality of remnant or autotransplant parathyroid tissue, and follow-up), effective rate (parathyroid hormone [PTH], phosphorus, calcium, clinical symptomatic improvement, radiological changes, and persistence rate), short-term outcomes (the operative time, in-hospital stay, hypocalcemia rate, the requirement for calcium and vitamin D analogues), and long-term outcomes (time to recurrence, recurrence rate, and reoperation rate) of different surgical procedures. Quality assessment and analysis of risk of bias of all included full-text articles were performed by YQQ and LYQ using Newcastle-Ottawa Scale (Supplement Table 3).

Statistical analysis

Statistical analysis was performed using RevMan software (Version 5.3. Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2014). For outcome measurements, differences were considered to be significant at $P < 0.05$. Heterogeneity was evaluated by visually inspecting the forest plot combined with the results of the test for heterogeneity and the I^2 statistic. $I^2 > 50\%$ was considered to be substantial heterogeneity. A fixed effects model was used in the meta-analysis unless significant heterogeneity exists among the studies. The odds ratio (OR) with 95% confidence interval (CI) was used to quantify this association.

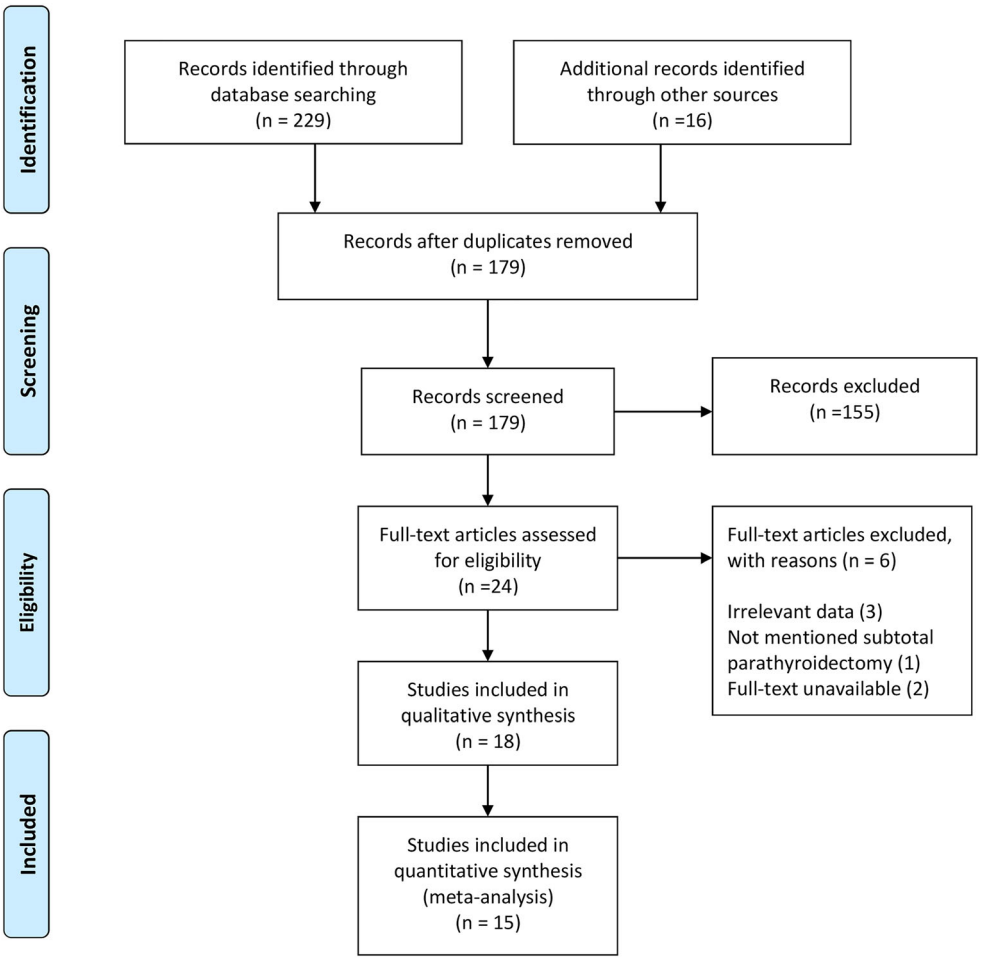

Fig. 1 Flowchart of article selection according to PRISMA statement

Results

Study identification

A flowchart describing the article selection process is shown in Fig. 1. The literature search retrieved a total of 229 articles (69 from PubMed, 86 from EMBASE, 74 from Cochrane Library, and 16 additional records identified through other sources or manual searching). Finally, 179 unique articles were reviewed after the duplicates were removed. With the application of the inclusion and exclusion criteria to the titles and abstracts, 155 articles were excluded and 24 potentially relevant full-text articles were obtained and reviewed. The characteristics of the included studies are as summarized in Table 1. A total of 18 studies were included in this review, and 15 studies were included in quantitative synthesis: two randomized controlled trials (RCTs), ten respective cohort studies, and four prospective cohort studies. The years of publication of the included articles ranged from 1979 to 2018. Five studies were conducted in the USA [9, 11, 16, 17, 25]. three in the UK [19, 21, 27], two in France [13, 15], two in Canada [14, 20], two in Germany [22, 24], one in Sweden [26], one in Romania [18], one in Turkey [23], and one in Brazil [12].

