Aus der Chirurgischen Klinik Campus Charité Mitte | Campus Virchow-Klinikum
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Effect of Cinacalcet Therapy on Surgical Outcome in Patients with Renal Hyperparathyroidism

Zur Erlangung des akademischen Grades
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Table of contents

1. Zusammenfassung

Die vorliegende Arbeit stellt die Ergebnisse der operativen Behandlung von Patienten mit renalem Hyperparathyroidismus (HPT) nach einer präoperativen Therapie mit Cinacalcet vor.

Diese sind in Form einer retrospektiven Studie untersucht.

Der renal HPT ist eine der späten Komplikationen der fortgeschrittenen Niereninsuffizienz und erhöht die Morbidität von diesen Patienten. Die Nierentransplantation führt nicht immer zur Heilung des renalen HPT. Ausdruck dieser hormonellen Störung ist die renale Osteopathie, steigende kardiovaskuläre Morbidität und Mortalität, Nierentransplantatdysfunktion.

Der renal HPT wird konservativ mit Vitamin D und Phosphatbindern behandelt, zudem ist seit 2004 eine Targettherapie mit Cinacalcet, allosterischer Modulator der Ca-sensing Rezeptoren, verfügbar. Die konservative Behandlung kann den renalen HPT über einen Zeitraum kontrollieren. Wenn das Versagen der medikamentösen Therapie auftritt, bleibt die chirurgische Behandlung die einzelne Option. Es werden subtotale, totale Parathyreoidektomie (mit oder ohne Autotransplantation) durchgeführt, mehrere Studien haben diese Operationen als effektive Behandlung belegt. Keine Studie hat die Ergebnisse der operativen Behandlung bei Patienten unter Cinacalcetbehandlung untersucht.

Die vorliegende Studie mit 191 Patienten im Zeitraum 2008-2015 analysiert die Ergebnisse der chirurgischen Therapie der Patienten im Charité Campus Virchow Klinikum. Die Studie fokussierte sich auf den Vergleich von Patientengruppen mit und ohne präoperativer Cinacalcetbehandlung. Cinacalcet wurde durch niedergelassenen Nephrologen verordnet, diese Entscheidung war von den Chirurgen an der Charité unabhängig. Die weitere medikamentöse Therapie unterscheidet sich im Wesentlichen nicht, sowie die demographische Patientendaten, Komorbiditäten etc.

Daten zu der operativen Behandlung wurden analysiert: Operative Effektivität, Komplikationen, Rezidivrate. Im frühen postoperativen Verlauf wurden die Calcium und Parathormon von besonderem Interesse.

Wir verfügten über die Laborwerte in jährlichen Abständen nach der Operation. Daten über Nierentransplantation und Graftfunktion, kardiovaskulären Ereignissen und Mortalität, Osteopatie und Auftreten einer Hypoparathyroidismus oder eines Rezidivs des HPT wurden erhoben.

Es gab keine signifikanten Unterschiede in den unmittelbaren Operationsergebnissen (Effektivität) und Komplikationsraten zwischen den Studiengruppen. Präoperativer Serum-Ca war in der Gruppe mit Cinacalcet signifikant niedriger, 2.28±0.23 vs. 2.41±0.23 mmol/l (p=0.0002), was die Therapieeffektivität beweist.

Die aktuelle Studie ist die erste publizierte Analyse der chirurgischen Therapie der renalen HPT, die sich auf Effekte der präoperativen Cinacalcetbehandlung fokussiert. Es wurden keine signifikanten Unterschiede in Effektivität sowie Sicherheit der operativen Behandlung zwischen Patienten mit und ohne Cinacalcet gesehen. Rate der Blutungen, Nervenparesis, Infektionen, kardiovaskulären Komplikationen, postoperative Hypokalziämie wiesen keinen Gruppenunterschied auf.

Die chirurgische Behandlung stellte sich in der Studiengruppe trotz teils multimorbider Patienten als eine sichere Option dar.

2. Conclusion.

This retrospective cohort study presents the results of surgical therapy in patients with renal hyperparathyroidism (HPT) receiving cinacalcet preoperatively.

Renal HPT is a late complication of chronic kidney disease; it worsens the prognosis in this predominantly multimorbid group of patients. Renal HPT doesn't always resolve after renal transplantation. Renal osteopathy, cardiovascular complications and mortality, impairment of renal graft function are the main outcomes of renal HPT.

Modern therapy of renal HPT consists of active forms of Vitamin D and phosphate binders; since 2004 is a target therapy with cinacalcet, an allosteric modulator of calcium sensing receptor, available. The renal HPT can be effectively pharmacologically treated over a period of time. An operation is the only option after the failure of medical treatment. Subtotal and total parathyroidectomy (with or without autotransplantation) are performed, and the outcomes of all types of operations analyzed in many retrospective studies have shown their comparable effectiveness. There are no studies comparing the surgical outcomes in patients relative to cinacalcet therapy.

Current study included 191 patients operated in 2008-2015 in Charité Campus Virchow Klinikum. The study was aimed at comparison of patients with and without cinacalcet preoperatively. Cinacalcet was prescribed by the attending nephrologists and the surgical team had no influence on that decision. The remaining medical therapy did not differ significantly between the study groups, neither there were differences in demographic data, overall morbidity etc.

Outcomes of surgical treatment studied included efficacy, complication rate, rate of recurrence. Laboratory values – serum calcium and parathyroid hormone were of higher interest in the first days after operation.

Our study provided yearly controls of laboratory values. Renal transplantation status and data on graft function, cardiovascular morbidity and mortality, renal osteopathy, signs and symptoms of hypoparathyroidism, and recurrence of hyperparathyroidism were analyzed.

The efficacy of surgical treatment was similar in both groups, as was the rate of complications. Preoperative serum Ca was significantly lower in the cinacalcet group, 2.28±0.23 vs. 2.41±0.23 mmol/l ($p=0.0002$), confirming the existing treatment effect.

Actual study is the first to compare the results of surgical treatment of renal HPT with focus on preoperative cinacalcet therapy. Efficacy and safety of the surgical treatment was proved to be similar in both groups. There was no difference in rates of bleeding, nerve palsy, infections, cardiovascular complications and postoperative hypocalcemia.

Surgical treatment of renal HPT has proved to be as a safe option in this patients group despite their multimorbidity.

3. Introduction

Small things often go unnoticed. This is applicable to the parathyroid glands. Even today in spite of new developments in medicine, diseases associated with these glands are difficult to diagnose and cure [1].

Parathyroid surgery became effective only when the role of parathyroid glands in bone and mineral metabolism disorders was described. Though the anatomical description of parathyroid glands was made in 1850´s, only in the 20th century, due to hormonal assessment and visual diagnostic methods, adequate treatment became possible. However many fundamental questions still remain unsolved [2].

4. Parathyroid glands

4.1. History

In 1850 Sir Richard Owen (an anatomist and curator of the Natural History Museum in London) was the first to describe the parathyroid glands as he dissected a rhinoceros that died in the London Zoo. That time he made no histological confirmation. In 1887 a Swedish medical student, Ivar Sandstrom, described new glands in 50 dissected human bodies and called them "glandula parathyroideae". He gave their full anatomical description [1]. The physiology of parathyroid glands, namely the relation between parathyroid gland function and tetany, was clarified by the French Physiologist Eugene Gley in his experiments on rats and rabbits. He showed that the removal of parathyroid gland performed either with or without thyroidectomy invariably caused tetany in both cases [1].

In 1920´s parathyroid hormone (PTH) was described as the most important calcium(Ca) regulating hormone that was produced by the parathyroid gland [3]. Since that time many investigators had used parathyroid gland extract to treat postoperative tetany in animal experiments. It was shown that those extracts were able to cure tetany and to raise serum Ca as well as to induce osteoporosis when administered over a prolonged period [1].

The first parathyroidectomy (PTx) performed by Felix Mandel in Wien opened the era of surgical treatment of hyperparathyroidism (HPT). He operated on a man with 'osteitis fibrosa cystica' - the result of primary hyperparathyroidism (pHPT) [4]. Nowadays, with the development of long-time substitution therapy and renal transplantation surgery caused by the rising number of chronic kidney diseases (CKD) leading to renal failure, the number of patients with renal HPT has substantially increased [1].

In 1959, due to contemporary technologies, Aurbach G.D., Rasmussen H. and Craig J.C. isolated, purified and determined the structure of PTH [3]. The desoxyribonucleic acid (DNA) sequence of the PTH gene was identified in 1977. In 1993 Edward M. Brown et al. cloned and structurally characterized the parathyroid calcium-sensing receptor (CaSR) [5]. Advances in the field of parathyroid studies have led to the introduction of new drug substances and progress in the treatment of parathyroid gland diseases.

4.2. Anatomy

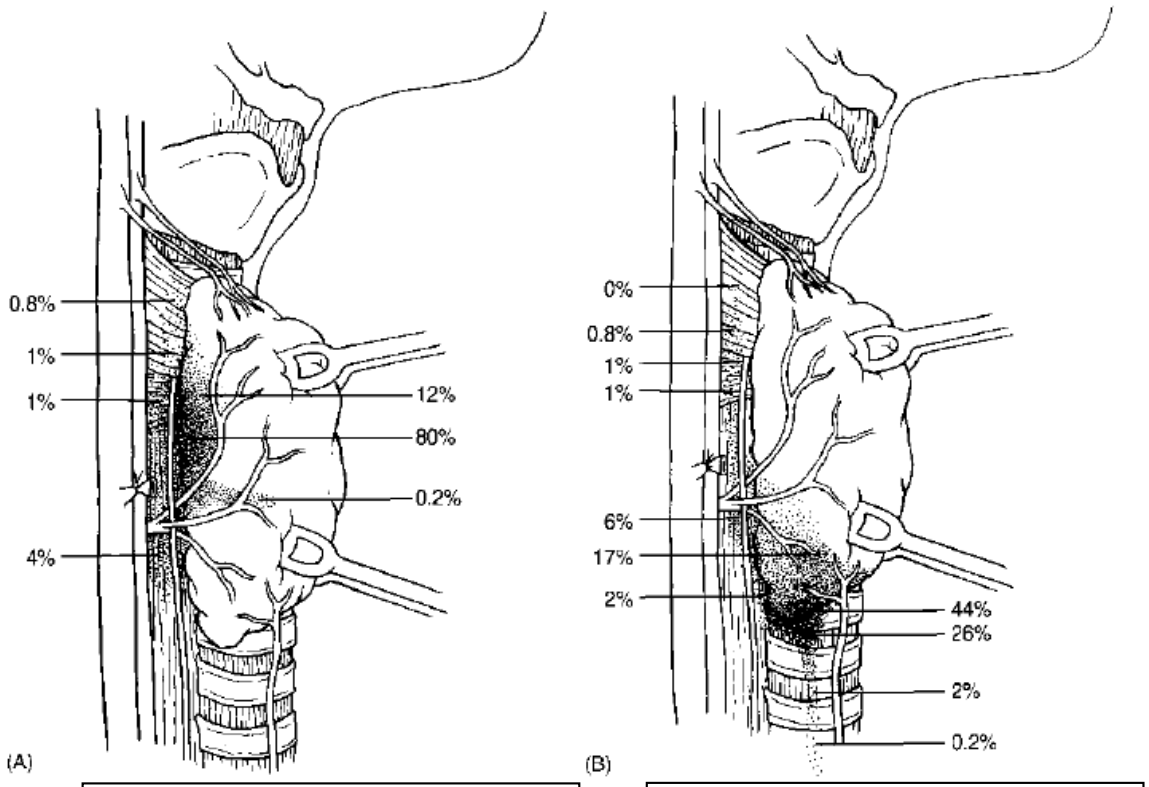


Figure 1: The frequency of locations (in percents) of superior (A) and inferior (B) parathyroid glands from «Endocrine Surgery» by A.Schwartz et al. [6].

