LITHUANIAN UNIVERSITY OF HEALTH SCIENCES
MEDICAL ACADEMY

FACULTY OF MEDICINE CLINIC OF SURGERY

Eden Simonov

Surgical treatment of renal hyperparathyroidism

(MASTER THESIS)

Thesis supervisor

Dr. Virgilius Krasauskas

Kaunas 2023

TABLE OF CONTENTS

Contents

1. SUMMARY

Master thesis by Eden Simonov

Title- Surgical treatment of renal hyperparathyroidism.

Introduction- Secondary hyperparathyroidism (SHPT) a complication of chronic kidney disease (CKD). It's characterized by an increased level of parathyroid hormone as a result of calcium and vitamin D deficiency.
Most of the patients have symptoms of bone pain, osteoporosis, kidney stones, calciphylaxis, pruritus, and muscle weakness. Options of treatment can be medical, and in severe cases or cases where a patient is resistant to medical treatment, parathyroidectomy (PTX) becomes the main option of treatment.
In this thesis, we will compare 3 options of surgical management, including total PTX without autografting, total PTX with autografting, and subtotal PTX**.**

The aim of the theses- To evaluate the methods of surgical treatment of patients with secondary hyperparathyroidism.

Objectives of the study-

1. To assess the demographic and clinical characteristics of patients with secondary hyperparathyroidism.
2. To analyze the indications for surgery and the types of performed surgeries.
3. To analyze recent literature and estimate the results of surgical methods used for treatment of secondary hyperparathyroidism.

Methodology- this study was conducted performing the research of recent scientific articles in PubMed**.** The articles included using PRISMA guidelines, the review include 1 randomized clinical trial and 17 retrospective articles

Results and conclusions- All 3 surgeries proved as effective for treatment of SHPT and reducing symptoms and PTH blood values. tPTX is the most effective in reduction of PTH level and recurrence of the disease is the lowest in this type of surgery. The conclusion is that sPTX is the most suitable surgery for patients with SHPT. sPTX proved as effective method, with good short term results and decrease complications and mean hospital stay in comparing to tPTX and tPTX+AT. Although, the rate of reoccurrence is higher in comparing to two other approaches, the focus should be on the complications.

2. ACKNOWLEDGMENT

I would like to thank the supervisor, Dr. Virgilius Krasauskas for his expert advice and encouragement throughout the master thesis process.

3. CONFLICT OF INTEREST

The author reports no conflicts of interest.

4. CLEARANCE ISSUED BY THE ETHICS COMMITTEE

My thesis was approved by the ethics committee

Kode: 302536989

5. ABBREVIATIONS

CKD- chronic kidney disease

HPT- hyperparathyroidism

PHPT- Primary hyperparathyroidism

PTH- parathyroid hormone

RLN- recurrent laryngeal nerve

sHPT- Secondary hyperparathyroidism

sPTX- subtotal parathyroidectomy

tPTX- Total parathyroidectomy

tPTX + AT- total parathyroidectomy with autotransplantation

6. INTRODUCTION

In this thesis the issue that is important among surgeons who deal with secondary hyperparathyroidism is analyzed. Hyperparathyroidism is a medical condition in which the parathyroid glands produce an increased amount of parathyroid hormone, resulting in an imbalance of calcium and phosphorus levels in the body.

There are 3 types of HPT: primary, secondary, and tertiary HPT.

Primary hyperparathyroidism is caused by one or more parathyroid gland tumors, which cause them to produce increase amount out of normal of PTH.
Secondary hyperparathyroidism, is caused by a calcium or vitamin D deficit in the body. It is common in patients with chronic renal disease, whose prevalence is almost 86% in end-stage renal disease (11, 12).
Tertiary hyperparathyroidism occurs when the parathyroid glands release an excess of PTH, generally after a lengthy period of secondary hyperparathyroidism. Some authors reserve this name for secondary hyperparathyroidism that occurs after a successful kidney transplant (27).
In healthy individuals, vitamin D activation occurs by the kidneys; in cases of renal disease, the normal kidney's function is impaired and less activated vitamin D produce, resulting in less calcium reabsorption.
In addition, in renal disease there is decreased secretion of phosphate, and as a result the body produces insoluble calcium phosphate, which also removes calcium from the circulation. Those two pathways lead to hypocalcemia, usually leading to 4 gland hyperplasia, an increase in the level of PTH and the formation of secondary hyperparathyroidism (13).

Due to overproduction of PTH, sHPT patients experience symptoms like metabolic bone disease, osteoporosis (renal osteodystrophy) neurological damage, calciphylaxis, cardiovascular damage, muscle weakness, neurologic dysfunction, and depression (16,13).

sHPT is managed with dialysis in most cases. However, 15% of patients after 10 years and 38% of patients after 20 years of dialysis will need parathyroidectomy due to aggravation of the condition (7,13). In addition to dialysis medical treatment, vitamin D and calcimimetics are also available, but these medications are not always effective

(11) and are expensive (12). Therefore, 1-2% of sHPT patients require surgery every year (12).

The surgical management of SHPT has evolved over the past few decades and the number of successful operation is increased (23). At present, there are three principal operational approaches for treating secondary hyperparathyroidism: subtotal parathyroidectomy, total parathyroidectomy, or total parathyroidectomy with autotransplantation of parathyroid tissue (11).

Subtotal parathyroidectomy is parathyroid surgery in which a portion, usually 3 and 1/2 of the parathyroid glands are removed.
In total parathyroidectomy, all 4 glands are removed. In some cases, the surgeon will implant parathyroid tissue in the muscle of the patient to provide residual parathyroid function, this type of procedure is called total parathyroidectomy with autotransplantation.

All three procedures have clear and definite efficacy in reducing PTH levels and improving patient's clinical symptoms (12). More than that, the quality of life and symptoms have been shown to improve after parathyroidectomy as well reduce all case mortality (12). There is also mounting evidence that PTX in patients with poorly controlled secondary hyperparathyroidism prolongs renal allograft survival (13).

Although quality of life improves, there are also post-operative complications, transient hypocalcaemia is the most common complication (5). Other complications that occur in all types of surgery include paralysis of the recurrent laryngeal nerve, postoperative hemorrhage, and postoperative hypocalcemia (6).

Among surgeons, there is always the question of which surgery is the best option for the patient. The purpose of the study is to compare the three existing types of surgery and determine which procedure have the best results.

The results of the thesis show that All 3 surgeries proved as effective for treatment of SHPT and reducing symptoms and PTH and phosphorus blood values. tPTX is the most effective in reduction of PTH level and recurrence of the disease is the lowest in this type of surgery. Complications and mean hospital stay are the lowest in sPTX compare to tPTX and tPTX+AT. sPTX show good short term results while tPTX+AT show good long and short term results.

7. AIM AND OBJECTIVES OF THE THESIS

The aim of the theses- To evaluate the methods of surgical treatment of patients with secondary hyperparathyroidism.

Objectives of the study-

1. To assess the demographic and clinical characteristics for patients with secondary hyperparathyroidism.
2. To analyze the indications for surgery and the types of performed surgeries.
3. To analyze recent literature and estimate the results of surgical methods used for treatment of secondary hyperparathyroidism.

8. LITERATURE REVIEW

Secondary hyperparathyroidism is a medical condition characterized by an excess of parathyroid hormone production by the parathyroid gland. This overproduction occurs due to calcium and phosphorus abnormalities in the blood and often leads to hyperplasia of the parathyroid glands. SHPT is a common complication of chronic kidney disease due to diminished renal function and reduced vitamin D metabolism. According to recent research, patients with SHPT have a higher risk of CKD progression (19).

PTH is responsible for regulating calcium and phosphorus levels in the blood. As a result of decreased calcium and vitamin D and the elevation of phosphorus levels, there is an elevation of PTH and the development of SHPT. Normally, PTH levels need to be between 10 and 65 pg/mL (1.6-6.89 pmol/L). As kidney function declines, PTH levels slowly increase. In CKD, the parathyroid hormone level is around 150–300 pg/mL (15.9-31.8 pmol/L), while in SHPT, the hormone level is 2–9 times higher (19). As a result of overfunctioning of the parathyroid gland, hyperplasia can be seen.

Most of the patients are initially asymptomatic, but as the disease progresses, symptoms start to appear. Most common symptoms are weak or fragile bones (osteoporosis), bone pain, weakness, kidney stones, muscle and joint pain, itching, and calcylaxis (9). Long-term SHPT is frequently linked to arterial and visceral calcifications, which cause disruptions of bone turnover and eventually cardiovascular morbidity and death (21).

The diagnosis of the disease can be made by biochemical blood levels of calcium and phosphate, bone biopsy (rarely performed) or X-ray, and parathyroid gland assessment by high-resolution sonography with color Doppler (US-CD), 99m Tc-MIBI scintigraphy, CT, MRI, PET, and SPECT (20).

There are different methods for treating SHPT. Because the condition arises as a result of kidney disease, most of the patients will undergo dialysis for toxin removal from the body or a kidney transplant. Kidney transplantation is the best treatment, but the number of available kidneys for transplantation is limited; hence, medical and surgical treatments become the main ways to deal with SHPT (24).

Often, it is effective to treat the SHPT with medical treatment that includes vitamin D analogs, calcimimetics, and phosphate binders (22); Vitamin D supplementation helps increase levels of calcium in the blood, leading to a reduction in PTH, and phosphate binders are useful in reducing the high phosphate condition. Calcimimetics, first introduced to the US in 2004 (23), are molecules that mimic calcium and, as a result, can lead to a reduction in PTH secretion.
All those medical management strategies proved effective in controlling SHPT in dialysis patients (23); however, surgical intervention (parathyroidectomy) may be necessary in refractory cases or in patients who cannot tolerate or do not respond to medical treatment.

The surgical management of SHPT has evolved over the past few decades. In the past, surgeries were unsuccessful, tedious, and prolonged. But, now that advances in surgical techniques and preoperative imaging allow for more targeted and effective parathyroidectomy, resulting in improved outcomes (23), in-hospital mortality rates after PTX for SHPT steadily declined between 2002 and 2011 and were <1% in recent years (23).