Operative time and in-hospital stay

Two studies recorded the operative time of SPTX and TPTX + AT [11, 17], and the in-hospital stay was described in four studies [11, 14, 17, 18]. Standard deviation was not recorded in these studies; data were unable to be pooled. The TPTX + AT was associated with longer operative time (median 150 vs. 120 min, $P < 0.001$; 133 min vs. 120 min, $P < 0.01$) and prolonged hospital stay (adjusted mean 5.0 vs. 4.1 days, $P < 0.001$; 4 days, IQR 3, 7 vs. 4 days, IQR 2, 6, $P < 0.01$) compared to SPTX [11, 17]. However, the average length of hospital stay was 5 (range 3–10) days for SPTX and TPTX + AT group recorded in a cohort study of Neagoe et al. [18]. Hargrove et al. reported that the median number of in-hospital days was significantly less for the TPTX + AT group 7.5 days vs. 9.5 days for the SPTX group ($P < 0.0003$) [14].

Serum calcium and PTH levels

A total of seven studies reported data on the calcium values pre- and postoperatively [12–14, 20, 21, 24, 25]. The unit or the measured methods were not consistent in these studies; hence, data were unable to be pooled. It was reduced

Table 1 The characteristics of the included studies

Author	Year	Country	Study design	Age		Sample size		The quality of remnant or autotransplant parathyroid tissue		Follow-up		In-hospital stay (days)	
				SPTX	TPTX + AT	SPTX	TPTX + AT	SPTX	TPTX + AT	SPTX	TPTX + AT	SPTX	TPTX + AT
Anderson et al. [11]	2017	USA	RCS	/	/	765	365	/	/	/	/	/	/
Cordell et al. [9]	1979	USA	RCS	38.3 (15–66)	38.3 (15–66)	36	8	30 mg	the size of 1 normal parathyroid gland	/	/	/	/
Filho et al. [12]	2018	Brazil	RCT	48 (35–56)	48 (35–56)	35	66	the size of 2 normal parathyroid glands	45, 90 fragments, 2 mm^3	12	12	/	/
Gagne et al. [13]	1992	France	RCS	44.8 ± 2.4	49.8 ± 2.3	21	28	1/3–1/2 of the gland on the vascular pedicle	150-200 mg	52	65	/	/
Hargrove et al. [14]	1999	Canada	RCS	/	/	28	8	40 mg	30-40 mg	28	23	9.5	7.5
Henry et al. [15]	1990	France	RCS	/	/	79	152	50 mg	(16–20) fragments, 1 mm^3	/	/	/	/
Koonsman et al. [16]	1994	USA	RCS	/	/	53	24	1/3–1/2 of the gland on the vascular pedicle	15 fragments, 3 mm^3	54	54	/	/
Kuo et al. [17]	2014	USA	RCS	49 (3–59)	49 (38–57)	662	236	/	/	/	/	4 (2, 6)	4 (3, 7)
Neagoe et al. [18]	2016	Romania	PCS	50.0 ± 10.6	51.1 ± 11.1	24	19	1/3–1/4 of the gland on the vascular pedicle	(9–15) fragments, 1 mm^3	38	18	4 (2–9)	3 (2–6)
Neonakis et al. [19]	1995	England	RCS	52 (1.5–105)	52 (1.5–105)	15	52	50 mg	the size of 1 normal parathyroid gland	52	52	/	/
Nichols et al. [20]	1990	Canada	RCS	41.2	41.6	34	39	50 mg	50 mg	108	108	/	/
Nicholson et al. [21]	1996	England	PCS	53 (42–62)	41 (33–48)	11	13	1/2–2/3 of the gland on the vascular pedicle	(10–15) fragments, 1–2 cubes	24	24	/	/
Rothmund et al. [22]	1991	Germany	RCT	44.8	45	20	20	60-80 mg	60 mg	40 ± 7	43 ± 9	/	/
Sakman et al. [23]	2014	Turkey	RCS	36.4 ± 11.7	42.6 ± 14.5	25	25	40-50 mg	50-60 mg	66.84 ± 32.5	64.44 ± 33.0	5 (3–10)	5 (3–10)
Schneider et al. [24]	2012	Germany	PCS	48.5 ± 0.57	48.5 ± 0.57	21	504	200 mg	/	57.6 ± 2.4	57.6 ± 2.4	/	/
Sicard et al. [25]	1980	USA	PCS	44	44	8	6	30 mg	/	17.8	9.4	/	/
Tominaga et al. [26]	1992	Sweden	RCS	44	44	19	212	40-60 mg	90 mg	/	/	/	/
Welsh et al. [27]	1984	England	RCS	43.3 (30, 57)	43.3 (30, 57)	8	15	the size of 1 normal parathyroid gland	8 fragments, 1 mm^3	60	60	/	/