Parathyroid glands, usually four**,** are located on the posterior surface of the thyroid gland each in a separate connective tissue capsule. Alternatively, parathyroid glands can be localized in the thyroid gland capsule, and in thyroid gland tissue. Other ectopic sites are the carotid bifurcation region and the upper mediastinum often in the thymus. Some individuals have supernumeric parathyroid glands (normally 5), others only have three glands [7].

Studies report 5-16.5% of supernumeric glands in surgically removed tissue, in 5.7% of cases only three parathyroid glands were found [8-10]. In a classical 1984 autopsy study of 503 non-hyperparathyreotic patients, the rate of supernumeric glands was 13%, whereas in 3% of

dissected cadavers only three parathyroid glands were found [11]. The rate of ectopic glands was as large as 19% [10].

Blood supply to the parathyroid glands normally comes from the inferior thyroid artery, blood supply to ectopic glands varies respectively to their localization [7].

4.3. Physiology/Pathophysiology

Parathyroid glands regulate mineral metabolism through secreting PTH, as demonstrated on the scheme below (figure 2).

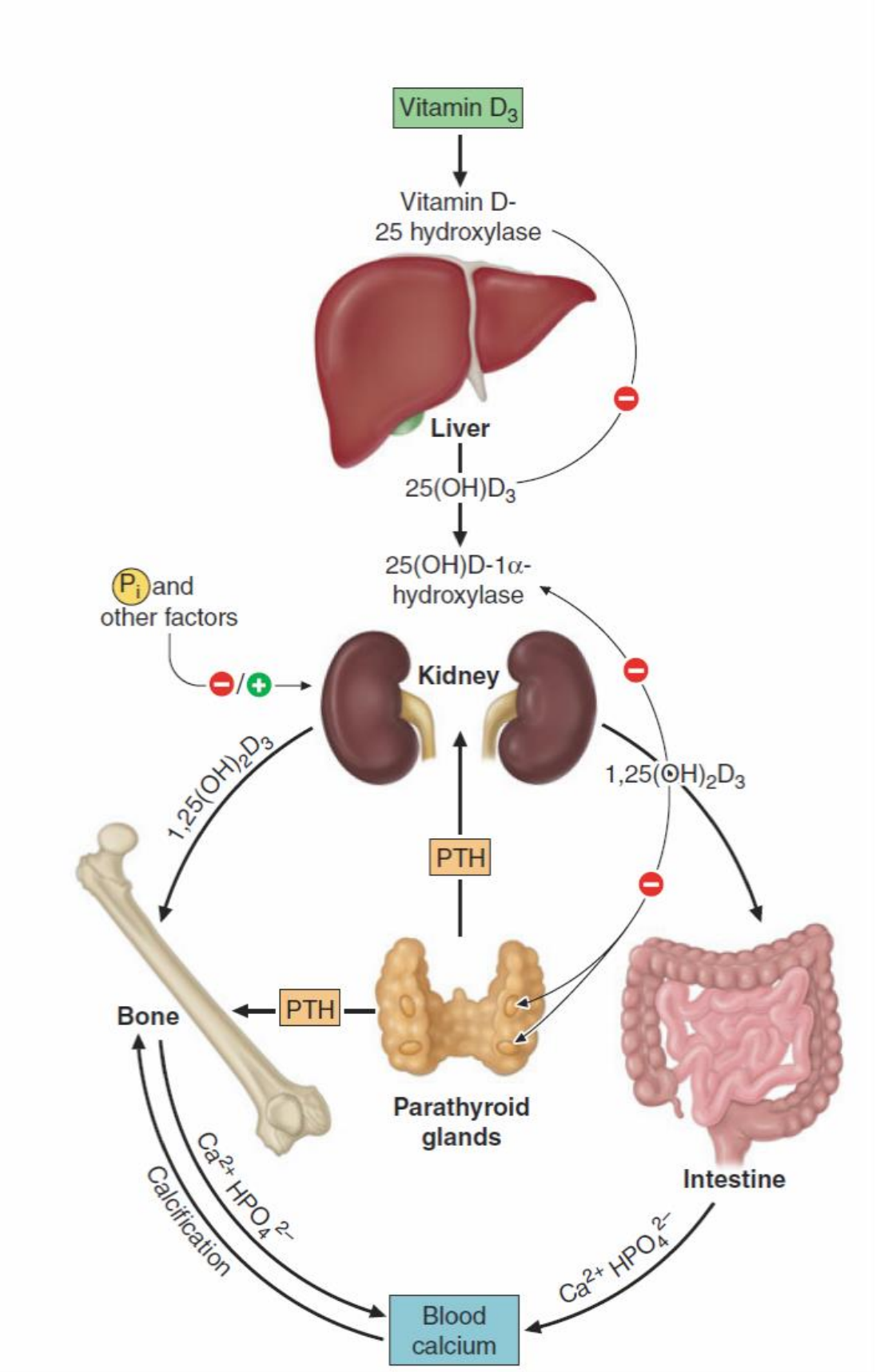

Vitamin D_3
Vitamin D-
25 hydroxylase
Liver
$25(OH)D_3$
25(OH)D-1α-
hydroxylase
P_i and
other factors
Kidney
$1,25(OH)_2D_3$
$1,25(OH)_2D_3$
PTH
PTH
Bone
Parathyroid
glands
Intestine
Ca^{2+} HPO_4^{2-}
Calcification
Ca^{2+} HPO_4^{2-}
Blood
calcium

Figure 2: Schematic representation of hormonal control loop, from Harrison Endocrinology [12]. Legend: $25(OH)D_3$- *25-Hydroxyvitamin D*; Pi – *phosphate*; $1,25(OH)_2D_3$ - *25-Dihydroxyvitamin D*; PTH – *parathyroid hormone*.

The metabolic functions of PTH in regulating serum Ca levels can be summarized as follows: it increases the renal tubular reabsorption of Ca, thereby conserving free Ca; it increases the conversion of vitamin D to its active dihydroxyform in kidneys. PTH increases urinary phosphate excretion, thereby lowering serum phosphate levels. PTH augments gastrointestinal Ca absorption (figure 2) [13].
The kinetic analysis of PTH shows an extremely short half-life time in peripheral blood, approximately four minutes [14].
In normal conditions parathyroid glands have a very low rate of mitosis in an adult human [2]. Under specific conditions, such as hypocalcemia, hyperphosphatemia and uremia, parathyroid glands first show cell hypertrophy, and then begin to proliferate, which ends in autonomous monoclonal cell growth [13]. The process of regress or apoptosis of these cells is not described, even when the initial triggering factor is removed [2].

5. Primary hyperparathyroidism

PHPT is a relatively common condition, mostly diagnosed through abnormally elevated serum Ca levels. Clinical findings in pHPT include bone disease, nephrolithiasis, gastrointestinal disturbances, central nervous system alterations, neuromuscular abnormalities, aortic and heart valve calcifications. The course of the disease is asymptomatic in many cases. In 85-90% of these cases a solitary adenoma is found in a previously normal parathyroid gland. Diffuse hyperplasia associated with hereditary syndromes is found in 5 to 20% of patients with pHPT: multiple endocrine neoplasia-1 (MEN-1), MEN-2, familial hypercalciuric hypercalcemia and hyperparathyroidism-Jaw tumor syndrome. Parathyroid cancer is a very rare disease, app. less than 1% of pHPT cases [2, 13].

6. Hyperparathyroidism in renal insufficiency

6.1. Pathophysiology

Renal, or secondary HPT (renal HPT, or sHPT) is detected even in the early stages of CKD, progressing with the level of renal insufficiency. All patients on haemodialysis have renal HPT [15].

The mechanisms by which chronic renal failure induces sHPT are complex and not fully understood. A decrease in serum Ca, excess of serum phosphate and low $1,25(OH)_2D_3$ level play the leading role here [6].

Ca binding to CaSR suppresses PTH production, and hypocalcemia is a stimulating factor for PTH production because of the reciprocal character of this interaction [5].

Chronic renal insufficiency is associated with decreased phosphorus (P) excretion, which in turn results in hyperphosphatemia. Elevated serum P levels directly depress serum Ca levels and thereby stimulate parathyroid gland activity [15].

In addition, the loss of renal substance reduces the availability of α-1-hydroxylase necessary for the synthesis of the active form of vitamin D_3, which suppresses PTH synthesis by binding to the vitamin D receptor (VDR). Low $1,25(OH)_2D_3$ levels also reduce intestinal absorption of Ca [12].

Another factor suppressing PTH synthesis is fibroblast growth factor-23 (FGF23) which acts binding to its receptor, FGFR. FGF23 modulates P/vitamin D_3 interaction, and its serum level is elevated in CKD patients [13, 16].

Parathyroid activity may become autonomous and excessive, with resultant hypercalcemia, a process that is sometimes termed "tertiary hyperparathyroidism". The synonymous term "autonomous hyperparathyroidism" describes the missing feedback mechanism more accurately [13].

6.2. Clinical features of renal HPT

Common clinical presentations of renal HPT are bone pain, ectopic calcification and pruritus. CKD-Mineral and Bone Disorder (CKD-MBD) describe all clinical abnormalities of mineral and bone metabolism associated with CKD [17]. Renal osteodystrophy is a term used to describe bone disease in patients with chronic renal failure. It is characterized by such parameters as turnover, mineralization and volume [18]. There are several types of renal osteodystrophy according to the American Society for Bone and Mineral Research classification, and the golden standard to diagnose it is a bone biopsy [1]. Osteitis fibrosis cystica is the most common disorder (over 40%) characterized by high-turnover dystrophy due to high PTH levels. Adynamic (aplastic) bone disease is found in up to 40% of patients and is a low-turnover dystrophy. Low PTH levels (<100pg/ml) in renal HPT patients are highly predictable for the development of adynamic bone disease. A mixed type of bone dystrophy is found in appr. 20% of patients. Contemporary studies show a low incidence of osteomalacia due to broad use of vitamin D_3 analogues. Aluminium deposition in bones used to cause an osteomalacia-like picture in X-ray studies, nowadays this pathology is rare due to non-aluminium based phosphate binders and

thorough water treatment in dialysis [12]. Histological confirmation is not available in most cases because the procedure of bone biopsy is expensive and invasive. In clinical practice serum PTH levels are used as an indirect indicator of bone disease [12].
CKD-associated pruritus is frequent in patients with end-stage renal disease. Many of them suffer from generalized pruritus that has negative influence on patient´s quality of life. Effective treatment options are limited because of unclear pahtophysiological mechanisms [19].
The disturbances of Ca-P homeostasis, misbalance of other regulatory factors – FGF23, CaSR expression, osteo/chondrogenic differentiation, vesicle release, apoptosis and loss of inhibitors, and degradation of extracellular matrix in CKD patients are associated with a higher rate of vascular calcification [20].
Vascular calcification of the coronary arteries, aortic branches, renal and peripheral arteries is manifested in patients with CKD III, and is associated with a high risk of cardiovascular events and mortality from cardiovascular diseases [21]. According to pathological studies, the prevalence of mortality due to cardiovascular events was over 50% in patients with CKD V [22].
If HPT persists after kidney transplantation (KTx), graft vessel calcification can be detected as soon as six months after the KTx. HPT also correlates with inferior graft function [23].
Other HPT associated symptoms are depression and non-specific psychological distress, leading to decreased quality of life [24, 25].