SHPT was treated surgically by removing one or more hyperactive parathyroid glands in order to overcome his hyperfunctioning. By removing glands, less or no PTH is produced, and in that way, electrolyte abnormalities can be corrected.
There are several indications for surgery treatment, and they include:
a) HPT that is resistant to medical treatment and calcimimetics;
b) severe SHPT, PTH > 800-1000 pg/mL (84.8- 106 pmol/l) on dialysis for more than a year without improvement with medical therapy;
c) persistent severe hyperphosphatemia;
d) cases of calciphylaxis (accumulation of calcium in small blood vessels of fat, skin, and tissues) with PTH over 500 pg/mL who do not respond quickly to calcimimetics;
e) complications associated with SHPT (22-23)

There are 3 main types of surgeries for managing SHPT, including total PTX without autografting, total PTX with autografting, and subtotal PTX (9). The optimal surgical procedure in SHPT treatment is far from established; this issue has been the subject of continuous controversy in the literature (14).

Total PTX is a procedure in which all 4 parathyroid glands are removed, resulting in a complete reduction of PTH secretion that is replaced with lifelong calcium and vitamin D supplementation (23). The risk of this type of procedure is the development of permanent hypoparathyroidism and hypocalcemia; however, the risk of recurrence is usually low.

Total PTX with auto-transplantation is a procedure in which all 4 parathyroid glands are removed, but a small amount of the healthy parathyroid tissue is implanted into the forearm or neck muscle (23). Comparing to total PTX, in this procedure there is no complete fall of PTH, which can still reserve parathyroid gland function, and therefor the risk for permanent hypoparathyroidism and hypocalcemia is lower, but the chance of recurrence is higher.

In a meta-analysis including 1108 patients performed between 1991 and 2016, it was found that both approaches were useful for SHPT treatment, but tPTX was superior for reducing the risk of SHPT recurrence and reoperation than tPTX + AT (24). Other meta-analyses that compiled nine cohort studies and one randomized controlled trial, comprising 1283 patients, found that tPTX is superior to TPTX + AT, while referring to the rate of recurrent SHPT (25).

Subtotal PTX is a less aggressive surgical approach compared to others, and it is generally recommended for patients with mild to moderate SHPT. In this procedure, three and a half of the four parathyroid glands are removed, leaving a small amount (about 40 to 80 mg) of most normal tissue in place to maintain the function of the parathyroid glands (23). It is important to note that this procedure carries a higher risk of recurrent HPT compared to the other approaches and may require recurrent surgeries.

For example, a meta-analysis of 18 studies with 3656 patients found that both SPTX and TPTX + AT are effective in the treatment of SHPT, but the rate of recurrence of the patients with SHPT was higher with subtotal PTX compared to total + AT PTx (26).

It is proven among studies that PTX improves clinical outcomes in patients with end-stage renal disease by improving biochemical parameters of mineral and bone metabolism, cardiovascular health, and mortality (22). Recent studies show that the

symptoms improved after surgery in 93.3% for TPTX plus AT and in 89.0% for SPTX (26).

Surgical management can have a variety of complications. Common complications include incision site pain and discomfort, bleeding, infection, hematoma formation, recurrent nerve injury, hypocalcemia, and hypoparathyroidism. Anesthesia-related complications such as allergic reactions, respiratory distress, or cardiovascular events are also possible.

SHPT and PTX make a small part of the surgical pathology, and they're not very popular; therefore, information about those different approaches is limited. The long-term outcomes of each of those surgeries are not very clear, so for highlighting the subject, we need further research in this area.

To sum up, we have discussed different methods of treatment for SHPT. Most often, in cases when it is resistant to medication, surgery will be required. In this research, we will try to summarize recent studies and provide more information about each method surgery and its outcome that may be helpful for further management of the disease.

9. RESEARCH METHODOLOGY AND METHODS

The main question of the systematic literature review

what is the preferred method of surgery for patients with secondary hyperparathyroidism? The research question was formulated based on population, intervention, comparison, findings and studies design (PICO) study.

- Population- patients diagnosed with SHPT and underwent surgery
- Intervention- parathyroidectomy (total, total with autotransplantation, and subtotal)
- Comparison- the patients was compared according the type of the surgery they underwent.
- Outcomes- all 3 procedure were compared in inclusion criteria, biochemical analysis, complications, rate of efficacy and recurrence.
- Study design- retrospective clinical trials, case-control clinical trials, randomized clinical trials

Systematic literature review protocol

The protocol for systematic literature review was drawn up based on PRISMA (English Preferred), 18 clinical trials that were analyzed were selected for the review.

Inclusion criteria:

Randomized clinical trials, retrospective studies

Published in English.

Published from 2005/01/01 to 2023/01/01.

Articles with full text.

Exclusion criteria:

Meta-analysis, books, literature analysis, literature review, analyzed one clinical case.

Works written not in English.

Not contain enough information.

Not relevant title or abstract.

Published in 2004/12/31 or earlier.

Information sources:

the information source was MEDLINE (PubMed) (https://pubmed.ncbi.nlm.nih.gov) and science direct (https://www.sciencedirect.com/).

Terms used:

Subtotal parathyroidectomy, total parathyroidectomy, indications for surgery, surgery, renal hyperparathyroidism, secondary hyperparathyroidism, parathyroid surgery, surgery complications, parathyroid auto-transplantation, dialysis, parathyroid surgery, parathyroid hormone

Data search and collection strategy

For this literature review PRISMA 2009 statement and checklist were used as the main resource for research methodology (28). The main search engine was PubMed (https://pubmed.ncbi.nlm.nih.gov) and science direct (https://www.sciencedirect.com/) which yielded about SHPT research work published from 2005/01/01 to the present day. Included randomized clinical trials, retrospective studies, systematic and literature reviews. (Figure 1)

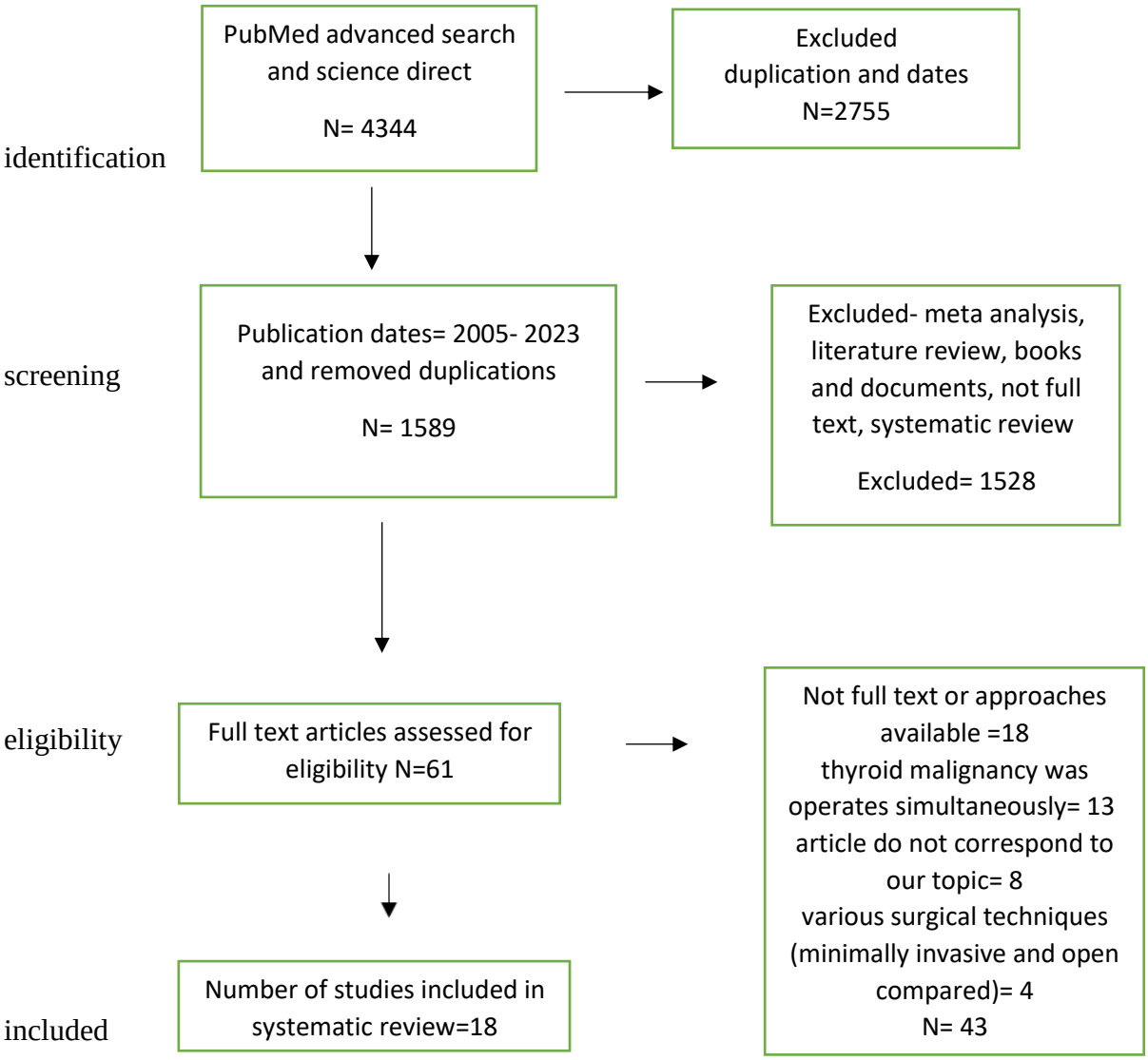

Figure 1. Selection of the articles according to PRISMA statement.

The selection of the articles according to PRISMA statement:

The information in the articles followed by specific questions made in advance for providing enough information on the topic. the information conclude;
number of sample size, age and gender, indications for surgery, duration of dialysis, symptoms before surgery and after, CDK etiology, methods for investigation, lab test results before and after the surgery, complications following surgery, rate of recurrence and symptoms relief, hospital stay duration , rate of renal transplantation after surgery and main position of the authors.

10. RESULTS AND DISCUSSION

1. Main characteristics of research

The main characteristics of the research are described in Table 1 below.
All the studies focus on one or more types of surgeries used to manage SHPT, including total parathyroidectomy (tPTX), total parathyroidectomy with autotransplantation (tPTX+AT), and subtotal parathyroidectomy (sPTX).
The table presents the main characteristics of 18 articles, including the main authors, dates of article publishing, types of research, total number of participants, samples taken for surgery, years of data collection, age, gender, and main allocation criteria.