RCS retrospective cohort study, *RCT* randomized controlled trial, *PCT* prospective cohort study, *SPTX* subtotal parathyroidectomy, *TPTX + AT* total parathyroidectomy with autotransplantation.

significantly between pre- and postoperative serum calcium or PTH levels. Hargrove et al. reported that there was no significant difference between groups for PTH levels, but there was a trend to a longer time to recurrence and a lower median PTH level for the TPTX + AT group [14]. The only significant difference was related to the postoperative 1-month serum calcium level, which were significantly lower in the TPTX + AT group, with a mean ± SD value of 7.56 ± 0.96 mg/dL in this group and 8.47 ± 1.16 mg/dL in SPTX group ($P < 0.001$) [18]. However, 1-month median PTH level was not significant between SPTX and TPTX + AT (28 pg/mL vs. 20 pg/mL, $P = 0.77$) [18].

Symptomatic improvement

A total of 11 studies reported data on symptomatic improvement including pruritus, bone pain, muscle weakness, soft tissue calcifications, cramps, depression, and hypertension [12–14, 16, 18, 19, 21–23, 25, 27]. High clinical symptomatic improvement was documented for the surgical approaches, 224/240 (93.3%) for SPTX and 250/281 (89.0%) for TPTX + AT (Fig. 2a). There was no statistically significant difference between the two groups in the cohort studies or RCTs. The aggregate OR, which incorporated cohort studies and the RCTs, was 0.99 (0.17 to 5.67; $I^2 = 74\%$). Immediate postoperative correction of the hyperparathyroid state in response to TPTX +AT was more marked than in response to SPTX. Koonsman et al. reported that pruritus, bone pain, and muscle weakness would be improved at the second or third postoperative day, and soft tissue calcifications would be significantly improved by 6 to 12 months after SPTX or TPTX + AT [16].

Radiological changes

Overall, radiological changes of bone disease were improved in six studies [20–23, 25, 27]. A total of 85.4% (82/96) patients in SPTX group and 85.3% (93/109) patients in TPTX + AT group showed apparent improvement of radiological changes. The approach of SPTX had a slightly higher rate of radiological improvement, but the difference was not statistically significant (OR 0.95; 95% CI 0.42 to 2.16; $P = 0.91$) (Fig. 2b). Heterogeneity was detected between these studies ($I^2 = 37\%$).

Hypocalcemia rate and vitamin D analogues requirement

With respect to hypocalcemia, there were 11 studies recorded and no significant differences existed in the two groups [13, 14, 16, 18–23, 25, 27]. The surgical approach of TPTX + AT was related with more cases of severe symptomatic hypocalcemia (18.1% [45/248]), which required treatment with calcium (intravenously and orally) and vitamin D analogues orally compared with SPTX, after which there were 16.6% (41/247, $P = 0.29$) cases. Between-study heterogeneity was found ($I^2 = 1\%$) in a fixed effect model (Fig. 3a).

Koonsman et al. [16] retrospectively reviewed 77 patients with ESRD underwent parathyroidectomy for an average of 4.5 years follow-up. On the long-term follow-up, 26 of 53 (49%) patients in SPTX group and 15 of 24 (62%) patients in TPTX + AT group were maintained on oral calcium and vitamin D analogues. The requirements for vitamin D analogues at 12 and 24 months after operation between the two groups were similar [16]. Nicholson et al. [21] compared the requirement of postoperative calcium and vitamin D analogues at 12 and 24 months after operation. A higher proportion of patients in the TPTX + AT group were receiving vitamin D analogues than those in the SPTX group ($P = 0.0175$) at 12 months, but this difference lost statistical significance at 24 months ($P = 0.087$). Overall, hypocalcemia rate and the need for calcium and vitamin D analogues tend to be higher in the TPTX + AT group but it does not reach significant difference because of the limited sample size.

Persistence rate

The data of persistent hyperparathyroidism were extracted from 4 studies [12, 13, 18, 20], seven persistent cases occurred among 114 patients in the SPTX group (6.1%), and 3 of 152 patients occurred in the TPTX + AT group (2.0%) (Fig. 3b). The difference was not statistically significant (OR 2.51; 95% CI 0.69 to 9.13; $P = 0.16$). Filho et al. have not distinguished the patients who encountered postoperative recurrent or persistent hyperparathyroidism [12]. Gagne et al. did not describe the detailed cause of persistence. In Neagoe et al.' study, two patients of persistent hyperparathyroidism post-SPTX were found a fourth (missed) inferior parathyroid in the anterior mediastinum, and a left superior gland in an upper retroesophageal ectopy respectively [18]. A large adenoma was discovered on reoperation in one patient who encountered persistent hyperparathyroidism post-SPTX in Nichols et al.'s study [20]. No heterogeneity was detected between these studies ($I^2 = 0$).