6.3. Epidemiology

There are app. 70.000 patients with terminal CKD in Germany as to 2009, according to DGfN statistics (Deutsche Gesellschaft für Nephrologie), the prevalence is 17.5/100,000 in the local population [26].
In the 1991 pan-European report on CKD statistics, parathyroidectomy (PTx) was indicated in 15% of patients 10 years after the start of chronic dialysis and in 38% of patients after 20 years of dialysis [27]. The annual incidence of renal HPT was estimated at 0.7-1.4% in the late 1990-s according to the literature review by F.Triponez et al. [28].
In the International population study DOPPS, a decline in the rate of PTx was stated (starting from study Phase 3, 2005-2008), after cinacalcet with active vitamin D_3 analogues became available for the conservative treatment of renal HPT [29].

6.4. Indication for surgical treatment

Despite expensive therapy with active Vitamin D_3 analogues, phosphate binders and calcimimetics, surgical treatment will be indicated for up to 32% of patients with renal HPT [30].
Even after KTx, an ultimate method of restoring bone-mineral metabolism, 0.6-5.6% of patients

will require a parathyroidectomy according to a review by P. Evenepoel et al. [31]. There is a direct correlation between the need for parathyroid surgery in transplanted patients and the duration of dialysis before KTx [32], as well as parathyroid gland size on ultrasound [33]. Indications for the operations are given in tight cooperation between surgeons and nephrologists. A cost-effectiveness analysis has shown, that an early surgical treatment in patients meeting the K/DOQI (Kidney Disease Outcomes Quality Initiative) criteria is favourable compared to a prolonged medical therapy [34]. Patients with a high ASA score (American society of Anesthesiology), high risk of perioperative complications, persistent or recurrent HPT are subjects for discussion [30].

6.5. Medical treatment

Conservative treatment of renal HPT consists of dietary phosphate restriction, the use of phosphate binders, correction of hypocalcemia during the dialysis, and application of vitamin D_3 sterols [17].

Even the use of non-Ca based phosphate binders (sevelamer hydrochloride, lanthan-based) and active vitamin D_3 analogues does not always lead to the regression of Ca, Ca-P product, and PTH to target levels [35].

Fundamental studies of mineral metabolism regulation have led to the development of targeted therapy with precise action on a molecular level. Substances selectively binding to CaSR and so downregulating the secretion of PTH are called calcilytics but they have never been used in clinical practice. Calcimimetics, drugs modulating the CaSR, represent a drug group with similar action and have shown clinical efficacy [36].

6.6. Surgical treatment

The K/DOQI 2003 guidelines state in §14 that parathyroidectomy is indicated in patients with severe HPT (intact PTH>800 ng/l in serum) associated with hypercalcemia, hyperphosphatemia refractory to conservative therapy. Calciphylaxis is one more indication for parathyroidectomy [34].

Indication for parathyroidectomy in renal HPT

- Hypercalcemia:
  - Spontaneous
  - Induced by medical treatment
  - Persistent (>1 year) even after KTx
- Severe renal osteopathy (x-ray or histological confirmation required)
- Vascular calcifications or soft tissue calcifications*
- Calciphylaxis*
- Hyperphosphatemia*, resistent to medical treatment
- Pruritis*, resistent to medical treatment

*supplementary criteria: -when PTH>800 pg/ml (>88 pmol/l) and no effect of medical treatment, -when PTH>100 and <800 pg/ml, an adynamic bone disease should be excluded **Contraindication** for operation is PTH <100 pg/ml which stands for adynamic bone disease

Table 1: Indications for parathyroidectomy in renal HPT from C.Dotzenrath, 2010 [37].

According to K/DOQI guidelines, the three operative procedures - total PTx (tPTx), subtotal PTx (sPTx), and total PTx with autotransplantation (tPTx with AT) - are equally effective in view of the outcome [34].

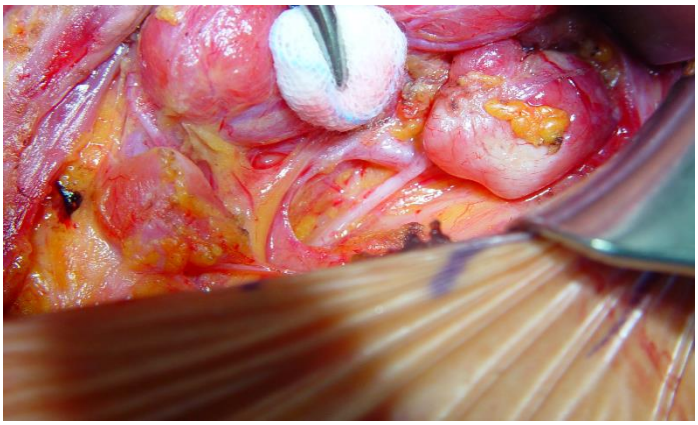


Figure 3: Intraoperative view of enlarged parathyroid glands in a patient with renal HPT, visualized from one side (Picture's ownership: Prof. N.Rayes, Charité hospital, 2015).

PTH does not always decrease following KTx [28, 38]. In transplanted patients with severe tertiary HPT (tHPT) a temporary postoperative hypoparathyroidism after PTx could comprise graft function. For this reason PTx prior to KTx is favourable [32, 38].

Indication for PTx after successful KTx are:

a) persistent hypercalcemia that doesn't resolve under medical treatment, and

b) symptomatic HPT defined as graft calcification, renal osteopathy, soft tissue calcifications, muscle or bone pain [38].

Surgical treatment modalities are subtotal parathyroidectomy and total parathyroidectomy. Total parathyroidectomy can be performed with or without autotransplantation (AT) of parathyroid tissue into the upper limb muscle. Both operations are listed as standard treatment in the actual 2003 K/DOQI guidelines [34].

All four parathyroid glands are to be identified during the operation. When a gland is missing, the fat tissue on the caudal thyroid gland poles should be explored; additionally a cervical thymectomy should be performed. Routine cervical thymectomy is recommended if preoperative imaging with ultrasound or scintigraphy with 99-Technecium sestamibi (99mTc) has shown an ectopic parathyroid gland in the thymus [6].

Cryopreservation of parathyroid tissue is a method allowing a delayed AT, an operation known for over 30 years. Effectiveness of AT (rate of graft function) is estimated at 60% [39], at the same time the need for this procedure is low, as reported in a large retrospective study, 13/606=2.1% [40].

- SPTx consists of removing 3 ½ - 3/4 of parathyroid glands. The remaining minimal part of the parathyroid gland is marked with a non-resorbable suture or with a clip. The advantage of this operation is short duration and no need for cryopreservation (not available in some clinics)

and low risk of postoperative hypoparathyroidism. At the same time, defining an adequate blood supply of the remaining tissue is technically challenging, as are the reoperations in case of recurrent HPT in the neck [6].

- In tPTx with AT all four PT glands are removed. A small part of the visually least structurally altered parathyroid gland is sliced and a part of it is transplanted into the forearm muscle of the non-shunt bearing arm. The advantage is a very low reoperation rate on the neck for recurrent disease. Disadvantages are a higher rate of postoperative hypoparathyroidism (the transplanted auto-tissue starts to function after an average of few months) and a relatively higher rate of overall HPT recurrences. An additional possible source of recurrent HPT is hyperfunction of the transplanted tissue in the forearm. Once the renal insufficiency with hyperphosphatemia and hypocalcemia are persisting, the transplanted PTG tissue may proliferate as well necessitating a surgical removal [6].
- TPTx, removal of all PT glands without AT, is an operation of choice in older patients and when no KTx is planned. This operation offers low to zero recurrence rates if no ectopic glands were overlooked. A cryopreservation of parathyroid tissue is an option allowing a delayed AT in cases of otherwise uncontrollable hypoparathyroidism [6, 41].

According to the analysis of questionnaires sent to hundreds of clinics, one of these three operations was reported as a standard procedure in the vast majority of nephrological centers all over the world. [42]. The results of the survey showed the rarity of other types of surgical interventions.

The debates about the preference of sPTx or tPTx with AT are still ongoing in literature [28, 40, 42-44]. In a meta-analysis by Richards et al. [43] 51 studies of recurrent and persistent HPT after sPTx versus tPTx + AT were analyzed. A higher rate of recurrences was recorded in the total PTx + AT group, namely the cases of recurrent disease in the forearm graft.

This finding was confirmed in a retrospective study by C. Dotzenrath et al. [44], where a cohort of 303 patients with 9% of reoperations (5.8% for recurrent ad 3.1% for persistent disease) was analyzed. There was no recurrent disease in the neck in the sPTx group when 3½ glands were removed, i.e. there was no hyperfunction in the remnant in the neck, as opposed to 6% (5/99) rate of graft hyperfunction in the forearm.

In a meta-analysis of 41 studies, the transitory hypocalcemia rate was 0 to 10% after sPTx and up to 100% in tPTx with/without AT. The analyzed studies have shown that the autotransplanted tissue begins to function a few months after the operation. A persistent hypoparathyroidism was noticed in 0 to 10% of cases, with a higher prevalence in the tPTx + AT group. Considering a high rate of hypoparathyroidism the authors recommended a sPTx in patients after KTx [28].

Schneider et al. examined long-term outcomes in patients who underwent KTx after any of the three above mentioned types of PTx – none of the patients required a delayed AT of parathyroid tissue, neither were there clinical presentations of adynamic bone disease (specific markers were not tested). The existing data on the risk of adynamic bone disease did not allow the authors to recommend a tPTx as a standard procedure [40]. Other contemporary studies do not report the development of adynamic bone disease either. [45, 46].

6.7. Surgical complications

Most complications in parathyroid surgery are similar to those in thyroid surgery [7]:

Complication type	Complication rate	Source
laryngeal recurrent nerve injury:		
transient	6.0-11.6%	[38, 40, 46]
persistent	0%	[38, 40, 46]
neck hematoma and wound infection	0-3.1%	[40, 46]
transient postoperative hypocalcemia	< 10%	[28]

Table 2: Rates of complications in parathyroid surgery

Specific rare surgical complications are injury of the superior laryngeal nerve, vagus nerve, intraoperative vascular injury and injury of neighboring organs (trachea, esophagus) [7]. Technical complications listed above have falling numbers in experienced surgical teams, and the postoperative hypocalcemia is well controlled by existing protocols of Ca substitution and vitamin D_3 analogues [6].

The one specific complication is persistent HPT or recurrent HPT. If the PTH level drops to normal values after the operation and rises afterwards, it is defined as a recurrent HPT. If there is no drop of PTH after the operation, it is defined as a persistent HPT. This concept is nowadays widely accepted in the professional community [17].

Persistent HPT may result from the failure in finding a parathyroid gland when it is ectopic or supernumerary [7]. It may also be a result of functionally active parathyroid tissue, intentionally left during sPTx or autotransplanted into the forearm muscle when the driving factors of renal insufficiency are present [41]. In these conditions the hormonal activity of parathyroid tissue (typically in thymus), may become clinically significant [47].

Despite the multimorbidity of the patients undergoing this special type of operations, a thorough preoperative selection of patients and adequate operative techniques lead to very low perioperative mortality rates [48].

7. Cinacalcet

7.1. Mode of action

Cinacalcet hydrochloride is a positive allosteric modulator of the cell surface CaSR. Activation of CaSR inhibits the PTH secretion, stimulates the calcitonin secretion and lowers the Ca level in serum [49]. Currently cinacalcet is the only calcimimetic drug available on the market; it is a second generation substance of this class [50].