The study includes articles that were published from 29 October 2008 to 30 January 2022 and data that was collected from 1991 to 2020. 17 studies were retrospective, and one was a randomized controlled pilot trial. The table is oriented from the first large sample size of 1500 participants (14) to the last sample size that includes a total of 25 participants (18). The age of most of the subjects is from 40–60 years, with both genders—male and female—included in each study (figure 2).

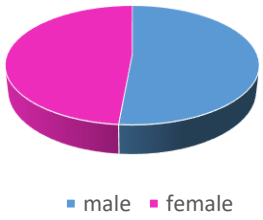

Figure 2. Comparison between the two genders in studies (n).

In most of the articles, the participants were divided by the type of surgery they underwent. Some of the articles collected the material from the surgical registry, and some of them divided the participants by other reasons, for example, willingness to undergo kidney transplant (7).

Table 1. Main characteristics of research.

Research authors	**Research date**	**Type of research**	**Total number and year of data collection**	**Samples**	**Age and gender**	**Allocation of subject group criteria**
Shasha Zhao and others (1)	2022	retrospective study	T: 1500 years: 2008-2019	tPTX= 1419	mean age: 47.14 ± 10.80 F: 609; M: 810	1500 parathyroid operations for patients suffering from refractory secondary hyperparathyroidism.
				tPTX+AT= 54	mean age: 44.68 ± 11.78 F:24 ; M: 30	
				sPTX= 7		
Anderson, K and others (2)	2017	retrospective review	T: 1130 years: 2005-2013	tPTX+AT= 365	Median age: 47 F:178; M:187	looked at a total of 1130 patients who underwent either subtotal parathyroidectomy or total parathyroidectomy with auto transplantation
				sPTX= 765	Median age: 48 F:383; M:382	
Elin Isaksson and others (3)	2018	retrospective study	T: 824 years: 1991-2013	tPTX= 388 (78%+AT)	Median age: 61 F:201; M:187	The study used the Swedish Renal Registry, the surgical registry for thyroid and parathyroid surgery, and the National Inpatient Registry to identify patients who underwent parathyroidectomy
				sPTX= 436	Median age: 60 F:203; M:233	
van der Plas and others (4)	2020	retrospective study	T: 195 years: 1998-2016	tPTX= 77	mean age: 57 ± 15 F:49; M:28	The Endocrine Surgery Unit of the University of Sydney collected surgical data prospectively of all patients undergoing PTx
				sPTX (<3 glands)= 27	mean age: 57 ± 16 F:17 ; M:10	
				sPTX (3-3.5 glands)= 91	mean age: 54 ± 15 F:58 ; M: 33	
Willemijn Y. and others (5)	2018	retrospective study	T: 187 years: 1994-2015	tPTX+AT= 109 sPTX= 78	Median age: 46 F:94; M:93	patients undergone PTx and kidney transplantation
Katja Schlosser and others (6)	2016	randomized controlled pilot trial	T: 100 years: 2007-2010	tPTX= 52	Median age: 52 F:20; M:32	patients on long term dialysis with otherwise uncontrollable SHPT
				tPTX+AT= 48	Median age: 48 F:15; M:33	
Ming-Lang Shih and others (7)	2008	retrospective review	T: 94 years: 1995-2006	tPTX=44	median age: 50.5 years F: 33; M:11	Patients are divided into subjects groups according to expectation of a kidney transplant

				tPTX+AT=50	median age: 46 years F: 33; M:17	
Parameswaran Rajeev and others (8)	2015	Retrospective cohort study	T: 81 years: 2006-2013	tPTX+AT= 57	Median age: 56.5 F:33; M:24	Patients with renal HPT who underwent TPTX þ AT and SPTX in a tertiary institution from 2006 to 2013 were studied
				sPTX =24	Median age: 54 F:16; M:8	
Onur Birsen and others (9)	2020	retrospective study	T: 79 years: 2008-2020	tPTX+AT= 35	Median age: 49.4 F:19; M:16	included 79 patients, 35 of which underwent TPTX+AT, and 44 of which underwent SPTX.
				sPTX= 44	Median age: 53.6 F:18; M:26	
Wellington Alves Filho and others (10)	2018	retrospective randomized trial	T: 69 years: 2012-2017	tPTX+AT (45 fragments)= 25	mean age: 48 F:39; M:30	randomized clinical trial comparing various parathyroidectomy strategies registered at Clinicaltrials.gov
				tPTX+AT (90 fragments)=21		
				sPTX= 23		
Y. LIANG and others (11)	2015	retrospective review	T: 63 years: 2010-2014	tPTX= 21 tPTX+AT= 21 sPTX= 21	Mean age: ±53.2 12.7 years F:25; M:38	patients were randomly divided to receive operation
Ramazan Sari and others (12)	2020	retrospective review	T: 62 years: 2012-2018	tPTX+AT= 25 sPTX= 37	F: 32 mean age 41.4 ±15.8 years M: 30 mean age of 43.1 ±16.7	patients operated upon to medical management between January 2012 and November 2018 in Baskent University's Adana Hospital, were included in the study.
Polina V Zmijewski (13)	2018	retrospective study	T: 46 years: 2006-2017	tPTX+AT =23	mean age: 48.4 ± 11.5 F:11 ; M: 12	46 dialysis patients carried a diagnosis of end-stage renal that require dialysis in operation undergoing PTX from 2006 to 2017 at a 719-bed tertiary care hospital
				sPTX= 23	mean age: 51.7 ± 15.1 F:12 ; M: 11	
Neagoe, R. M and others (14)	2016	retrospective study	T: 45 years: 2010-2014	tPTX+AT= 19	mean age: 51.1 ±11.1 F:9; M:10	Cooperatively analysed sPtx and tPtx + AT performed in the department between February 2010 and December 2014
				sPTX= 26	mean age: 50.0 ±10.6 F:8; M:16	

R. O. Santos and others (15)	2011	retrospective study	T: 38 years: 2000-2005	tPTX+AT =38	Mean age: 39.2 F: 24 ; M: 14	Included renal patients in dialysis treatment.
Xixiang Gong and others (16)	2022	retrospective study	T: 34 years: 2018-2021	tPTX= 34	mean age of 45.56 ±11.14 F:12; M:22	Yuxi People's Hospital, from January 2018 to January 2021 who had received tPTX, were retrospectively analyzed.
Chao Gu and others (17)	2019	retrospective study	T: 32 years: 2015-2018	tPTX+AT =12	mean age: 48.44±8.51 F:9 ; M: 7	Uremic patients who received parathyroidectomy (PTX) between May 2015 and May 2018
				sPTX= 20	mean age: 50.55±7.82 F:14 ; M: 8	
Min Song Kim and others (18)	2019	retrospective study	T: 25 years: 2002-2017	sPTX= 25	mean age: 53.4 ± 9.3 F:12 ; M: 13	25 patients with renal hyperparathyroidism who underwent subtotal parathyroidectomy from October 2002 to October

2. *Clinical presentation*

In Table 2 below, it is summarized the condition of the patients before surgery, the methods of investigation, and the clinical indication each study prescribed.
From all those 18 clinical trials, it is notable that the indication for PTX is approximately the same among the studies. The most common indications are high levels of PTH, SHPT that are resistant to medications, long term of SHPT and dialysis treatment, severe hypercalcemia, symptomatic patients, hyperphosphatasemia, soft tissue calcification, and calciphylaxis (1–18).
According to the findings, there are several symptoms that patients experience as a result of SHPT; the commonest are bone pain and fractures, osteodystrophy, joint and proximal muscle pain, pruritus, kidney stones, fatigue, weakness, and calciphylaxis.

One of the management options for SHPT as a result of chronic kidney disease is dialysis. The majority of patients undergo years of dialysis before PTX; in our collection of studies, the years of dialysis range from a median of 3.4 years (4) to a mean of 13 years (18) (figure 3).

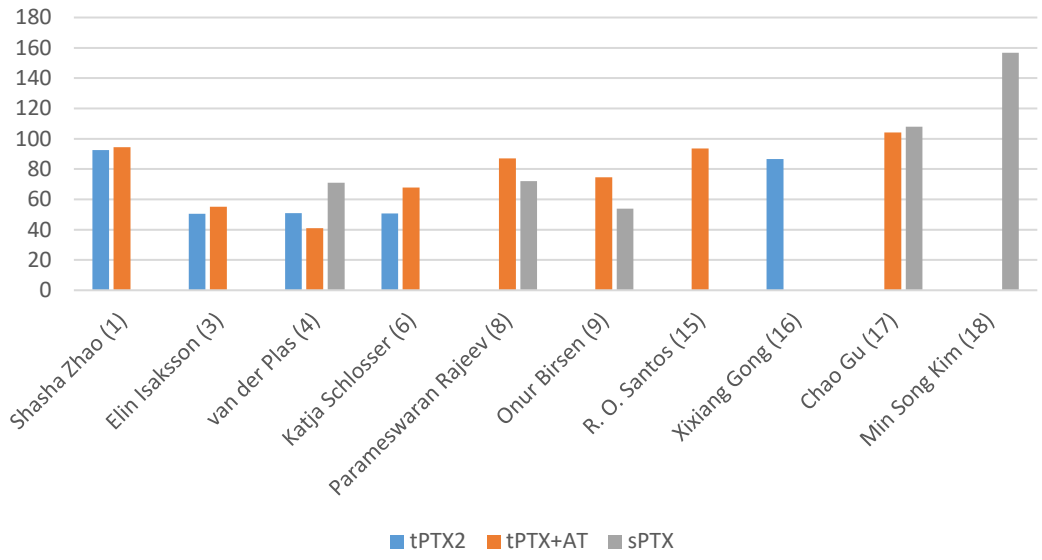

Figure 3. Duration of dialysis (months).

Several methods for investigation are available to SHPT, but most of the articles prescribe the same methods of visualization of the glands, including ultrasound and sestamibi scans; biochemical analysis (1) and CT scan is also used for diagnosis but

less commune (13,18). Those investigations give more information to the surgeons about the gland localization and often the size (7).

The etiology of chronic kidney disease varied among patients, with the most common causes being diabetes, APKD, glomerulonephritis, nephrosclerosis, pyelonephritis, and hypertension.