Time to recurrence

A total of 12 studies reported data on time to recurrence of hyperparathyroidism after operation [12–16, 18, 20–23, 26]. It was longer in SPTX group, ranging from 9 to 102 months compared to that reported in TPTX + AT group, ranging from 9 to 65 months, which did not reach significant discrepancy (mean difference 1.46; 95% CI − 15.66–18.58, $P = 0.87$) (Fig. 4a). Between-study heterogeneity was found ($I^2 = 94\%$). No significant difference was observed in the cohort studies (mean difference 1.98; 95% CI 22.31 to 26.27; $P = 0.87$). Data on time to recurrence were available from two

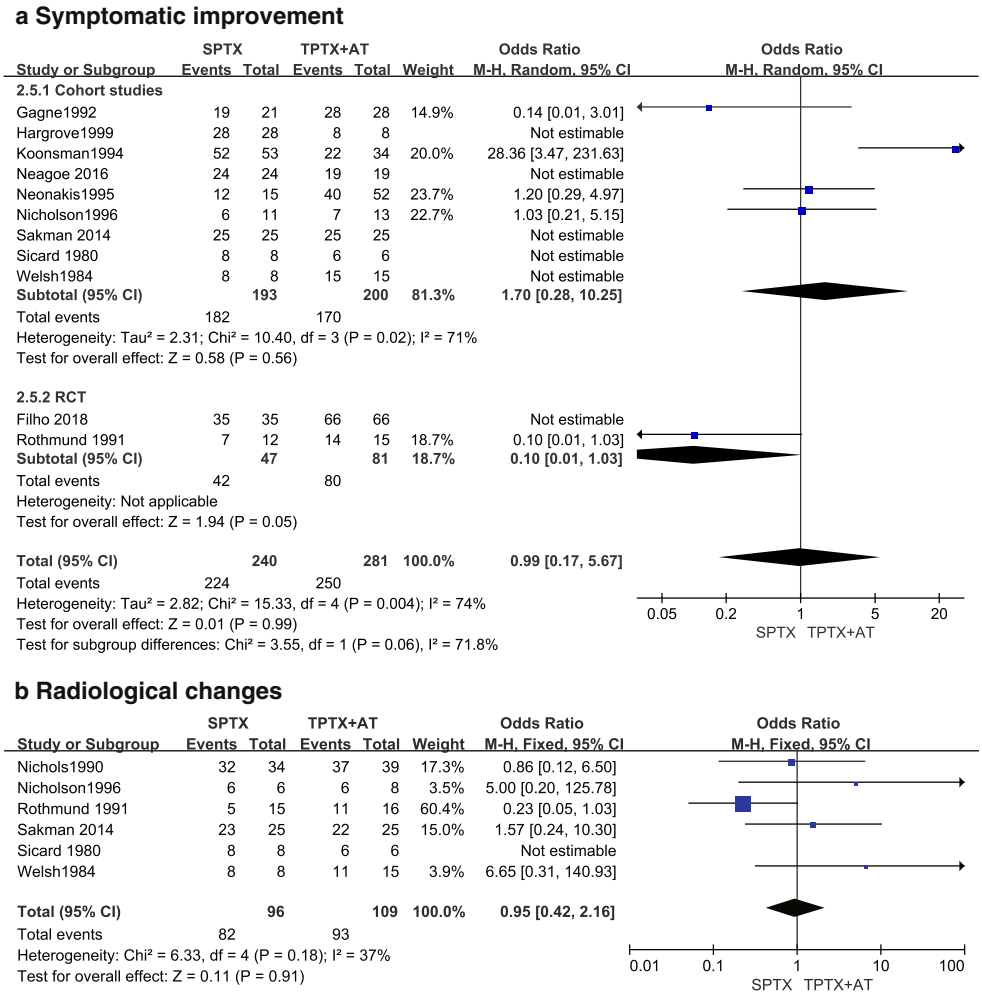

Fig. 2 Forest plot of proportion estimates. **a** Symptomatic improvement. **b** Radiological changes