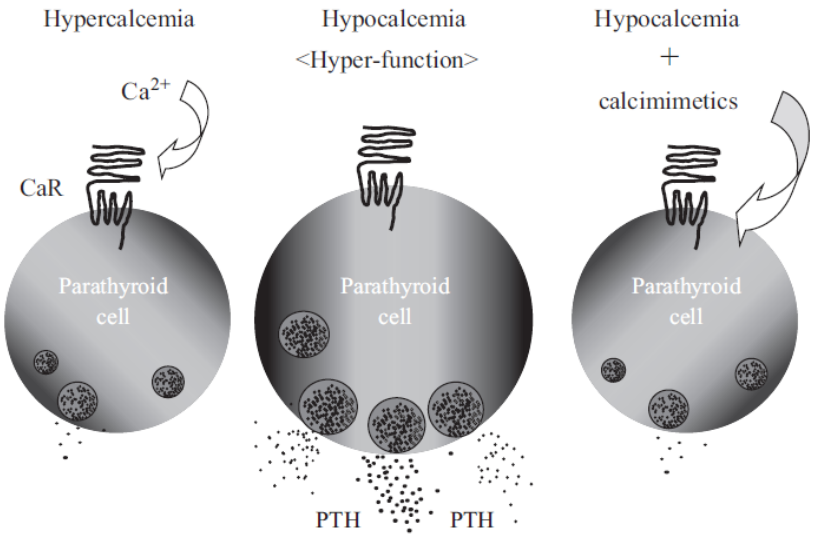


Figure 4: Action mode of calcimimetics. The images on the left and in the middle represent a physiologic response of parathyroid cells to high and low Ca levels. In a hypocalcemic state (right image) the CaSR may be activated through allosteric binding and a hypersecretion of PTH is thus avoided [51].

Other drugs from the group of calcimimetics are currently being tested, with alternative effect profiles, for example reducing PTH but not causing hypocalcemia in patients with CKD III-IV. An example of an emerging new calcimimetic is AMG416, velcalcetide [50, 52].

7.2. Clinical studies

In 2002 the corporation Amgen has synthesized cinacalcet [49]. Cinacalcet became commercially available for use in the US in May 2004 [53].
Multiple studies, ACHIEVE [35], ECHO [54], OPTIMA [55] and others were performed to define the properties and efficacy of the new drug.

ECHO was a pan-European study with observational design where patients with rHPT were included, both those with previous PTx and without it. The investigators focused the study on controlling the biochemical parameters as defined by K/DOQI. Cinacalcet has shown positive results in that the serum Ca, P, PTH levels were within K/DOQI treatment goals in most patients. There was no detailed report on the type of PTx operations performed [54].
In the US multicenter open-label randomized controlled ACHIEVE study cinacalcet + low-dose Vitamin D_3 was compared with flexible Vitamin D_3 therapy. The cinacalcet-treated patients have shown better therapy response according to K/DOQI treatment goals, and in a small proportion of these patients all four parameters decreased to reference ranges (Ca, P, Ca x P product, PTH) [35].
OPTIMA was a pan-European multicenter open-label randomized controlled study comparing cinacalcet-based therapy with conventional therapy with Vitamin D_3 analogues. The results were favourable for cinacalcet. Patients who were not responding to conventional therapy were more likely to achieve K/DOQI recommended target biochemical parameters on cinacalcet-based therapy [55].
In a 2016 meta-analysis patient-important outcomes in 24 published trials were reviewed. Patients receiving cinacalcet had significantly smaller number of parathyroidectomies performed, compared to standard therapy. There was no difference in mortality between the study arms [56].
Cinacalcet has shown to reduce PTH levels in patients with and without nodular hyperplasia and to reduce the volume of parathyroid gland measured with ultrasound [57, 58]. Another Japanese study has shown a reduction in serum PTH levels in patients either with or without nodular hyperplasia; however the reduction in parathyroid gland volume could not be confirmed [59].
Reviewing the study outcomes, Stubbs et al. [16] conclude that cinacalcet combined with $1,25(OH)_2D_3$ improves the overall CKD prognosis. It reduces the cardiovascular morbidity and mortality through multiple effects on RAAS (renin-angiotensin-aldosteron system) and FGF23, lowers the proteinuria, and reduces vascular calcification and inflammatory processes.

7.3. Indications for use

Cinacalcet is indicated for the treatment of rHPT in patients on chronic dialysis and to treat persistent/recurrent HPT after PTx in these patients [49, 60]. Combined therapy with cinacalcet and active Vitamin D_3 lowers PTH levels and improves Ca-P homeostasis in patients with renal HPT receiving chronic dialysis [35, 53]. There were also studies of cinacalcet in patients with CKD III and IV, showing a significant lowering of serum PTH and Ca, one of these was a

randomized double-blind controlled study by Chonchol et al. [61]. Yet cinacalcet was not approved by European authorities and the Food and Drug Administration (FDA) for this group of patients because of frequent occurrence of hypocalcemia in the treatment group as compared to placebo.

Recent studies have shown promising outcomes after de novo therapy with cinacalcet in patients with persistent HPT after KTx [54, 62, 63]. Nevertheless cinacalcet is not approved for routine use in this group of patients [64].

Other indications for the use of cinacalcet are:

- Cancer of the parathyroid glands [65]
- PHPT and as a part of MEN1 syndrome when an operation is not possible [66, 67]
- There are several described cases of treatment of familial hypocalciuric hypercalcemia [68].

7.4. Adverse effects

The most common adverse effects are those of the gastro-intestinal tract: nausea, vomiting and diarrhea, with mild to moderate intensity. Prevalence of nausea is reported as 10-43%, vomiting 4.7-30%, diarrhea 0.9-19% [35, 53-55, 64, 69, 70]. Clinical trials have shown that cinacalcet had no severe side effects, resulting in low rate of therapy discontinuation due to this reason, 6% according to some authors [35].

Hypocalcemia is another side effect in chronic dialysis patients receiving cinacalcet, in most reports this effect is asymptomatic although clinically relevant [53, 70].

8. Study design

In the present retrospective study the outcome of PTx in patients with or without cinacalcet treatment was analyzed. The emphasis was laid on the rate of perioperative, long-term cardiovascular and other complications, on the rate of recurrent and persistent HPT and on the renal graft function in transplanted patients.

9. Methods

9.1. Study design

9.1.1. Database

Inclusion criteria	Exclusion criteria
Renal HPT	pHPT
Operation in 01.01.2008 – 01.02.2015	Other types of HPT (as part of hereditary syndrome e.g. MEN-syndrome)
	Operations in other hospitals

Table 3: Inclusion/Exclusion criteria

A hospital-based database of patients with all types of HPT who underwent surgical treatment in Charité Campus Virchow Clinic was originally set up in 1998 and was retrospectively screened for patients with renal HPT in 2008-2015. Other types of HPT were not included in the research. There were two retrospective cohorts of patients, a cohort receiving cinacalcet preoperatively, and the other group without cinacalcet. The decision to prescribe cinacalcet was taken by the attending nephrologists. The surgical team had no influence on that decision.
There were few patients in the study who were operated on for persistent/recurrent HPT. Because of the small number of those patients (and lack of the exact data about the first operation) no separate analysis within that group was performed. The number of operations exceeded the number of patients due to reoperations. We used the term "case of HPT" and analyzed our study groups respective to the number of cases, not patients, when not explicitly noted otherwise. We did not include the cases of operations performed in other hospitals, whereas the operations for the recurrent disease performed in Charité were included and counted as independent cases.

9.1.2. Follow-up (Surveillance)

The above mentioned attending nephrologists treated the patients after discharge from hospital and performed the surveillance. They provided us on request (per fax, mail or e-mail) with most of the information on the follow-up as to 05.2015. Another source for the follow-up information was the European transplantation database "TBase" containing data on patients on the transplantation list.
Data on survival, diagnosis/comorbidities, and laboratory values of patients were acquired from the above two sources in addition to the conventional medical records in SAP Program.

9.2. Patient cohort

Standard demographic data: age, sex and age by the time of operation were routinely registered in all patients.

9.2.1. Medical treatment

Patients referred to the Charité hospital for operation continued to receive cinacalcet when it was prescribed by their physician. Cinacalcet was stopped after the operation was performed. Hemodialysis was performed at usual intervals.

9.2.2. Surgical treatment

Patients were referred to the clinic by the attending nephrologists. Indication for the operation was a result of an interdisciplinary nephrological-surgical conference.

All patients in both cohorts were operated on by the same surgical team.

The standard surgical treatment was sPTx.

A tPTx was performed in the following situations:

- high risk of recurrent HPT in patients not listed to KTx,
- intraoperative situation, when no suitable parathyroid tissue could be preserved (due to anatomical reasons).

A subtotal PTx was a standard operative procedure for tHPT in the Charité Clinic.

A neuromonitoring of the laryngeal recurrent nerve was performed in all cases.

Cervical thymectomy was not routinely performed. Indication for this procedure was a missing parathyroid gland.

Other surgical interventions were very rare and will be described individually.

AT was not routinely performed.

Simultaneous thyroid surgery was performed based on indication, either preoperatively or during the operation, or in search of missing parathyroid glands. The performed operations were hemi- and thyroidectomy, Dunhill-operation, subtotal resection and enucleating of nodes. The cases of simultaneously performed thyroid operations were separately documented and analyzed.

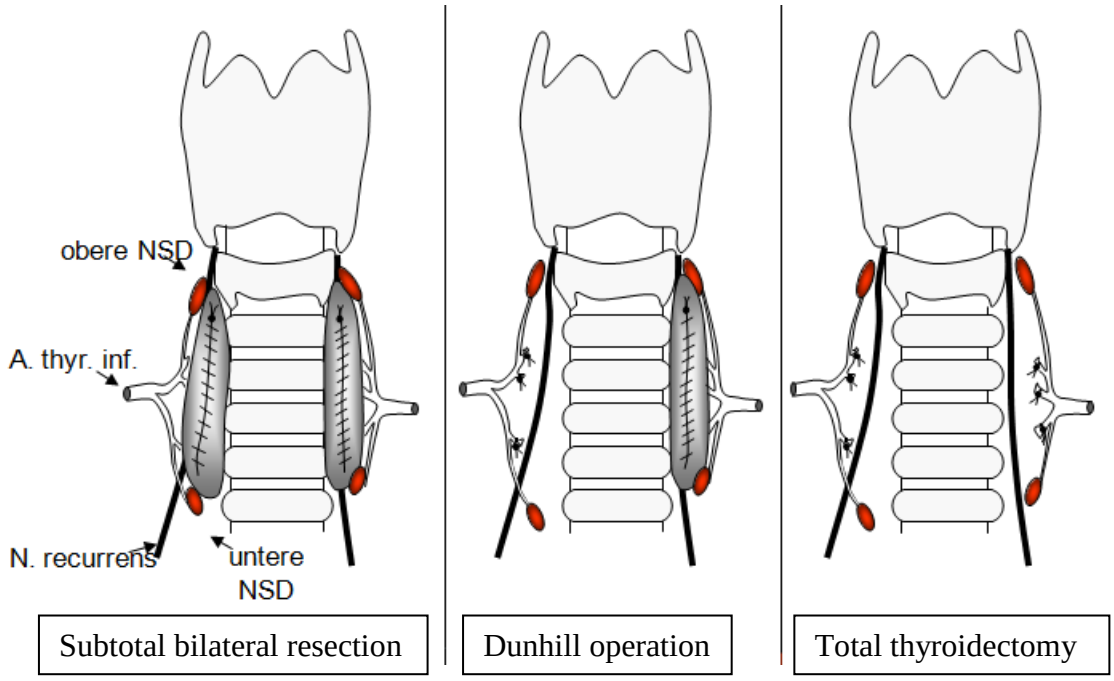


Figure 5: Different types of thyroid operations, image from: The surgical treatment of bilateral benign nodular goiter—balancing invasiveness with complications [71].