Amount of gland removal depends on the type of surgery. In total PTX, all 4 glands are removed, while in subtotal PTX, the number of glands removed varies from 3 to 3.5.

Table 2. Clinical presentation.

Research authors	**Samples**	Indication for surgery	Symptoms before surgery	Duration of dialysis	Chronic kidney disease etiology	method of investigation	size of gland number of gland exited
Shasha Zhao and others (1)	tPTX= 1419	PTH level > 500 pg/ml after regular drug treatment; parathyroid nodular or diffuse hyperplasia patients with related symptoms	Bone and joint pain, pathologic fractures, severe pruritus, and restless legs syndrome	92.56 ± 42.25 months	----------	ultrasound and sestamibi scan	----------
	tPTX+AT= 54			94.35 ± 53.85 months	----------		----------
	sPTX= 7			----------	----------		----------
Anderson, K and others (2)	tPTX+AT= 365 sPTX= 765	Patients with sHPT	----------	----------	----------	clinical evaluationlaboratory tests, and imaging studies.	----------
Elin Isaksson and others (3)	tPTX= 388 (78%+AT)	secondary hyperparathyroidism (SHPT) in patients with end-stage renal disease.	----------	4.2 years	APKD Diabetes Glomerulonephritis Nephrosclerosis Pyelonephritis	----------	----------
	sPTX= 436			4.6 years			
van der Plas and others (4)	tPTX= 77	Persistent SHPT and severe hypercalcemia, intractable pruritus, refractory bone pain or fractures, soft tissue calcification, and calciphylaxis.	Pruritus, bone pain or fractures, soft tissue calcification,	51 (31-83) months	----------	----------	39.5% underwent total PTx
	sPTX (<3 glands)= 27			41 (9-178) months			13.8% underwent a

			and calciphylaxis.				<3 gland removal
	sPTX (3-3.5 glands)= 91			71 (33-111) months			46.7% underwent a 3-3.5 gland removal
Willemijn Y. and others (5)	tPTX+AT= 109 sPTX= 78	Symptoms of SHPT Disease refractory to pharmacological treatment, intolerance to or noncompliance of cinacalcet, severe disease with elevated serum PTH and hypercalcemia, patient's preference, and recurrence of sHPT	----------	----------	Diabetes mellitus	----------	sPTx= 3.5 resected. Total PTx + AT= all four parathyroid glands
Katja Schlosser and others (6)	tPTX= 52	Patients on long term dialysis treatment with SHPT, high PTH	----------	50.7 ± 24.2 months	----------	----------	----------
	tPTX+AT= 48			67.8 ± 45.8 months			
Ming-Lang Shih and others (7)	tPTX=44 tPTX+AT=50	-symptomatic patient -iPTH >500 pg/ml, -hypercalcemia > 11 mg/dl, -calcium-phosphate production over 70 mg2/dl2 - other treatment failed	Bone pain, kidney stones, osteodystrophy, calciphylaxis, pruritus, osteoporosis, osteopenia, fatigue, weakness	----------	----------	neck sonography and Tc-99 m sestamibi scans	----------
Parameswaran Rajeev and others (8)	tPTX+AT= 57	Symptoms. PTH > 800 pg/Ml, hypercalcaemia and or hyperphosphataemia that were not controlled with medical therapy. pathological fractures or bone pain regardless of PTH levels.	Bone pain, fractures,	Median: 7 years (0-21)	----------	----------	
	sPTX =24			Median : 6 years (0-18)	----------	----------	(87.5%) had 3 glands removed (12.5%) had 2 glands removed
Onur Birsen and others (9)	tPTX+AT= 35	SHPT patients on waiting list	Fatigue, kidney stones, Proximal muscle and	74.6 (39-115) months	----------	scintigraphy (99mTec sestamibi) and	----------

		for renal transplantation and had been treated long term with Hemodialysis or peritoneal dialysis as a renal replacement therapy.	bone pain, joint pain, bone fracture and Calcylaxis			neck ultrasound	
	sPTX= 44			53.8 (28-92) months			3 glands were excised in 38 patients (86.3%) and 2 glands were excised in 6 patients (13.6%).
Wellington Alves Filho and others (10)	tPTX+AT (45 fragments)= 25 tPTX+AT (90 fragments)=21 sPTX= 23	Symptomatic SHPT, high PTH levels (> 500 pg/mL), detection of one or more enlarged parathyroid gland (> 500 mm 3 or diameter greater than 1 cm), (3) hypercalcemia (> 10.2 mg/dL) and/or hyperphosphatemia (> 6mg/dL).	----------	----------	----------	----------	----------
Y. LIANG and others (11)	tPTX= 21 tPTX+AT= 21 sPTX= 21	- preoperative secondary hyperparathyroidism - no symptom improvement after 3-6 months of medical therapy - blood PTH >1000 ng/L - severe hypercalcemia or hyperphosphatemia - >1 parathyroid hyperplasion lesion	Bone pain, pruritus	----------	----------	ultrasonography	----------
Ramazan Sari and others (12)	tPTX+AT= 25 sPTX= 37	Symptoms of SHPT elevated PTH	Bone pain and malaise	----------	----------	Scintigraphy and ultrasonography	----------
Polina V Zmijewski (13)	tPTX+AT =23	SHPT patient on dialysis, symptomatic disease	bone pain and fatigue.	----------	----------	sestamibi and 4-dimensional CT imaging	weight of the parathyroid glands removed was 4.4 ± 5.0 g
	sPTX= 23						weight of the parathyroid

							glands removed was 2.4 ± 1.7 g
Neagoe, R. M and others (14)	tPTX+AT= 19 sPTX= 26	symptomatic secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on maintenance dialysis.	Osteoarticular pains, pruritus, and muscle weakness	----------	----------	neck ultrasonography and Tc-99m sestamibi parathyroid scans	----------
R. O. Santos and others (15)	tPTX+AT =38	persistent hypercalcemia not responsive to medical interventions and/or persistent hyperphosphatemia despite the continued use of dietary phosphorus restriction and SHPT symptoms	Pruritus, severe bone pain, fractures or high risk of fracture, skeletal deformities, extra skeletal calcifications, development of calciphylaxis, and osteodystrophy.	7.8 (1–13) years	----------	----------	four-gland excision
Xixiang Gong and others (16)	tPTX= 34	Severe SHPT that did not respond to medical treatment and was ineligible for kidney transplantation	Bone pain, arthralgia,, decrease limb movement, pruritus,	86.6 ± 32.2 months	Glomerulonephritis, hypertension, Diabetes mellitus, Gout, nephropathy and Congenital single kidney	----------	142 parathyroid glands were removed, 21 ectopic glands (14.78%).
Chao Gu and others (17)	tPTX+AT =12	Symptomatic SHPT, hyperparathyroidism secondary to uremia	Bone pain and muscle weakness	104.13± 52.25 months	diabetes, Chronic glomerulonephritis, hypertensive renal cirrhosis, chronic pyelonephritis, polycystic kidney	----------	----------
	sPTX= 20			107.95± 45.12 months			3 semi parathyroid glands are removed
Min Song Kim and others (18)	sPTX= 25	(iPTH; usually >500 pg/mL) and hypercalcemia despite adequate medical treatment	Bone and joint pain, arthralgia, pruritus, fatigue, diarrhea, and	156.8±79.5 months	Hypertension, glomerulonephritis, polycystic kidney disease,	99mTc-sestamibi scanning, neck	----------

		and those with osteoporosis or subjective symptoms.	abdominal pain. asymptomatic (44%)		diabetes mellitus, hydronephrosis, renal cell carcinoma, and systemic lupus erythematosus	ultrasonography (US), and computed tomography (CT)	

3. Blood test results

Table number 3 presents a summary of the PTX effect on biochemical analysis. The values of PTH, calcium, and phosphate measured before and after the surgery were used to evaluate the effectiveness of the surgery. Some of the studies prescribed the biochemical change after a longer follow-up, which helps with understanding the long-term results of parathyroid surgery.

The studies prove that the levels of PTH after all types of PTX dramatically decrease by more than 80%. The highest pre-operative value is 2,390.77±891.67 [pg/mL] (253.34 ± 94.5 [pmol/L]), which dropped to 61.67±49.19 [pg/mL] (6.5 ± 5.2 [pmol/L]) after PTX, this means that the doping was approximately 97.4% (17). Another example is a study with 1500 patients who undergo tPTX and tPTX+AT; the reduction of PTH level was 99% (1).
In addition to these facts, in the table is notable that in the follow-up period of patients who undergo tPTX, the level of PTH continues to decrease (may be minor elevation in small studies) and there is no evidence of big elevation in the case of successful surgery (4, 6, 11, 16), whereas in patients who undergo tPTX+AT or sPTX, we can observe a elevation of PTH in the follow-up period.

While comparing the 3 types of surgeries, in the aspect of PTH reduction it is notable that the most effective surgery for reduction of short- and long-term PTH is tPTX. Comparing to sPTX, tPTX+AT is superior in the reduction of PTH.

In the aspect of pre- and post-operative calcium, we can observe that the calcium level remains steady with a slight reduction in all types of surgeries that provided information about the first sample. Also, in the follow up period the calcium is steady with minor elevation or reduction.

Phosphorus levels decreased in all types of operations, with the most effective reduction in tPTX (4) compared to tPTX+AT and sPTX. Also we can see that tPTX+AT have better reduction compered to sPTX (8, 9, 10, 14).

So, table number 3 suggests that PTX leads to a sustained decrease in all biochemical parameters: PTH level, calcium level, and phosphorus level. There is evidence that tPTX is most effective in most aspects.

Table 3. Blood test results.