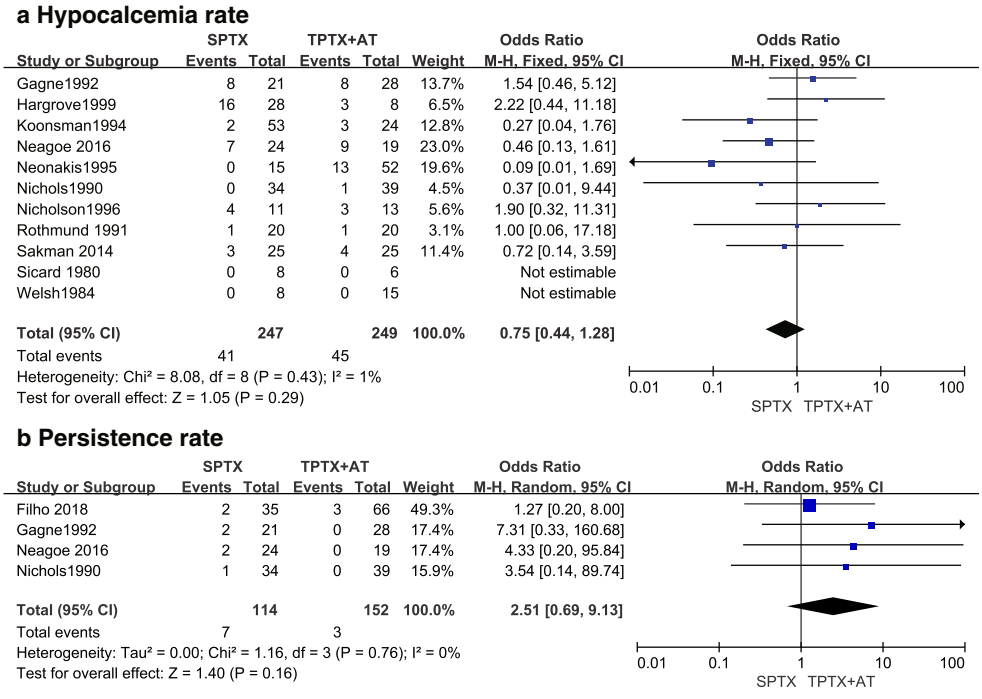

Fig. 3 Forest plot of proportion estimates. **a** Hypocalcemia rate. **b** Persistence rate

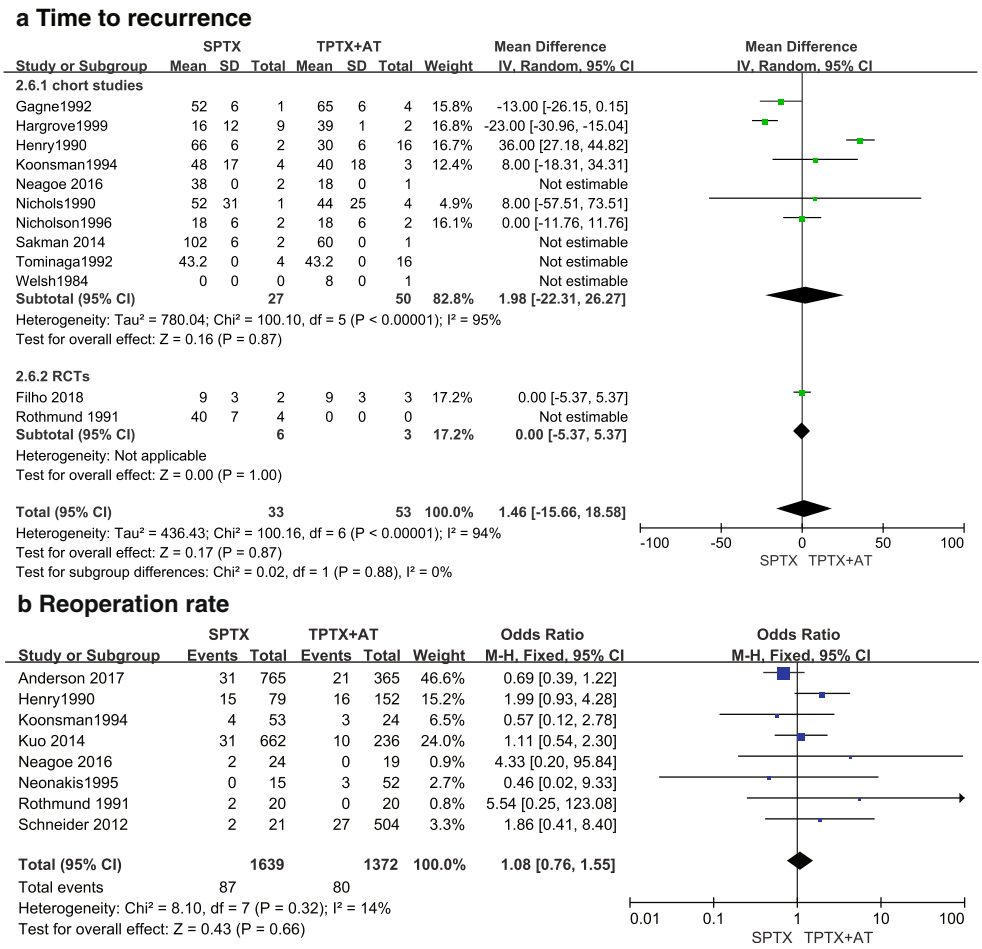

Fig. 4 Forest plot for time to recurrence (**a**) and reoperation rate (**b**)

RCTs, in which the difference was not statistically significant in a random-effect model. The high heterogeneity might arise from the dissimilar quality and pathological status of remnant or autotransplant parathyroid tissue, the different definition of recurrent hyperparathyroidism, and the variable follow-up. These variant factors might lead to the non-significant data on time to recurrence, which might have no difference actually.