Resected tissue was pathologically processed and a histological confirmation of the parathyroid tissue was obtained. Cryopreservation was performed in all cases.
The rate of surgical complications was registered, including bleeding and hematomas, wound infection and nerve damage.
The duration of in-hospital stay after the operation was determined based on medical records.

9.2.3. Outpatient treatment

A long-term medical therapy was prescribed by attending nephrologists and was continued with required modifications during the in-hospital stay.
Dialysis in respective patients was performed at usual intervals; the date of the first chronic dialysis session was registered.
Stage of CKD and preoperative serum creatinin level were documented. Duration of dialysis in patients with transplanted kidneys, who were no longer susceptible to it, was registered.
Referring nephrologists were performing surveillance including assessment of graft function after hospital discharge, corresponding data were obtained from the TBase, missing data were provided on request.

9.2.4. Perioperative treatment

Postoperative daily Ca-controls and a PTH control on the 1-st postoperative day were performed. In cases of symptomatic hypocalcemia, additional controls were performed. In cases with high

postoperative PTH levels they were repeatedly controlled. With falling PTH levels the operation success was stated and standard surveillance was recommended. In cases of non-falling PTH levels an individual diagnostic and treatment protocol was developed. If a persistent hyperparathyroidism was present, diagnostic tests (PTH selective venous sampling, MIBI SPECT) were done.

1000mg Ca was given orally three times a day. When the Ca level was falling on the following day, 2000mg or more were given orally. For most of the patients this regimen was sufficient, and for patients with Ca below 1.6 mmol/l and symptoms of tetany a parenteral substitution was indicated. Another factor stabilizing serum Ca was haemodialysis with a supplementation of Ca, which was the case in many of the patients. In addition, Vitamin D_3 (calcitriol 0,5µg once a day) was administered.

The discharge of patients depending on their serum Ca levels was possible only when those were stable in daily blood samples, defined as two non-falling Ca levels in 2 subsequent days under oral substitution.

9.3. Study instruments

9.3.1. Laboratory values

The preoperative Ca and PTH level, as well as creatinin, AP (alkaline phosphatase), and P were measured using the routine laboratory technique in Charité Clinic. Reference ranges are presented in the table below. The surveillance of laboratory values was performed by external physicians and these were recalculated in SI units respectively.

Laboratory test	Measure units (SI)	Reference ranges
AP	U/l	35-105
Ca	mmol/l	2.15-2.5
Creatinin	mg/dl	0.5-0.9
P	mmol/l	0.87-1.45
PTH	ng/l	14.9-56.9

Table 4: Laboratory tests and reference range

The following definitions for CKD staging were used:

CKD V, or terminal CKD

CKD IV or preterminal CKD

CKD II, III or compensated CKD

CKD I termed in this report as “no kidney insufficiency” on the graphs.

According to K/DOQI guidelines, in patients with terminal CKD target range of PTH was defined as 150-300 ng/l [34].

9.3.2. Ear-nose-throat specialist evaluation

Each patient was evaluated by an independent ear-nose-throat (ENT) specialist before and after the operation. Vocal cord status was documented with special emphasis on transient/persistent palsy as a sign of laryngeal nerve trauma. If recurrent nerve palsy did not resolve within six months, it was defined as persistent. In cases of newly diagnosed recurrent nerve palsy the attending physicians were individually contacted and the patients were followed up by Charité phoniatric clinic.

9.4. Statistical methods

The data were analyzed with STATISTICA 7.0 software (Stat Soft Inc., USA). All numerical results are presented in means ± standard deviation (independent from normality of the distribution) and categorical results – as percentages. Numerical data were tested on normality with Kolmogorov-Smirnov test (K-S test).

Normally distributed data was tested with an unpaired t-test after comparing the variances with Levin-test. In the analysis of nonparametric data in independent groups Kolmogorov-Smirnov test was used for continuous variables. Chi-square (χ^2) test with Yates's correction or Kruskal-Wallis H test was used for nominal variables. Nonparametric data in dependent groups were analyzed with Wilcoxon matched pair test. A Kaplan-Meier survival analysis with Log-Rank test for group comparison was performed.

Statistical significance was defined by $p<0.05$.

10. Results

10.1. Demographic data

The study included 191 patients resulting in 196 operations (cases). There were 80 cases (41%) with cinacalcet therapy. Basic population data are presented in the table below.

	With cinacalcet, n=80	No cinacalcet, n=116
Sex	39 male /41 female (49/51%)	76 male /40 female (66/34%)
Age (mean±SD)	51.2±13.3 years	51.5±12.7 years

Table 5: Demographic data

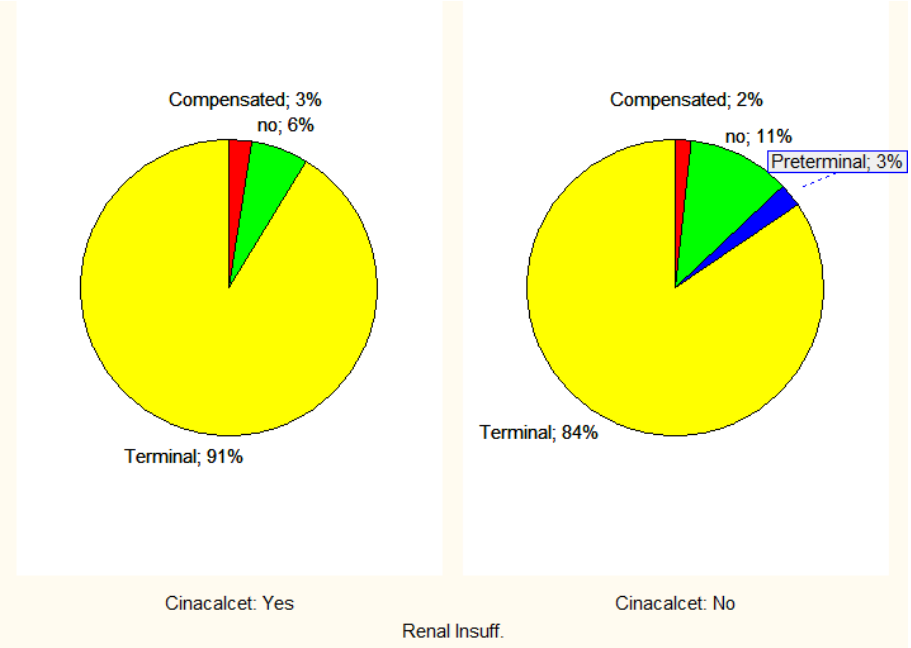
10.2. Chronic Kidney Disease

The diagnoses leading to CKD (counted per capita, not by case numbers) are listed in the table below in descending order:

	Count	Percent	
Diabetic nephropathy	30	16%	Σ=71%
Polycystic kidney disease	25	13%	
Chronic glomerulonephritis	20	10%	
Focal segmental glomerulosclerosis	16	8%	
Hypertensive nephropathy	15	8%	
IgA Nephropathy	11	6%	
Interstitial nephritis	9	5%	
Membranoproliferative glomerulonephritis	10	5%	
Other	56	29%	

Table 6: Diagnoses leading to CKD

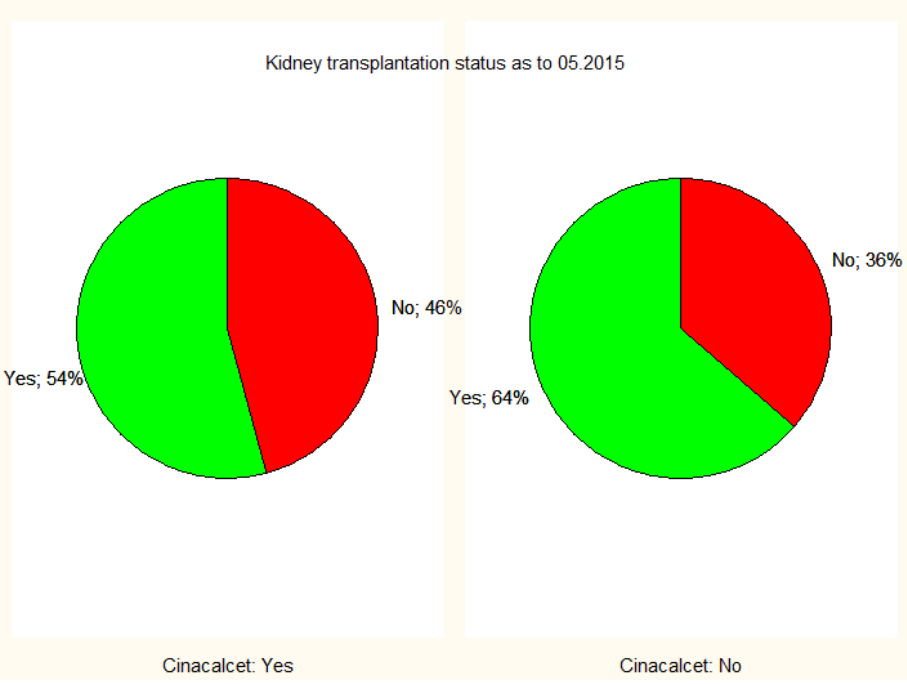
The CKD stage at the moment of operation was distributed as follows:



Graph 1: Diagram of renal insufficiency status by the time of PTx

The patients without renal insufficiency all had a functioning kidney graft. They constitute a group with renal HPT even after the KTx.

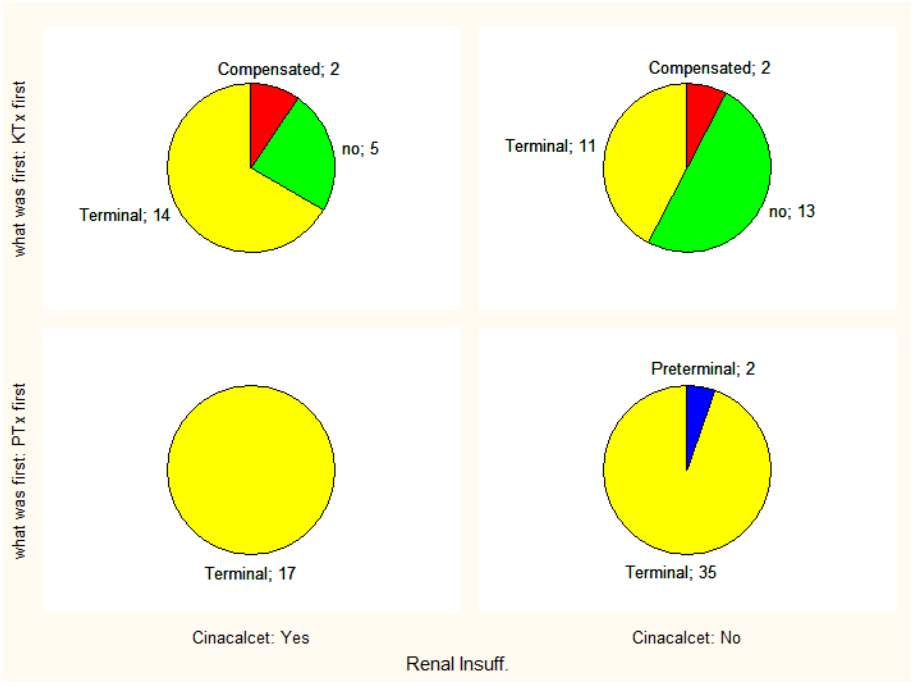
There were 60% of transplanted patients in the study group as to May 2015 (counted per capita):



Graph 2: Diagram of KTx status in patients related to cinacalcet therapy

The PTx operation could be performed either before or after the KTx.