Research	**Samples**	**PTH level**			**Calcium level**			**Phosphate level change**
		Before surgery (mean)	**After surgery** first sample	**Follow up**	**Before surgery**	**After surgery** First sample:	**Follow up**	
Shasha Zhao and others (1)	tPTX= 1419	1413.90 [pg/mL]	2.7 [pg/mL]	----------	2.46 ± 0.24 (mmol/l)	1h :2.35 ± 0.25	1d: 2.09 ± 0.34 2d: 2.23 ± 0.34 3d : 2.21 ± 0.30	From: 2.24 ± 0.56 (mmol/l) to 1 h: 2.07 ± 0.57 1d: 1.77 ± 0.56 2 d: 1.41 ± 0.46
	tPTX+AT= 54	1313.50 [pg/mL]	6.2 [pg/mL]	----------				
Elin Isaksson and others (3)	tPTX= 388 (78%+AT)	Median IQR: 104.0	Median IQR: 4.6	----------	----------	----------	----------	----------
	sPTX= 436	Median IQR: 79	Median IQR: 11	----------	----------	----------	----------	----------
van der Plas and others (4)	tPTX= 77	1,070 [pg/mL]	7 [pg/mL]	3m: 4 6m: 4 1y: 4 [pg/mL]	2.54 [mmol/L]	2.28 [mmol/L]	3m: 2.28 6m: 2.26 1y: 2.30 [mmol/L]	From 1.77 to 1.22 mmol/L (31.07% reduction)
	sPTX (<3 glands)= 27	471 [pg/mL]	35 [pg/mL]	3m: 25 6m: 19 1y: 119 [pg/mL]	2.53 [mmol/L]	2.29 [mmol/L]	3m: 2.21 6m: 2.28 1y: 2.17 [mmol/L]	From 1.31 to 1.21 mmol/L (7.6 % reduction)
	sPTX (3-3.5 glands)= 91	1087 [pg/mL]	23 [pg/mL]	3m: 37 6m: 32 1y: 63 [pg/mL]	2.56 [mmol/L]	2.37 [mmol/L]	3m: 2.27 6m: 2.33 1y: 2.36 [mmol/L]	From 1.66 to 1.30 mmol/L (21.6% reduction)
Willemijn Y. and others (5)	tPTX+AT= 109 sPTX= 78	866 pg/mL (median)	61 pg/mL (median)	reduction During surgery: 86%; after 3m: 93%	2.6 pg/mL (median)	2.3 pg/mL (median)	----------	----------
Katja Schlosser and	tPTX= 52	1329.8 ± 1048 ng/L	54.7 ± 201.7 ng/L	36 m: 31.7 ± 43.6 ng/L	2.5 ± 0.2 ng/L	2.0 ± 0.2 ng/L	24 m: 2.2 ± 0.2 ng/L	----------

others (6)	tPTX+AT= 48	1163.5 ± 725.3 ng/L	53.4 ± 103.3 ng/L	24 m: 98.2 ± 156.8 ng/L	2.4 0.2 ng/L		24 m: 2.1 ± 0.2 ng/L	----------
Ming-Lang Shih and others (7)	tPTX=44	1262 (pg/dl) (median)	----------	----------	10.8 [mg/dL] (median)	----------	----------	Pre operation 6.8 [mg/dL] (median)
	tPTX+AT=50	1039 (pg/dl) (median)	----------	----------	10.9 [mg/dL] (median)	----------	----------	Pre operation 6.2 [mg/dL] (median)
Parameswaran Rajeev and others (8)	tPTX+AT= 57	216.0 (pmol/L)	0.8(pmol/L)	----------	2.58 (mmol/L)	2.01 (mmol/L)	----------	From 2.07 to 0.93 (mmol/L) (55% reduction)
	sPTX =24	175.0 (pmol/L)	13.5 (pmol/L)	----------	2.49 (mmol/L)	2.08 (mmol/L)	----------	From 1.95 to 1.07 (mmol/L) (45% reduction)
Onur Birsen and others (9)	tPTX+AT= 35	1446.8 SD 289 pmol/L	39.6 SD 17 pmol/L	----------	9.3 SD 1.2 mmol/L	6.9 SD 1.3 mmol/L	----------	From 2.4 SD 0.6 to 1.2 SD 0.4 mmol/L
	sPTX= 44	1358.7 SD 315 pmol/L	146.9 SD 45 pmol/L	----------	9.1 SD 0.8 mmol/L	6.8 SD 1.1 mmol/L	----------	From 2.1 SD 0.9 to 1.3 SD 0.6 mmol/L
Wellington Alves Filho and others (10)	tPTX+AT (45 fragments)= 25	Median: 1630 [pg/mL]	6m: Median: 66 [pg/mL]	12m: Median-80 [pg/mL]	9.8 [mg/dL]	6m: 8.5 [mg/dL]	12m:8.8[mg/dL]	From 5.4 to 4.6 (6m) [mg/dL] (14.8% reduction)
	tPTX+AT (90 fragments)=21	Median:1329 [pg/mL]	6m: Median: 124 [pg/mL]	12m: Median-126[pg/mL]	9.8 [mg/dL]	6m: 8.2[mg/dL]	12m: 8.9[mg/dL]	From 4.7 to 4.1 (6m) [mg/dL] (12.7% reduction)
	sPTX= 23	Median: 1552 [pg/mL]	6m: Median: 90 [pg/mL]	12m: Median: 121[pg/mL]	9.7 [mg/dL]	6m: 8.4 [mg/dL]	12m:8.5[mg/dL]	From 5.8 to 5.3 (6m) [mg/dL] (8.6% reduction)
Y. LIANG and others (11)	tPTX= 21	1985.22 ± 684.15 ng/L	54.43 ± 10.22	1m:65.41 ± 19.41 3m:60.41 ± 18.41 6m: 55.42 ± 17.56 ng/L	2.26 ± 0.49 [mg/dL]	2.20 ± 0.34 [mg/dL]	1m: 1.39 ± 0.40 3m: 1.55 ± 0.52 6m: 1.60 ± 0.45 [mg/dL]	----------
	tPTX+AT= 21	1798.32 ± 785.4 ng/L	48.57 ± 14.43	1m:72.68 ± 25.41	2.18 ± 0.55 [mg/dL]	2.12 ± 0.24 [mg/dL]	1m: 1.56 ± 0.91	----------

				3m:80.21 ± 20.41 6m: 85.12 ± 26.41 ng/L			3m: 1.90 ± 0.88 6m: 2.27 ± 0.78 [mg/dL]	
	sPTX= 21	1895.42 ± 542.27 ng/L	185.43 ± 85.4	1m: 190.22 ± 90.89 3m: 205.46 ± 85.41 6m: 225.8 ± 90.21 ng/L	2.21 ± 0.48 [mg/dL]	2.15 ± 0.78 [mg/dL]	1m: 2.10 ± 0.89 3m: 2.25 ± 0.48 6m: 2.40 ± 0.52 [mg/dL]	----------
Ramazan Sari and others (12)	tPTX+AT= 25	1649.8 ng/L	135.5 ng/L	1w:192.8 1m:226.5 6m:270.6 ng/L	9.262 [mg/dL]	7.367 [mg/dL]	1w: 7.738 1m: 7.51 6m:7.971 [mg/dL]	----------
	sPTX= 37	1418.1 ng/L	154.4 ng/L	1w:164.2 1m:257.8 6m:320.9 ng/L	9.603 [mg/dL]	7.452 [mg/dL]	1w: 8.103 1m: 7.803 6m:8.265 [mg/dL]	----------
Polina V Zmijewski (13)	tPTX+AT =23	1936.7±1076.1 [pg/mL]	9.5 ± 4.2 [pg/mL]	6m: 87.3 ± 98.7 [pg/mL]	9.3 ±1.0 [mg/dL]	7.9 ± 1.3 [mg/dL]	6m: 8.5 ± 1.2 [mg/dL]	----------
	sPTX= 23	1,599.7 ± 794.0 [pg/mL]	32.6 ± 26.0 [pg/mL]	6m: 238.7 ± 302.8 [pg/mL]	9.0±0.9 [mg/dL]	7.7 ± 0.8 [mg/dL]	6m: 8.7 ± 1.2 [mg/dL]	----------
Neagoe, R. M and others (14)	tPTX+AT= 19	Median: 2439 [pg/mL]	1m: 36.6 [pg/mL]	18m: 61.2 [pg/mL]	9.50± 0.51 [pg/mL]	1m: 7.56± 0.96 [mg/dL]	18 m: 8.66± 0.74 [mg/dL]	From 5.86± 1.31 [pg/mL] to 3.25±0.61 [mg/dL]
	sPTX= 26	Median: 2131 [pg/mL]	1m: 28 [pg/mL]	18m: 45.3 [pg/mL]	9.02± 0.84 [pg/mL]	1m: 8.47± 1.16 [mg/dL]	18 m: 8.68± 0.8 [mg/dL]	From 6.17± 0.76 to [pg/mL] 3.91±1.61 [mg/dL]
R. O. Santos and others (15)	tPTX+AT =38	1711 [pg/mL]	1 y: 73.5 [pg/mL]	3y: 82 5y: 133 [pg/mL]	----------	----------	----------	----------
Xixiang Gong and others (16)	tPTX= 34	1338.10 pg/mL (median)	9.68 pg/mL (median)	1w: 1.47 6m: 17.88 pg/mL (median)	2.36 (mmol/L) (median)	2.04 (mmol/L) (median)	1w: 2.10 6m: 2.05 mmol/L) (median)	From 2.32 (mmol/L) to 1.11 (mmol/L)

Chao Gu and others (17)	tPTX+AT =12	1,788.02±789.15 [pg/mL]	26.61±18.38 [pg/mL]	1m: 28.36±24.21 6m: 32.98±5.36 12m: 56.73±16.88	----------	----------	----------	----------
	sPTX= 20	2,390.77±891.67 [pg/mL]	61.67±49.19 [pg/mL]	1m: 55.61±49.18 6m: 73.14±33.19 12m: 85.22±29.52	----------	----------	----------	----------
Min Song Kim and others (18)	sPTX= 25	1199 ± 571.3 [pg/mL]	49.2 ± 47.6 [pg/mL]	----------	10.5 ± 1 [mg/dL]	6m: 8 ± 1 [mg/dL]	----------	----------

4. Complications

Among all the clinical trials that were included in the study, the most concerning issue that arose was the complication following PTX. In table number 4, all the common complications that can occur following each one of the surgeries prescribed are summarized, including tPTX, tPTX+AT, and sPTX. The most common complications mentioned in the articles are: hypocalcemia, hypoparathyroidism, permanent or transient vocal cord palsy, neck hematoma, wound infection or sepsis, postoperative bleeding, and cardiopulmonary complications. It is also important to note that not all the articles provide information about the complication following surgery.

The results show that the postoperative complication rate is ranging from 7.9% (5) to 36.2% (1), but this information is not mentioned in all articles, which makes it difficult to come to a conclusion.