Recurrence rate

Recurrent hyperparathyroidism was described for 15 studies with a six or more months follow-up after surgery [12–16, 18–27]. In total, 37 of the 401 (9.2%) patients who underwent SPTX and 84 of 1183 (7.1%) patients who underwent TPTX + AT had recurrent hyperparathyroidism. The surgical technique of TPTX + AT showed a little higher recurrence rate (OR 1.10, 95% CI 0.59 to 2.07) (Fig. 5), but the difference was not statistically significant ($P = 0.76$). Heterogeneity was found between these studies ($I^2 = 29\%$). And there was no statistically significant difference between the two groups in the cohort studies (OR 0.98; 95% CI 0.50 to 1.94; $P = 0.96$). Recurrence rate data were available from two RCTs, in which this difference was not statistically significant (OR 2.75; 95% CI 0.34 to 22.44; $P = 0.34$). Rothmund et al. [16] randomized 40 patients with SHPT to either SPTX or TPTX + AT group, describing significantly less recurrences after the latter surgery. Despite this clear statistical conclusion, the sample size was too small to determine a preferred surgical approach of TPTX + AT in SHPT.

Reoperation rate

Reoperation resulting from persistent/recurrent hyperparathyroidism was recorded for 3011 patients in eight studies, 87 of 1639 (5.3%) patients in SPTX group, and 80 of 1372 (5.8%) patients in TPTX + AT group [11, 15–19, 22, 24]. Forearm or cervical reoperations were performed in TPTX + AT group, which seemed a little higher reoperation rate, but the discrepancy was not significant (OR 1.08, 95% CI 0.76 to 1.55; $P = 0.66$) (Fig. 4b). Patients in the TPTX + AT group developed recurrence were reoperated on the graft first. Henry et al. [15], Koonsman et al. [16], Nicholson et al. [21], and Tominaga et al. [26], all of them totally removed the graft to normalize the PTH level; however, most of the patients were not cured by removal of the grafts (Table 2). In the study of Nichols et al.

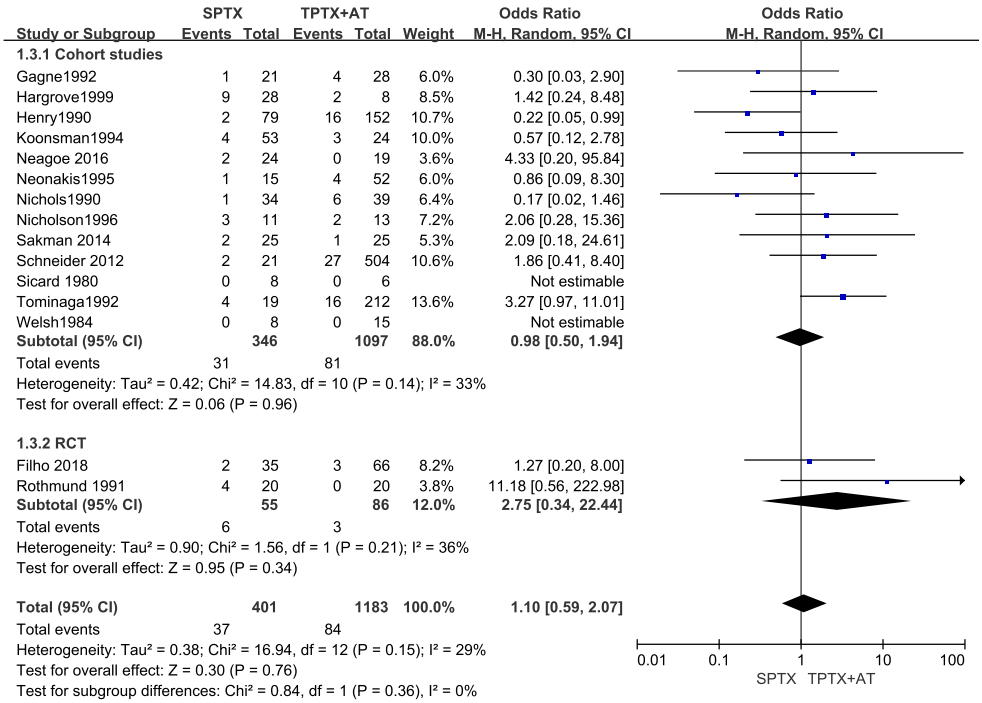

Fig. 5 Forest plot for recurrence rate

[20], four of the patients were confirmed to have definite recurrent graft, one patient had a fifth ectopic parathyroid, and one patient had three glands resected at initial operation. One of four recurrent hyperparathyroidism in the study of Neonakis et al. had been removed the graft tissue from the greater pectoral muscle [19].