The status of graft function is presented below (only transplanted patients are included). Patients are sorted in groups related to cinacalcet therapy and according to the order of operations: those undergoing PTx before KTx are in the lower row.



Graph 3: Diagram of the CKD stage in transplanted patients related to the time of PTx and cinacalcet therapy.

There were six patients with more than one KTx, detailed data on chronological order of their operations is presented below:

Patient No. /sex/age by operation	KTx date	KTx date	KTx date	Graft function at the time of PTx	PTx date	KTx date	Graft function as to 2015
1/w/47	1985	1987	1997	No	2011		No
2/m/50	1983	1990	2000	No	2014		No
3/w/49	1984	-	-	No	2009	2010	Yes
4/m/69	2005	-	-	No	2009	2010	Pat. deceased
5/m/40	1997	-	-	No	2012	2014	Yes
6/w/51	1998	-	-	No	2009	2014	Yes

Table 7: Detailed data on patients with more than one KTx

10.3. Comorbidities

The study patients had a high rate of multimorbidity. The following chronic diseases were registered:

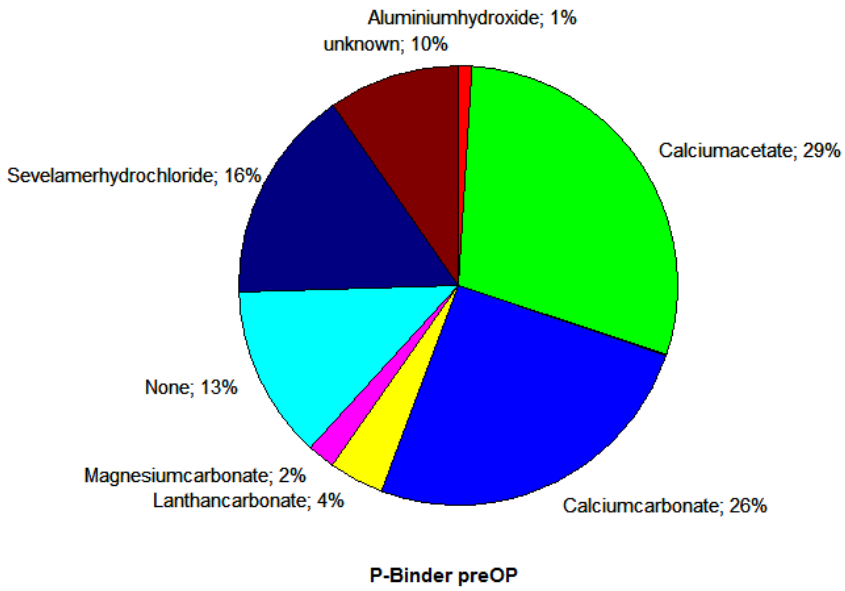
Diagnosis	With cinacalcet	Without cinacalcet
aHT	100%	100%
DM Type I	4%	3%
DM Type II	24%	22%
Adipositas	9%	13%
Ischemic heart disease	30%	27%

Table 8: Major comorbidities in the study population

10.4. Medical treatment

The prevalence of cinacalcet therapy was 41%, with no missing data.

In 82% of the cases patients were receiving phosphate binders, in 13% this therapy wasn't applied, in 5% of the cases the data were missing. The diagram represents the type of phosphate binders used in the whole group.



Graph 4: Diagram of distribution of phosphate binders in the study group.

In 86% of the cases active vitamin D_3 analogues were given, 8% didn't receive this treatment, in 6% the data were missing.

The preoperative use of phosphate binders and vitamin D_3 analogues in the groups relative to cinacalcet is presented below. The distribution did not differ between the two groups (χ^2 test, p=0.7512).

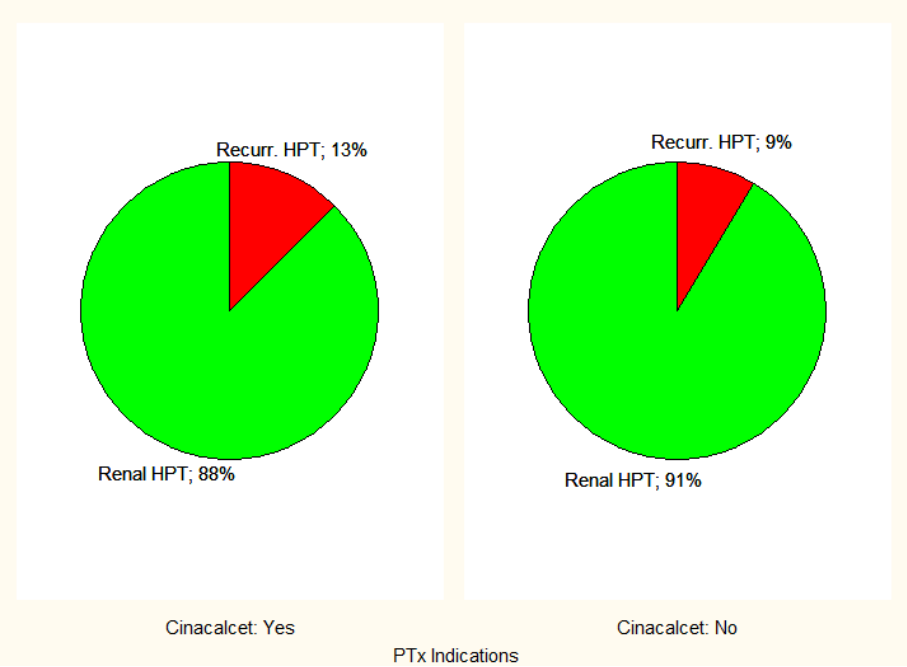
	Preoperative cinacalcet	No cinacalcet
Phosphate binders	66	86
Vitamin D	70	98

Table 9: Data on medical therapy, presented in case numbers.

10.5. Operative data

10.5.1. Operations

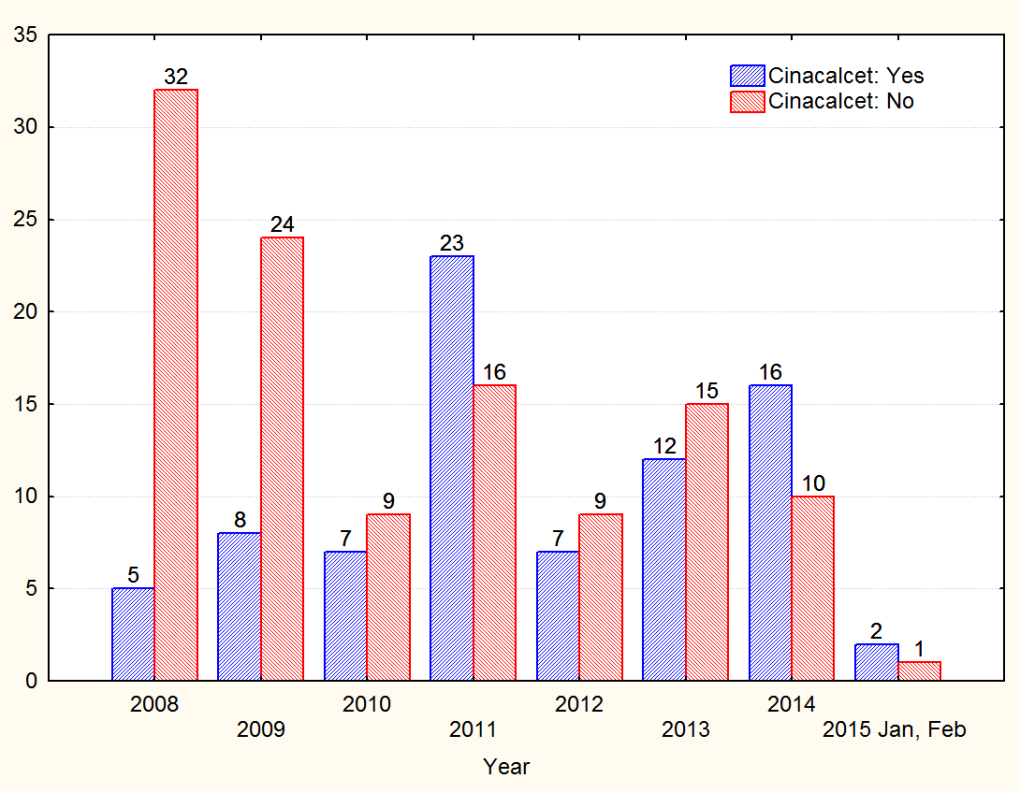
89% of all cases were primary operations for renal HPT; operations for recurrent HPT were performed in 11% of cases. The distribution in the two study groups was as follows:



Graph 5: PTx indications in groups with/without cinacalcet.

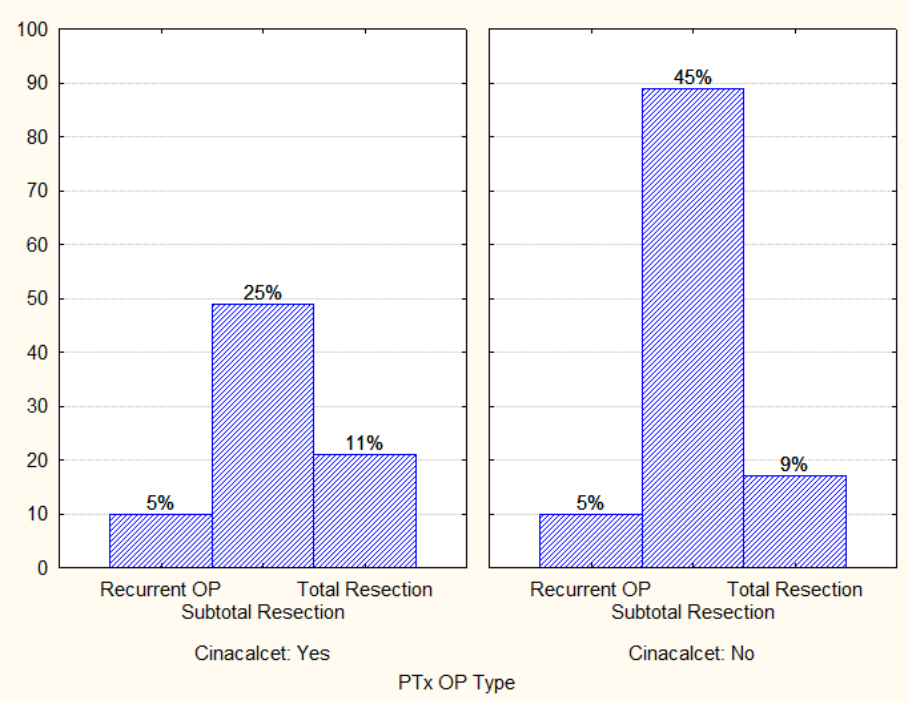
Operations for recurrent HPT were performed in 20 cases on 19 patients. Five patients were initially operated on in Charité Clinic and 15 patients had their first operations in other hospitals. One patient was operated twice for recurrent HPT within the study time range (2nd reoperation). Time interval between the first operation and reoperation was 915±771 days (mean±SD), range 215 to 1902.