The most common complication after PTX is hypocalcemia, ranging from transient hypocalcemia to a permanent one. The range of complications starts from 7% (4) to 100% (17) and it seems to be higher on both types of total PTX with or without autotransplantation (figure 4) compared to subtotal (11, 12, 13, 14). Although, there are some trails that hypocalcemia is higher in total PTX there are some articles that do not show difference in complications between groups (4, 8, 17).

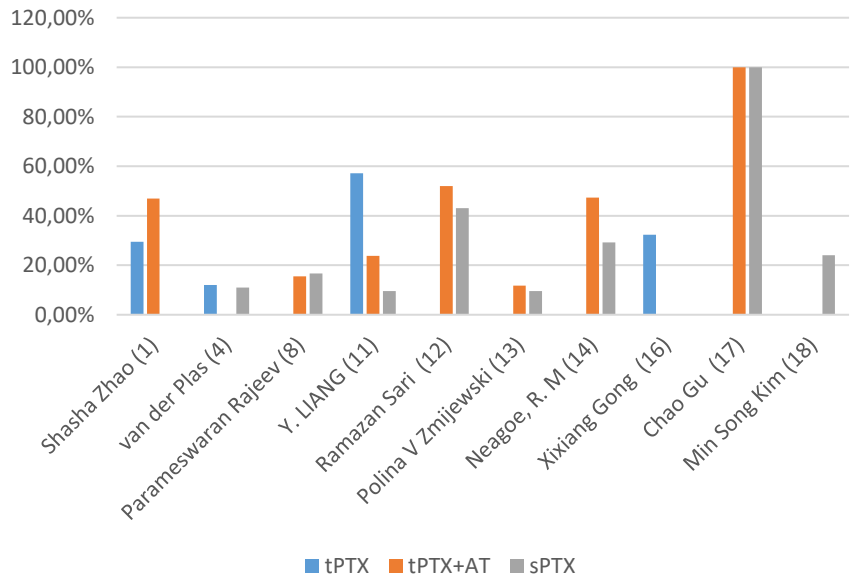

figure 4. postoperative hypocalcemia (%).

Other complications that can be observed are hypoparathyroidism, ranging from 0% (4) to 22% (12), and transient vocal cord palsy, ranging from 0% (4,8,16, 18) to 18% (7), but they are much less common than hypocalcemia.

Postoperative complications that are related to the procedure, including infection or sepsis of the wound that range from 0% (11, 16, 18) to 16.7% (17), bleeding at the site of surgery or neck hematoma that range from 0% (7, 11, 14, 16, 18) to 4.8% (11), and cardiopulmonary complications that range from 2.7% (2, 12) to 29% (3), are presented at lower rates than the other complication.

The incidence of complications varied among the studies, and the type of surgery performed may influence the rate and type of complications observed. As more invasive the procedure like tPTX or tPTX+AT, the more complications can be found.

Table 4. Complications.

Research	**Samples**	**Posoperative complication rate**	**Hypocalcemia**	**hypoparathyroidism**	**Permanent vocal cord palsy**	**Transient vocal cord palsy/ RLN injury**	**Neck hematoma**	**Wound infection/ sepsis**	**Postoperative bleeding**	**Cardiopulmonary**
Shasha Zhao and others (1)	tPTX= 1419	36.20%	Sever: 496 (29.48%)	----------	----------	37 (2.47%)	----------	62 (4.13%)	49 (3.27%)	----------
	tPTX+AT= 54	----------	Sever: 30 (46.94%)	----------	----------	----------	----------	----------	----------	----------
Anderson, K and others (2)	tPTX+AT= 365	15.1%	----------	----------	----------	----------	----------	Sepsis: 8 (2.2%)	6 (1.6%)	10 (2.7%)
	sPTX= 765	15.0%	----------	----------	----------	----------	----------	Sepsis: 14 (1.8%)	5 (0.7%)	35 (4.6%)
Elin Isaksson and others (3)	tPTX= 388 (78%+AT)	----------	----------	----------	7 (1.8%)	----------	----------	----------	----------	Cardiovascular event: 114 (29%)

	sPTX= 436	----------	----------	----------	11(2.5%)	----------	----------	----------	----------	Cardiovascular event: 59 (14%)
van der Plas and others (4)	tPTX= 77	----------	9 (12%)	0	----------	1 (1.3%)	----------	----------	2 (2.6%)	----------
	sPTX (<3 glands)= 27	----------	2 (7%)	0	----------	2 (7.4%)	----------	----------	0	----------
	sPTX (3-3.5 glands)= 91	----------	10 (11%)	0	----------	0	----------	----------	2 (2.2%)	----------
Willemijn Y. and others (5)	tPTX+AT= 109 sPTX= 78	7.9%	48.5%	----------	----------	----------	----------	3 (1.8%)	Pneumonia: 1 (1.2%)	
Katja Schlosser and others (6)	tPTX= 52	----------	----------	----------	----------	6 (14%)	----------	6 (11.5%)	5.7%	
	tPTX+AT= 48	----------	----------	----------	----------	2(5%)	----------	2(4.1%)	2%	
Ming-Lang Shih and others (7)	tPTX=44	18.2%	----------	----------	0	8 (18%)	0	----------	----------	----------
	tPTX+AT=50	12%	----------	----------	0	6 (12%)	1(2%)	----------	----------	----------
Parameswaran Rajeev and others (8)	tPTX+AT= 57	----------	9 (15.5%)	----------	----------	3 (5.2%)	----------	1 (1.7%)	----------	Pneumonia: 3 (5.2%) NSTEMI 2 (3.4%)
	sPTX =24	----------	4 (16.7%)	----------	----------	0	----------	0	----------	1 (4.2%)
Onur Birsen and others (9)	tPTX+AT= 35	----------	Most commune complication both groups	----------	----------	----------	----------	----------	----------	----------
	sPTX= 44	----------		----------	----------	----------	----------	----------	----------	----------
Wellington Alves Filho and others (10)	tPTX+AT (45 fragments)= 25	----------	----------	----------	----------	----------	----------	----------	----------	----------
	tPTX+AT (90 fragments)=21	----------	----------	----------	----------	----------	----------	----------	----------	----------

Y. LIANG and others (11)	tPTX= 21	----------	12 (57.1%)	----------	----------	----------	0	1 (4.8%)	----------	----------
	tPTX+AT= 21	----------	5 (23.8%)	----------	----------	----------	0	0	----------	----------
	sPTX= 21	----------	2 (9.6%)	----------	----------	----------	1 (4.8%)	0	----------	----------
Ramazan Sari and others (12)	tPTX+AT= 25	----------	Transient: 13 (52%) permanent 1 (4%)	4 (16%)	----------	----------	----------	----------	----------	----------
	sPTX= 37	----------	Transient: 16 (43%) permanent 2 (5.4%)	8 (22%)	----------	----------	----------	----------	----------	MI: 1 (2.7%)
Polina V Zmijewski (13)	tPTX+AT =23	----------	Severe: 11.7%	----------	----------	----------	1 (2%)	----------	----------	----------
	sPTX= 23	----------	Severe: 9.5%	----------	----------	----------		----------	----------	----------
Neagoe, R. M and others (14)	tPTX+AT= 19	----------	9 (47.36%)	----------	----------	----------	0	----------	----------	----------
	sPTX= 26	----------	7 (29.16%)	1 (3%)	----------	----------	1 (3%)	----------	----------	----------
R. O. Santos and others (15)	tPTX+AT =38	----------	----------	3 (7.8%)	----------	----------	----------	----------	----------	----------
Xixiang Gong and others (16)	tPTX= 34	----------	Posoperative- 11(32.35 %)	3 (8.82%)	0	----------	0	0	----------	----------
Chao Gu and others (17)	tPTX+AT =12	----------	100 %	----------	----------	0	----------	16.7%	----------	----------
	sPTX= 20	----------	100 %	----------	----------	0	----------	0%	----------	----------
Min Song Kim and others (18)	sPTX= 25	----------	6 (24%)	1 (4%)	----------	0	0	0	----------	----------

5. Final results

In table number 5, presented the collection of results and conclusions proceeding the 3 types of PTX including rate of symptoms relief, rate of recurrence/ reoperation, mean hospital stay, percentage of patients undergo renal transplantation after PTX and the main conclusion of the authors.

Not all studies describe the rate of symptoms relive, but those who did, show that the efficacy range from 76.2% (11) to 91.7% (17).

Rate of recurrence or reoperation of the disease was different among all groups (figure 5), but, it is important to note that not every case of recurrence of the disease lead to reoperation. For total PTX the rate range from 0% (6) to 23% (4), for total PTX+AT the rate range from 0% (14,17) to 18% (7) and for subtotal PTX rate range from 0% (17) to 38.1% (11). When facing the samples and compering tPTX and tPTX+AT the recurrence rate was higher in tPTX+AT(6, 7, 11). Comparing both tPTX and tPTX+AT to sPTX more articles show that the recurrence rate is higher in subtotal PTX (3, 6-14), although, some articles show the opposite (2, 4)

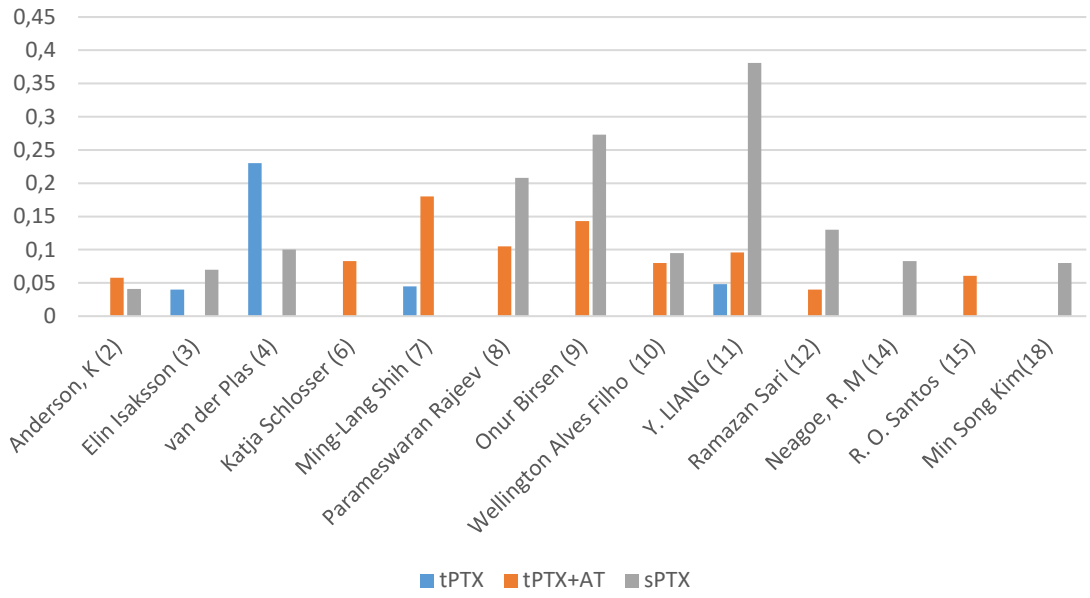

Figure 5. Rate of recurrence/ reoperation (%).