Discussion

Improvement in the treatment of SHPT in chronic renal failure have facilitated guidelines required in about 15% of patients after 10 years and 38% of patients after 20 years of ongoing dialysis therapy [2]. Parathyroid surgery significantly decreased all-cause mortality in ESRD patients with SHPT by almost 30% and had also a positive effect on cardiovascular death [28].

The SPTX, TPTX + AT and TPTX are accepted surgical approaches for SHPT in the ESRD population. In the meta-analysis comparing TPTX to TPTX + AT [29], there was no significant difference in the prevalence of surgical complications, all-cause mortality, persistent hyperparathyroidism, or symptomatic improvement [29]. TPTX could significantly reduce the risk of persistent hyperparathyroidism and reoperation compared with TPTX + AT or SPTX. Simultaneously, TPTX significantly increased the risk of hypoparathyroidism [29].

While comparing SPTX with TPTX + AT, previous meta-analysis [10] has confirmed that no significant differences were observed between the surgical approaches in the symptomatic improvement, the occurrence of recurrence, and the reoperation rate. Although multiple references have reported no differences in short- and long-term outcomes between SPTX and TPTX + AT, this was the first study to conclusively demonstrate that TPTX + AT had longer operative time ($P < 0.05$), prolonged in-hospital stay ($P < 0.05$), higher rate of hypocalcemia, longer requirement for calcium and vitamin D analogues, and shorter time to recurrence.

The pooled outcome of 14 cohort studies and 2 RCTs revealed that both operations resulted in good control of SHPT with excellent symptomatic improvement. SPTX was associated with shorter operative time ($P < 0.05$), shorter in-hospital stay ($P < 0.05$), a little higher rate of symptomatic improvement, higher radiological changes, lower hypocalcemia rate, lower requirement for calcium and vitamin D analogues, longer time to recurrence, and lower reoperation rate; the difference was not statistically significant. There were two RCTs newly included in the updated meta-analysis. Rothmund et al. randomized 40 patients with SHPT to either SPTX or TPTX + AT group according to a balanced random permutation [30]. Their results revealed that serum calcium and alkaline phosphatase normalized significantly more often in the TPTX + AT group. In addition, radiological signs and clinical signs like pruritus and muscle weakness also improved significantly more after TPTX + AT. Thus, they recommended that TPTX + AT should be considered as the method of choice in the surgical treatment of SHPT [22]. Filho et al. applied the Short Form 36 Health Survey Questionnaire to 69 patients undergoing parathyroidectomy through SPTX ($n = 23$), TPTX + AT of 45 fragments ($n = 25$), and TPTX + AT of 90 fragments ($n = 21$) [12]. The operation type was stored in a concealed opaque envelope that was opened at the induction of anesthesia. No significant difference was detected in the physical component summary score change among the three groups.

Table 2 The characteristics of persistence, recurrence, and reoperation in a single study

Author	Definition of persistence	Definition of recurrence	Reoperation site in the TPTX + AT group
Anderson et al. [11]	/	/	/
Cordell et al. [9]	/	/	/
Filho et al. [12]	Represented by an insufficient decrease of PTH few days after the procedure	Higher than 9 times the upper limit of normality after 6 months postoperatively	/
Gagne et al.[13]	/	> 500 pg/mL	/
Hargrove et al. [14]	/	Postoperative PTH levels × 300 ng/L (normal range 0–55 ng/L) or greater than preoperative PTH levels	/
Henry et al. [15]	Persistent or recurrent hyperparathyroidism was based on clinical signs (bone pains, pruritus, spontaneous fractures), typical radiological signs of fibroosteoclasia, soft tissue and vascular calcifications, and laboratory findings (spontaneous hypercalcemia, marked elevation of alkaline phosphatase and serum parathyroid hormone---iPTH).		16/16 graft
Koonsman et al. [16]	Immediate iPTH values > 300 pg/mL	IPTH level above 500 pg/mL (> 6 m)	3/3 forearm
Kuo et al. [17]	/	/	
Neagoe et al. [18]	/	/	
Neonakis et al. [19]	/	/	1/4 graft, 2/4 neck
Nichols et al. [20]	/	/	4/6 forearm, 2/6 neck
Nicholson et al. [21]	/	/	2/2 forearm
Rothmund et al. [22]	/	/	/
Sakman et al. [23]	/	A high level of iPTH persisting throughout the late postoperative follow-up period that fails to respond to medical/pharmacological management.	/
Schneider et al. [24]	/	PTH levels dropped below three times the normal upper limit within the immediate postoperative setting and rose above 5 times the normal upper limit six or more months after surgery.	/
Sicard et al. [25]	/	/	/
Tominaga et al. [26]	/	/	16/16 graft
Welsh et al. [27]	/	/	/