The distribution of all types of operations by years is shown in the bar chart below, divided in two study groups respectively. There is a trend of increased cinacalcet usage (Graph 6 below). The proportion of patients receiving cinacalcet preoperatively shows a statistically significant difference among the observation years (Kruskall-Wallis H test p<0.0001).



Graph 6: Histogram of number of operations sorted by years and cinacalcet therapy.

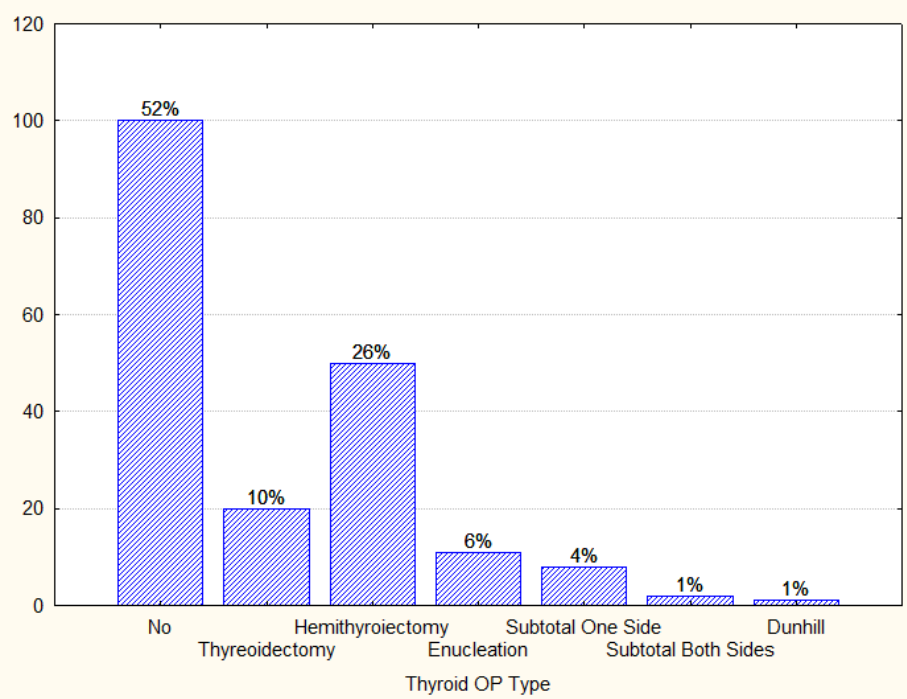
The operations performed were sPTx in 70% of cases (n=138), and tPTx in 20% of cases (n=38), the distribution in the study groups is presented below. The remaining 10% of operations were performed for recurrent HPT. A multigroup comparison didn´t detect a statistical significance in distribution of operation types (Kruskall-Wallis H test, p=0.0611).

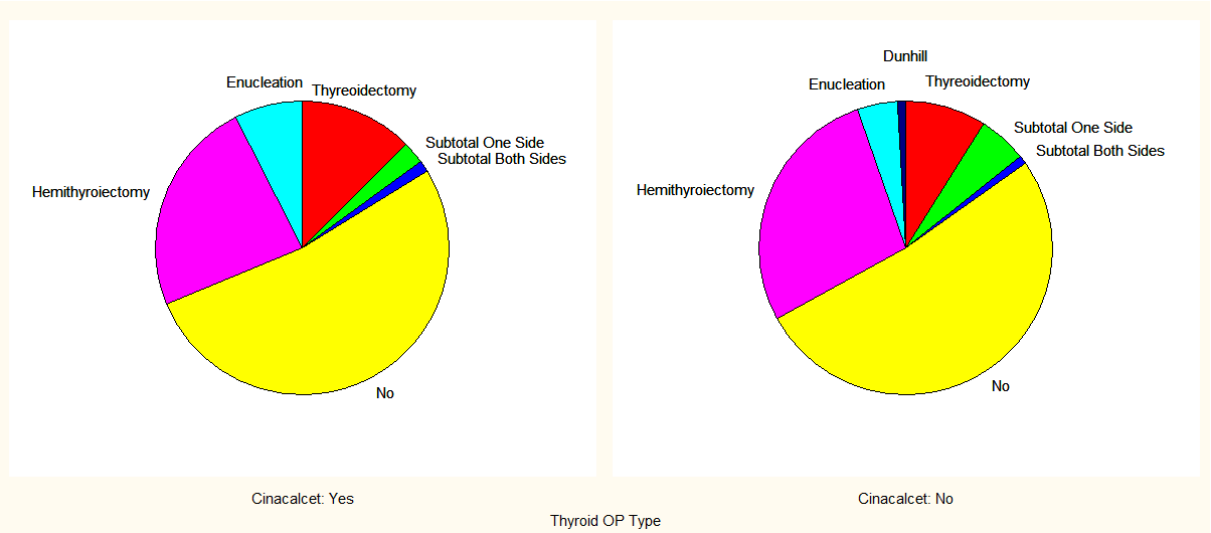


Graph 7: Types of operations related to cinacalcet therapy.

The type of operation for recurrent HPT was determined individually based on preoperative imaging studies. Among those two thoracoscopies for mediastinal adenomas were performed (both in the group without cinacalcet).

Simultaneous thyroid surgery was performed in 47% of cases; the types of operations are presented below (Graph 8). There was no statistical significance in their distribution between the study groups, Kruskal-Wallis H test p = 0.7344 (Graph 9).



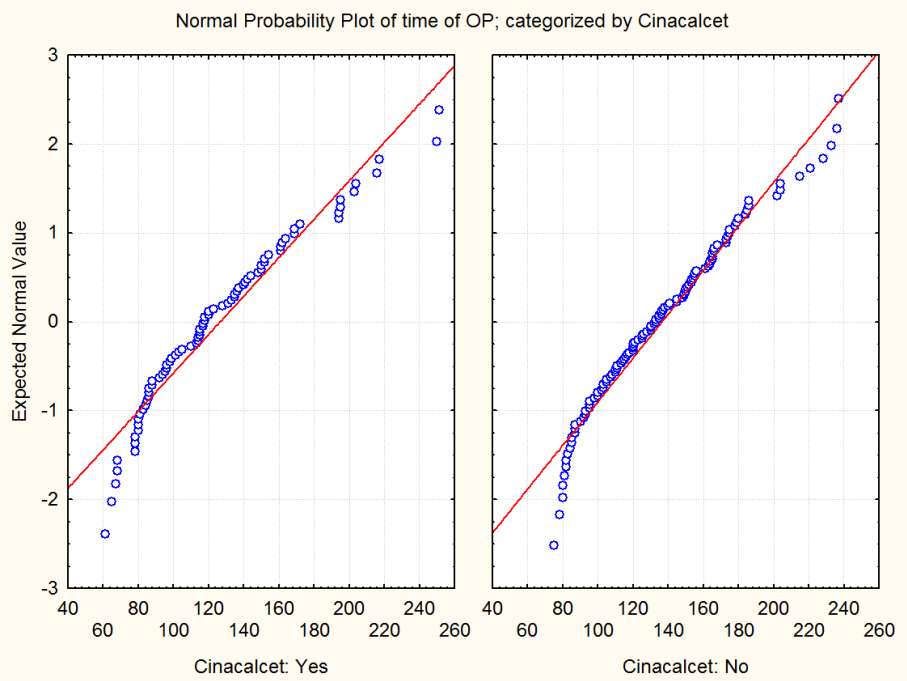


Graph 8, 9: Prevalence of simultaneous thyroid operations.

Indications for simultaneous thyroid surgery were toxic adenoma (n=1), multifocal toxicity (n= 2), potentially malignant thyroid nodules (n= 18), multinodular nontoxic goiter (n=56). Another indication for hemithyroidectomy was a missing parathyroid gland on the corresponding side and suspicion of intrathyroidal parathyroid glands (n=12).

In six patients thyroid cancer was histologically confirmed. There were four patients with papillary thyroid cancer and one with medullary thyroid cancer. One patient with hemithyroidectomy and no cancer at the time of PTx some years later developed cervical lymph node metastasis (adenocarcinoma of unknown origin).

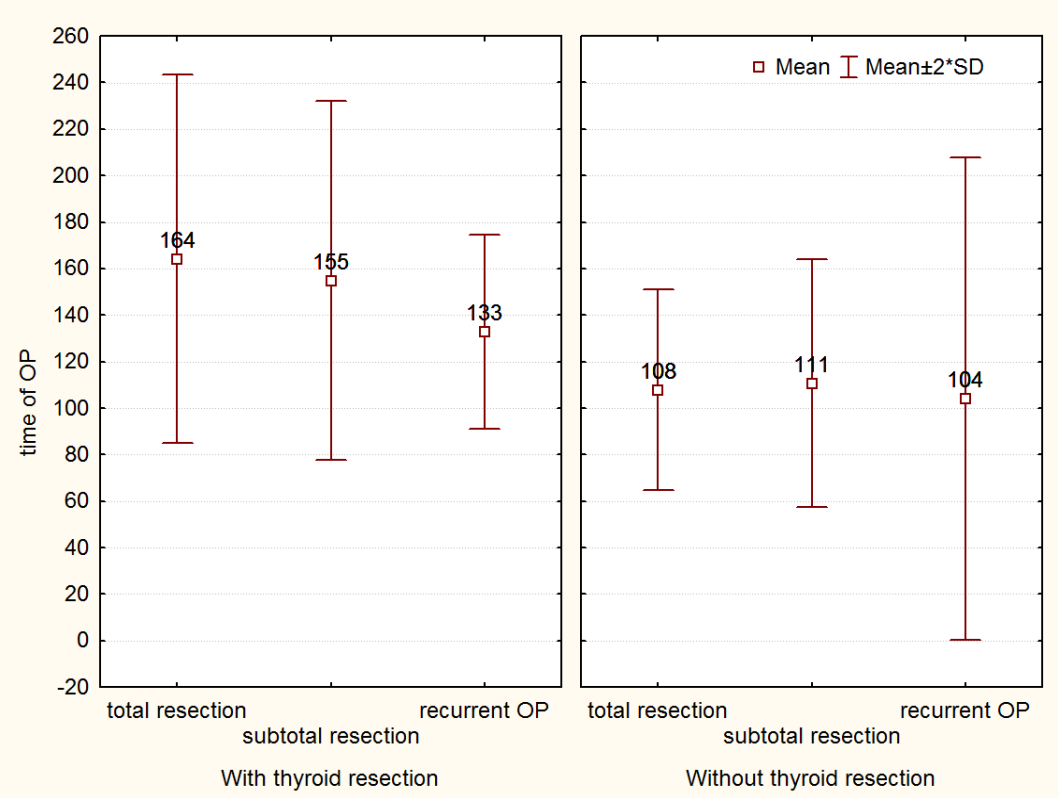
Operation time did not differ between the two study groups, 126±44 vs. 136±39 minutes with/without cinacalcet respectively (p=0.11, t-test), showing a normal distribution as in the figure below.



Graph 10: Operation time (in minutes) related to cinacalcet therapy.

Operation time in case of simultaneous thyroid surgery was higher compared to PTx alone, with means of 156.3 and 109.5 minutes respectively (p=0.02, t-test).