Mean hospital stay was also collected, for tPTX hospital stay in days range from 6 (7) to 10 (6, 11), for tPTX+AT range from 3 (14) to 12 (11) and for sPTX range from 3 (12) to 7.5 (11). So comparing to both total PTX to subtotal PTX, patients who

undergo subtotal PTX has lower hospital stay (2, 3, 11-13) with one exception in article 14 comparing to tPTX+AT.
in comparing tPTX+AT to tPTX, tPTX+AT have higher hospital stay (2, 7, 11) with one exception on article 6 where hospital stay was higher in tPTX.

One of the major causes of PTX is to provide a definitive treatment for patients with renal transplantation, although, not all patients take part in waiting list of renal transplant and undergo the procedure for reliving the disease. The rate of renal transplantation for tPTX range from 0% (16) to 38% (3), for tPTX+AT range from 0% (10, 14) to 28% (10), and for sPTX from 0% (14) to 29% (3).
When separately compering between tPTX to other approaches, rate of renal transplantation is higher in total PTX (3, 6), but, lower from sPTX in one study (4). The same happens when comparing tPTX+AT to sPTX which there is variation between those two approaches in the aspect of rate of transplantation (9, 10, 13), what makes it difficult to know which PTX is better for renal transplantation postoperatively.

Table number 5 presents the author position after the results of each study. Most of the articles consider PTX as safe and effective method for treatment of SHPT (1, 5, 10, 11, 12, 14, 15, 16, and 18). According that, tPTX consider as technique with lower risk of recurrent parathyroidectomy (16) compering to tPTX+AT and sPTX (3, 6). sPTX is less likely to have extended hospital stay and hypocalcemia development in compare to two other approaches (2, 11), and achieves a good short-term efficacy (17).
tPTX+AT have higher risk for recurrence of the disease and hypocalcemia than sPTX (13). Some authors consider that tPTX+AT is a better approach in the short- and long-term outcomes compares to sPTX (8,9) while there is one author that think that sPTX have better short term results (17).

Table 5. Final results.

Research authors	**Samples**	**Rate of symptoms relief/ efficiency**	**Rate of recurrence/ reoperation**	**Mean hospital stay (**days**)**	**Renal transplantation after PTX (n)**	**Conclusion of the author which method is superior**
Shasha Zhao and others (1)	tPTX= 1419 tPTX+AT= 54	----------	----------	----------	----------	Parathyroidectomy is a safe and effective treatment for refractory secondary hyperparathyroidism.
Anderson, K and others (2)	tPTX+AT= 365	----------	5.8%	5	----------	no statistically significant differences between the two surgical techniques in terms of these primary and outcomes or secondary outcomes sPTX is less likely to have extended hospital stay
	sPTX= 765	----------	4.1%	4.1	----------	
Elin Isaksson and others (3)	tPTX= 388 (78%+AT)	----------	17 (4%)	7.2	148 (38%)	There was a higher risk of cardiovascular events in patients after tPTX compared with sPTX, but a lower risk of recurrent parathyroidectomy.
	sPTX= 436	----------	32(7%)	6.9	125(29%)	
van der Plas and others (4)	tPTX= 77	----------	23%	----------	7 (14%)	sPTX is the optimal strategy in an era with an increasing availability of kidney transplantation and improved regimens of dialysis.
	sPTX (<3 glands)= 27	----------	15%	----------	4 (24%)	
	sPTX (3-3.5 glands)= 91	----------	10%	----------	21 (26%)	
Willemijn Y. and others (5)	tPTX+AT= 109 sPTX= 78	----------	7%	----------	----------	PTx is a safe and effective procedure
Katja Schlosser and others (6)	tPTX= 52	----------	0	10 ± 7.1	16 (31%)	tPTX seems to suppress PTH more effectively and showed no recurrences after 3 years.
	tPTX+AT= 48	----------	4 (8.3%)	8 ± 3.7	11 (23%)	
Ming-Lang Shih and others (7)	tPTX=44	88.6%	4.5%	6 (2-30 d)	----------	**tPTX** may be an option for treating patients with symptomatic sHPT who are not expected to receive kidney transplantation.
	tPTX+AT=50	80%	18%	9 (1-107 d)	----------	
Parameswaran Rajeev and others (8)	tPTX+AT= 57	----------	6 (10.5%)	----------	----------	tPTX+AT is superior to subtotal parathyroidectomy in short to intermediate term.
	sPTX =24	----------	5 (20.8%)	----------	----------	

Onur Birsen and others (9)	tPTX+AT= 35	----------	5 (14.3%)	----------	3 (8.5%)	tPTX+AT is superior in the short- and long-term outcomes preferred treatment option in countries where access to kidney transplantation is difficult
	sPTX= 44	----------	12 (27.3%)	----------	11 (25%)	
Wellington Alves Filho and others (10)	tPTX+AT (45 fragments)= 25	----------	2 (8%)	----------	0	PTX significantly improves quality of life in hemodialysis patients with SHPT, regardless of the type of operation.
	tPTX+AT (90 fragments)=21		1 (4.7%)		6 (28%)	
	sPTX= 23		2 (9.5%)		1 (4%)	
Y. LIANG and others (11)	tPTX= 21	81%	1 (4.8%)	10.1 ± 3.1	----------	There is no difference in short term efficacy and recurrence among three groups The occurrence of hypocalcemia was the lowest in patients who underwent sPTX
	tPTX+AT= 21	85.7%	2 (9.6%)	12.2 ± 3.8	----------	
	sPTX= 21	76.2%	8 (38.1%)	7.5 ± 2.0	----------	
Ramazan Sari and others (12)	tPTX+AT= 25	----------	1 (4%)	5(6)	----------	Both surgical techniques are comparably effective in the treatment of SHPT
	sPTX= 37	----------	2 (5.6%)	3(5)	----------	
Polina V Zmijewski (13)	tPTX+AT =23	----------	1 (4%)	4.4 ± 3.5	4 (17%)	long-term control of PTH elevation and avoidance of recurrent disease is improved with TPTX-AT, but carries a higher risk of long-term hypocalcemia
	sPTX= 23	----------	3 (13%)	3.7 ± 1.9	2 (8%)	
Neagoe, R. M and others (14)	tPTX+AT= 19	----------	0	Median: 3	0	both techniques have the same results concerning the clinical and laboratory outcomes and rates of postoperative HPT, at least in short- and medium-term follow-up.
	sPTX= 26	----------	2 (8.3%)	Median: 4	0	
R. O. Santos and others (15)	tPTX+AT =38	----------	6,06%	----------	----------	tPTX+AT is a feasible and safe surgical option in SHPT
Xixiang Gong and others (16)	tPTX= 34	91.18%	low	----------	0	tPTX was effective, safe, and reliable, with a low recurrence rate.
Chao Gu and others (17)	tPTX+AT =12	91.7%	0	----------	----------	sPTX achieves a better short-term efficacy, but tPTX + AT has a better long-term efficacy.
	sPTX= 20	85.0 %	0	----------	----------	

Min Song Kim and others (18)	sPTX= 25	----------	2 (8%)	----------	1 (4%)	sPTX is a safe and effective surgical treatment for SHPT

11. CONCLUSIONS

1. In most of the studies the ratio of both genders, male and female was approximately equal, and their mean age is 40–60 years.
   All the patients had SHPT, which was treated with years of dialysis before surgery and the most common symptoms were bone pain and fractures, osteodystrophy, joint and proximal muscle pain, pruritus, kidney stones, fatigue, weakness, and calciphylaxis.
   Laboratory tests are predominant for PTH and phosphorous elevation, while calcium levels are normal.

2. There are 3 main types of surgeries used to treat SHPT, which include tPTX, tPTX+AT, and sPTX.
   The indications for surgery were high levels of PTH and SHPT that are resistant to medications, long-term SHPT and dialysis treatment, and severe hypercalcemia in symptomatic patients, hyperphosphatemia, soft tissue calcification, and calciphylaxis.

3. All 3 types of surgeries proved as effective methods for treatment of SHPT and reducing symptoms and PTH blood values.
   tPTX is the most effective in reducing PTH levels, and recurrence of the disease is the lowest with this type of surgery.
   Complications and the mean hospital stay are the lowest in sPTX compared to tPTX and tPTX+AT.
   sPTX shows good short-term results, while tPTX+AT shows good long- and short-term results.

According to the results, sPTX is the most suitable surgery for patients with SHPT. sPTX proved to be an effective method with good short-term results and decreased complications and mean hospital stay compared to tPTX and tPTX+AT. Although the rate of recurrence is higher when compared to two other approaches, the focus should be on the complications.
Reoperation is now a condition that surgeons can treat, but complications are more difficult to avoid. As a result, sPTX as a less invasive procedure can be the best option to treat SPTX without causing lifelong damage.