TPTX + AT total parathyroidectomy with autotransplantation

Both the surgical approaches significantly reduced the PTH, serum calcium, and alkaline phosphatase levels, and no significant differences was observed between the SPTX group and TPTX + AT group postoperatively [12]. However, significant difference was revealed in one-month postoperative serum calcium levels, which were lower in the TPTX + AT group [18]. Furthermore, in the first postoperative month, symptoms concerning hypocalcaemia were severe, requiring important supplementation with calcium infusions and vitamin D analogues in the TPTX + AT group. Parathyroid autografts generally functioned well within 4 to 6 weeks, at which time vitamin D analogues could not be withdrawn in SHPT [31]. Wetmore et al. demonstrated that approximately 17% of patients who underwent any parathyroidectomy procedure were re-hospitalized for hypocalcemia within 90 days [32]. The requirement for vitamin D analogues was slightly larger in TPTX + AT group, and the time for calcium supplement could last for 24 months [18]. Our findings indicated that hypocalcemia rate for patients who underwent TPTX + AT was slightly higher, but the difference was not significant. Considering the potential occurrence of hypocalcemia associated with a large amount of requirement for calcium and vitamin D analogues, SPTX could be a better choice of surgical approach.

Persistent hyperparathyroidism was an insufficient decrease of PTH few days after the procedure. There was no difference in persistence of hyperparathyroidism in our meta-analysis. Persistence could arise from the missed fourth glands during the surgery, ectopic, and supernumerary parathyroid glands. Identification of ectopic/supernumerary parathyroid glands was challenging because parathyroid glands were not always in the same anatomic position. As described by Burgstaller et al., TPTX was "total" in only 73.4%, although applying a very radical concept in patients with SHPT [33]. A total of 15.9% of parathyroid gland were present in ectopic locations, with 11.6% in the neck and 4.3% in mediastinum [34]. A retrospective study reported by Pattou et al. revealed that supernumerary parathyroid glands were

present in 30% of patients with SHPT and were situated mainly in the thymus [35]. In Schneider et al.'s opinion, thymus resection should be performed only if fewer than two glands were detectable at regular positions at unilateral side [24].

Recurrent hyperparathyroidism following parathyroidectomy was a disturbing problem. A considerable quantity of functioning parathyroid tissue is needed to be left after both of the operations in order to build a balance between hypoparathyroidism and recurrent hyperparathyroidism. The quality of remnant or autotransplant parathyroid tissue ranged from 30 to 200 mg in SPTX group and from 8 fragments (1 mm^3) to 200 mg in TPTX group (Table 1). The nodular form of hyperplasia was more likely to be associated with recurrence than the diffuse form [36]. In addition, patients who did not undergo renal transplantation were on permanent dialysis, and continued uremia would stimulate the growth of remaining parathyroid tissue, increasing the potential for recurrence. Findings at reoperation included: supernumerary glands (20%), remnant hyperplasia (17%), a missed in situ hyperplastic gland (7%), a negative exploration (5%), and a hyperplastic implant inadvertently left in the neck (2%) [37].

This meta-analysis was limited by a number of factors, the most crucial of these was the majority observational design of the included studies with variable duration of follow-up and the variable measurement criteria for clinical and laboratory examinations. The results suggested that further investigation was warranted to examine the disparities in the short- and long-term outcomes after parathyroidectomy in a large population. For surgical systematic reviews of non-randomized studies, the optimal literature searches for RCT were MEDLINE and Web of Science; EMBASE did not contribute substantially to reviews with a surgical intervention [38]. This meta-analysis consisted of 14 cohorts studies and RCTs, which employed EMBASE instead of Web of Science.

Conclusions

The two surgical approaches were both effective at controlling SHPT in clinical and laboratory terms. The SPTX procedure provided higher symptomatic improvement, higher radiological changes, lower dose of calcium and vitamin D analogues, longer time to recurrence, and lower reoperation rate. TPTX + AT procedure provided lower persistence/recurrence rate. None of the data shown, however, were statistically significant. If patients had high possibility to undergo renal transplantation, SPTX was preferred. Conversely, TPTX + AT was preferred for patients with compelling reasons to avoid reoperative neck surgery. Thus, it was acceptable that surgeons chose either SPTX or TPTX + AT for SHPT according to patients' preoperative characteristics.

Acknowledgments The authors acknowledge the assistance of Prof. Xiao for language editing.

Authors' contributions Study conception and design: Gaosong Wu and Qianqian Yuan; acquisition of data: Qianqian Yuan, Yiqin Liao, and Jiuyang Liu; analysis and interpretation of data: Jianing Tang and Rui Zhou; drafting of manuscript: Qianqian Yuan; critical revision of manuscript: Gaosong Wu.

Compliance with ethical standards This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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