12. REFERENCES

1. Zhao, S., Gan, W., Xie, W., Cao, J., Zhang, L., Wen, P., Yang, J., & Xiong, M. (2022). A single-center experience of parathyroidectomy in 1500 cases for secondary hyperparathyroidism: a retrospective study. *Renal Failure*, *44*(1), 23–29. https://doi.org/10.1080/0886022X.2021.2016445
2. Anderson, K., Ruel, E., Adam, M. A., Thomas, S., Youngwirth, L., Stang, M. T., Scheri, R. P., Roman, S. A., & Sosa, J. A. (2017). Subtotal vs. total parathyroidectomy with autotransplantation for patients with renal hyperparathyroidism have similar outcomes. *American Journal of Surgery*, *214*(5), 914–919. https://doi.org/10.1016/j.amjsurg.2017.07.018.
3. Isaksson, E., Ivarsson, K., Akaberi, S., Muth, A., Prütz, K. G., Clyne, N., Sterner, G., & Almquist, M. (2019). Total versus subtotal parathyroidectomy for secondary hyperparathyroidism. *Surgery (United States)*, *165*(1), 142–150. https://doi.org/10.1016/j.surg.2018.04.076.
4. van der Plas, W., Kruijff, S., Sidhu, S. B., Delbridge, L. W., Sywak, M. S., & Engelsman, A. F. (2021). Parathyroidectomy for patients with secondary hyperparathyroidism in a changing landscape for the management of end-stage renal disease. *Surgery (United States)*, *169*(2), 275–281. https://doi.org/10.1016/j.surg.2020.08.014.
5. van der Plas, W. Y., Dulfer, R. R., Koh, E. Y., Vogt, L., Appelman-Dijkstra, N. M., Schepers, A., Rotmans, J. I., Pol, R. A., van Ginhoven, T. M., Hoorn, E. J., Nieveen van Dijkum, E. J. M., Engelsman, A. F., de Borst, M. H., & Kruijff, S. (2018). Safety and efficacy of subtotal or total parathyroidectomy for patients with secondary or tertiary hyperparathyroidism in four academic centers in the Netherlands. *Langenbeck's Archives of Surgery*, *403*(8), 999–1005. https://doi.org/10.1007/s00423-018-1726-6.
6. Schlosser, K., Bartsch, D. K., Diener, M. K., Seiler, C. M., Bruckner, T., Nies, C., Meyer, M., Neudecker, J., Goretzki, P. E., Glockzin, G., Konopke, R., & Rothmund, M. (2016). Total parathyroidectomy with routine thymectomy and autotransplantation versus total parathyroidectomy alone for secondary hyperparathyroidism results of a nonconfirmatory multicenter prospective randomized controlled pilot trial. *Annals of Surgery*, *264*(5), 745–753. https://doi.org/10.1097/SLA.0000000000001875.

7. Shih, M. L., Duh, Q. Y., Hsieh, C. B., Lin, S. H., Wu, H. S., Chu, P. L., Chen, T. Y., & Yu, J. C. (2009). Total parathyroidectomy without autotransplantation for secondary hyperparathyroidism. *World Journal of Surgery*, *33*(2), 248–254. https://doi.org/10.1007/s00268-008-9765-8.
8. Rajeev, P., Lee, K. Y., Tang, X. J., Goo, T. T., Tan, W. B., & Ngiam, K. Y. (2016). Outcomes of parathyroidectomy in renal hyperparathyroidism in patients with No access to renal transplantation in Singapore. *International Journal of Surgery*, *25*, 64–68. https://doi.org/10.1016/j.ijsu.2015.11.005
9. Birsen, O., Ozban, M., Ozden, A., Sungurtekin, U., Erdem, E., Kabay, B., Yilmaz, S., Aykota, M. R., Ozgen, U., Demirci, S., & Aydin, H. C. (2022). Surgery for Secondary Hyperparathyroidism. Total or Subtotal? *Indian Journal of Surgery*, *84*(1), 94–99. https://doi.org/10.1007/s12262-021-02821-2
10. Filho, W. A., van der Plas, W. Y., Brescia, M. D. G., Nascimento, C. P., Goldenstein, P. T., Neto, L. M. M., Arap, S. S., Custodio, M. R., Bueno, R. O., Moyses, R. M. A., Jorgetti, V., Kruijf, S., & Montenegro, F. L. M. (2018). Quality of life after surgery in secondary hyperparathyroidism, comparing subtotal parathyroidectomy with total parathyroidectomy with immediate parathyroid autograft: Prospective randomized trial. *Surgery (United States)*, *164*(5), 978–985. https://doi.org/10.1016/j.surg.2018.06.032.
11. Liang, Y., Sun, Y., Ren, L., Qi, X.-W., Li, Y., Zhang, F., Liang, Y., Sun, Y., & Zhang, F. (2015). *Short-term efficacy of surgical treatment of secondary hyperparathyroidism*.
12. *Ramazan Sari, Hakan Yabanoglu, Abdirahman Sakulen Hargura, Murat Kus and Ilker Murat Arer* (2020.) *Outcomes of Total Parathyroidectomy with Autotransplantationversus Subtotal Parathyroidectomy*.
13. Zmijewski, P. v., Staloff, J. A., Wozniak, M. J., & Mazzaglia, P. J. (2019). Subtotal Parathyroidectomy vs Total Parathyroidectomy with Autotransplantation for Secondary Hyperparathyroidism in Dialysis Patients: Short- and Long-Term Outcomes. *Journal of the American College of Surgeons*, *228*(6), 831–838. https://doi.org/10.1016/j.jamcollsurg.2019.01.019
14. Neagoe, R. M., Murean, M., Voidazan, S., Pacanu, I., Radu, C. P., & Sala, D. T. (2016). Subtotal parathyroidectomy versus total parathyroidectomy with autotransplant in secondary hyperparathyroidism - A single-centre prospective

cohort of 43 patients. *Endokrynologia Polska*, *67*(2), 202–209. https://doi.org/10.5603/EP.a2016.0013.

15. Santos, R. O., Ohe, M. N., Carvalho, A. B., Neves, M. C., Kunii, I., Lazaretti-Castro, M., Abrahão, M., Cervantes, O., & Vieira, J. G. H. (2012). Total parathyroidectomy with presternal intramuscular autotransplantation in renal patients: A prospective study of 66 patients. *Journal of Osteoporosis*, *2012*. https://doi.org/10.1155/2012/631243
16. Gong, X., Wang, Y. A., Li, C., Liao, X., Li, S., Yang, L., Jiang, X., Sun, Y., Xu, J., Tong, Z., & Lu, Y. (2022). Effect of total parathyroidectomy in patients with secondary hyperparathyroidism: a retrospective study. *International Urology and Nephrology*. https://doi.org/10.1007/s11255-022-03401-3.
17. Gu, C., Ye, Z., Wang, Y., Wang, Q., Qi, J., Chen, J., Chen, S., & Xu, Z. (2020). Therapeutic efficacy of two surgical methods on the secondary hyperparathyroidism. *Gland Surgery*, *9*(2), 321–328. https://doi.org/10.21037/gs.2020.03.08
18. Kim, M. S., Kim, G.-H., Lee, C. H., Park, J.-S., Lee, J. Y., & Tae, K. (2020). Surgical Outcomes of Subtotal Parathyroidectomy for Renal Hyperparathyroidism. *Clinical and Experimental Otorhinolaryngology*, *13*(2), 173–178. https://doi.org/10.21053/ceo.2019.01340.
19. Block, G. A., Klassen, P. S., Lazarus, J. M., Ofsthun, N., Lowrie, E. G., & Chertow, G. M. (2004). Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *Journal of the American Society of Nephrology*, *15*(8), 2208–2218. https://doi.org/10.1097/01.ASN.0000133041.27682.A2
20. Messa, P., & Alfieri, C. M. (2018). Secondary and Tertiary Hyperparathyroidism. *Frontiers of Hormone Research*, *51*, 91–108. https://doi.org/10.1159/000491041
21. Isakova T, Nickolas TL, Denburg M, Yarlagadda S, Weiner DE, Gutiérrez OM, Bansal V, Rosas SE, Nigwekar S, Yee J, Kramer H. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis. 2017 Dec;70(6):737-751.
22. Rodríguez, M., & Rodríguez-Ortiz, M. E. (2020). Recent advances in understanding and managing secondary hyperparathyroidism in chronic

kidney disease. In *F1000Research* (Vol. 9). F1000 Research Ltd. https://doi.org/10.12688/f1000research.22636.1

23. Rodríguez-Ortiz, M. E., Pendón-Ruiz de Mier, M. v., & Rodríguez, M. (2019). Parathyroidectomy in dialysis patients: Indications, methods, and consequences. In *Seminars in Dialysis* (Vol. 32, Issue 5, pp. 444–451). Blackwell Publishing Inc. https://doi.org/10.1111/sdi.12772
24. Li, C., Lv, L., Wang, H., Wang, X., Yu, B., Xu, Y., Zhou, X., & Zhou, Y. (2017). Total parathyroidectomy versus total parathyroidectomy with autotransplantation for secondary hyperparathyroidism: Systematic review and meta-analysis. *Renal Failure*, *39*(1), 678–687. https://doi.org/10.1080/0886022X.2017.1363779
25. Liu, M. E., Qiu, N. C., Zha, S. L., Du, Z. P., Wang, Y. F., Wang, Q., Chen, Q., Cen, X. X., Jiang, Y., Luo, Q., Shan, C. X., & Qiu, M. (2017). To assess the effects of parathyroidectomy (TPTX versus TPTX+AT) for Secondary Hyperparathyroidism in chronic renal failure: A Systematic Review and Meta-Analysis. In *International Journal of Surgery* (Vol. 44, pp. 353–362). Elsevier Ltd. https://doi.org/10.1016/j.ijsu.2017.06.029
26. Yuan, Q., Liao, Y., Zhou, R., Liu, J., Tang, J., & Wu, G. (2019). Subtotal parathyroidectomy versus total parathyroidectomy with autotransplantation for secondary hyperparathyroidism: an updated systematic review and meta-analysis. In *Langenbeck's Archives of Surgery* (Vol. 404, Issue 6, pp. 669–679). Springer. https://doi.org/10.1007/s00423-019-01809-7
27. Palumbo, V. D., Damiano, G., Messina, M., Fazzotta, S., Monte, G. lo, & Monte, A. I. L. (2021). Tertiary hyperparathyroidism: A review. In *Clinica Terapeutica* (Vol. 72, Issue 3, pp. 241–246). Societa Editrice Universo. https://doi.org/10.7417/CT.2021.2322
28. Moher D, Liberati A, Tetzalff j, Altman DG; PRISMA Group. Preferred reporting items for systhemic reviews and meta-analyses: the PRISMA statement. PLos Med. 2009 Jul 21;6(7):e1000097. doi: 10.1371/journal.pmed.1000097. Epub 2009 Jul 21. PMID: 19621072; PMCID: PMC2707599.) The main search engine was MEDLINE PubMed (https://pubmed.ncbi.nlm.nih.gov)