Operation time related to the type of parathyroid operation and simultaneous thyroid operation is presented below:



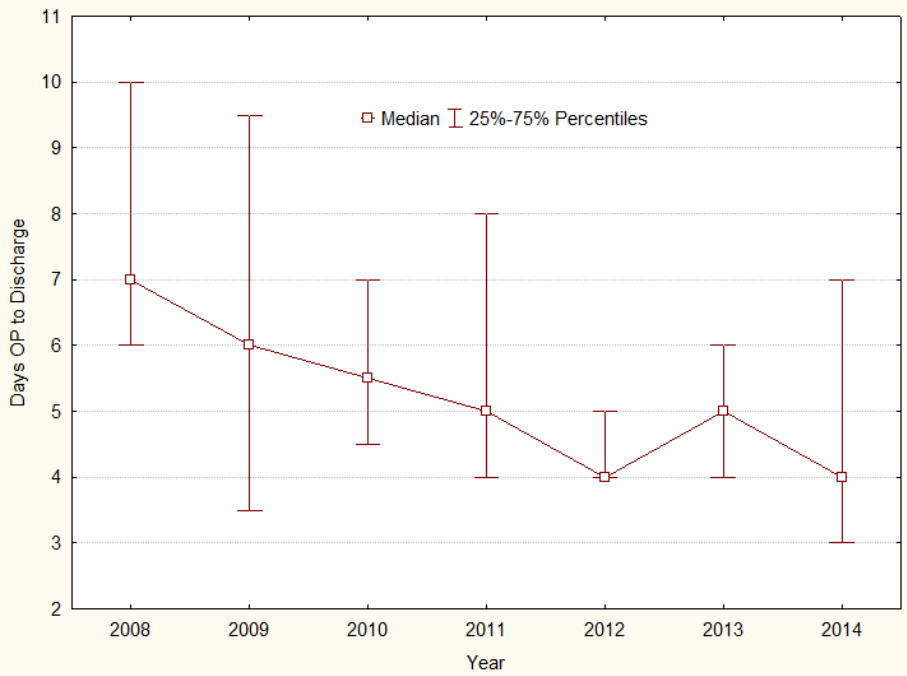
Graph 11: Operation time related to PTx type and simultaneous thyroid operation.

10.5.2. Replantation of cryopreserved tissue

Routine cryopreservation of PTG tissue was performed in all cases with a 0% rate of replantation during the study period.

10.5.3. Duration of (in-)hospital stay

Mean duration of in-hospital stay in our study was 7.0 days, similar in both groups (7.0 vs. 7.1 with/without cinacalcet, p>0.1, K-S test). Comparing the mean values in years a decreasing trend could be observed (presented as an interquartile range graph, year 2015 omitted because of only three performed operations):



Graph 12: Duration of in-hospital stay, median annual values (2008-2014).

10.6. Surgical complications

There were five recurrent nerve palsies, resulting in 5/196=2.6% complication rate. One case of laryngeal recurrent nerve palsy was confirmed to be persistent, the other four were temporary.

Patient No. /sex/age by operation	LRN palsy type	Type of PTx	Simultaneous thyroid operation	Cinacalcet therapy
1/w/31	Permanent	Recurrent operation	Hemithyroidectomy	Yes
2/w/38	Temporary	sPTx	Thyreoidectomy	No
3/w/65	Temporary	sPTx	None	No
4/m/34	Temporary	sPTx	Hemithyroidectomy	Yes
5/m/26	Temporary	sPTx	None	No

Table 10: Detailed data about patients with postoperative recurrent nerve palsy.

Reoperation rate due to wound complications was 3/196 =1.5%, there were two wound hematomas and one case of wound infection requiring revision operation.

The eight patients with high postoperative PTH levels ≥300ng/l (K/DOQI cut-off) were analyzed separately under the assumption of persistent HPT.

- Patients No. 1 and 4 have shown a reduction of PTH levels in laboratory controls by hospital discharge thus confirming the efficacy of surgical treatment.
- In patient No. 2 and 3 controls at discharge and two years after the operation respectively showed acceptable PTH levels.
- In patient No. 5 only 3 PTG were localized during the operation, and these were completely removed, and a hemithyroidectomy was performed, 1-year follow-up was not reached.
- Patient 6 was operated for recurrent HPT (initial OP in another hospital). During the neck exploration no PTG was found.
- Patient No. 7 was operated seven months after the initial OP for persistent rHPT. Initially a sPTx with a subtotal hemithyroidectomy was performed. During reoperation no additional PTG were found and a hemithyroidectomy on the other side was performed. One-year control showed low PTH level.
- Patient No. 8 had a supernumerary PTG in the neck, which was resected during a reoperation on the third postoperative day.

None of these patients needed cinacalcet therapy postoperatively (two patients are lost to follow-up).

Patient No. /sex/ age by operation	Year of operation	Preoperative PTH	Postoperative PTH	PTH at discharge	PTH 1 year after operation	PTH 2 years after operation	Death as to 05.2015
1/w/44	2009	537.0	366	83			No
2/w/70	2011	545.0	374	199			Unknown
3/w/53	2012	718.2	399	440	No data	161.5	No
4/m/50	2008	491	406	5			Yes
5/w/45	2014		415.5	326.8	No data		No
6/m/68	2014	957.2	851	851	No data		Unknown
7/m/54	2008	No data	440	382	6	5	No
8/m/38	2011	1241	300	12	8.3	14.7	No

Table 11: Data on patients with high postoperative PTH levels.

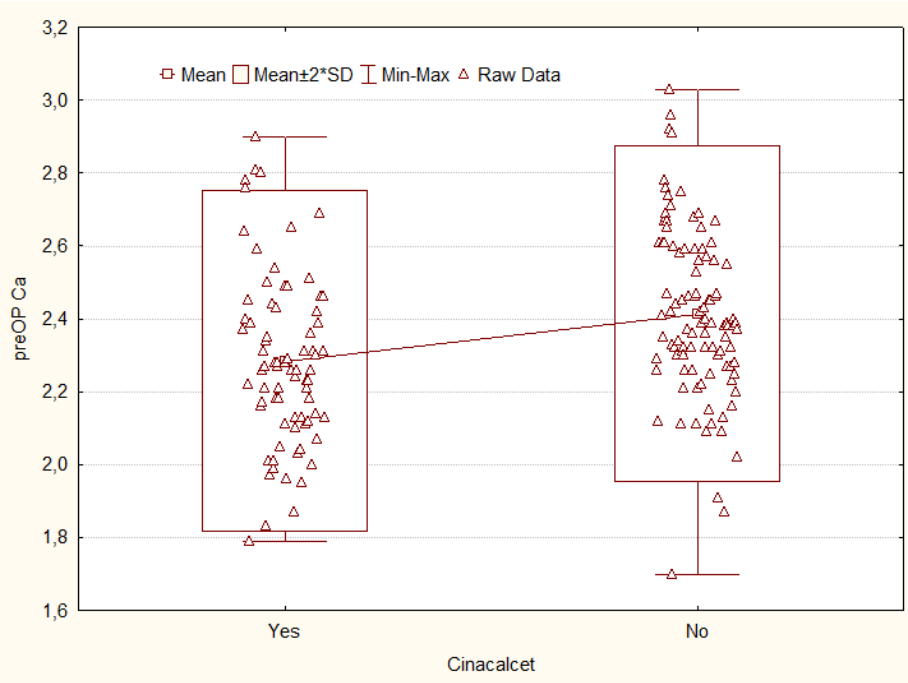
Persistent HPT was thus diagnosed in four cases (PTH at discharge >300ng/l).

There was one cardiovascular event in the postoperative period (group without cinacalcet): atrial fibrillation for a period of six hours, which was medically corrected.

There was no perioperative mortality; all patients were discharged from hospital.

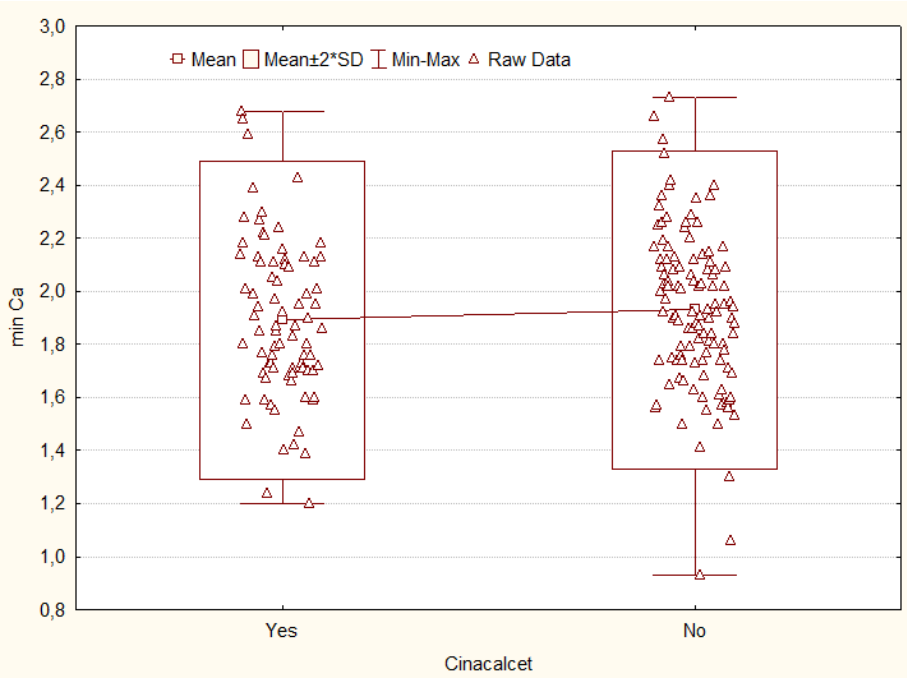
10.7. Perioperative Ca homeostasis

The preoperative serum Ca level was significantly lower in the cinacalcet group, 2.28±0.23 vs. 2.41±0.23 (p=0.0002, t-test).



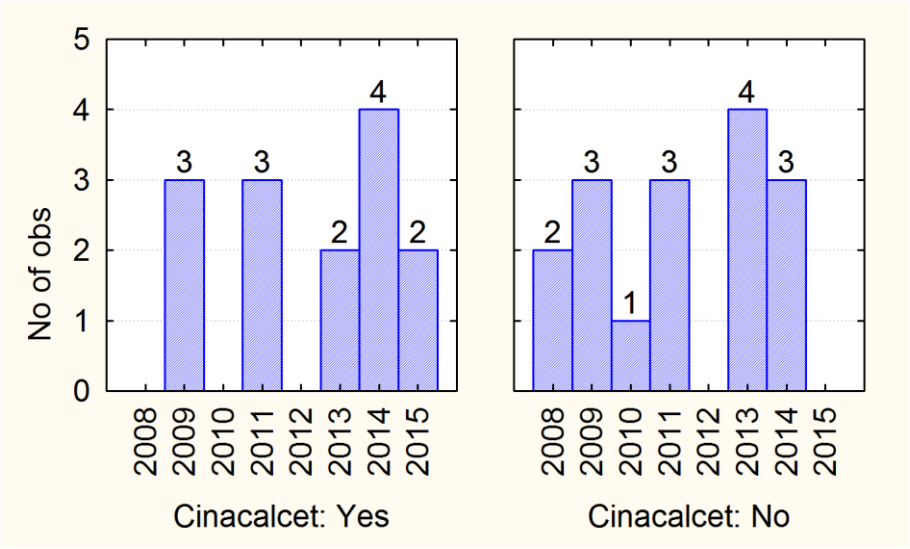
Graph 13: Preoperative serum Ca levels related to cinacalcet therapy.

The lowest postoperative serum Ca levels were not significantly different in the two groups, 1.89±0.30 vs. 1.92±0.30 (p=0.40, t-test).



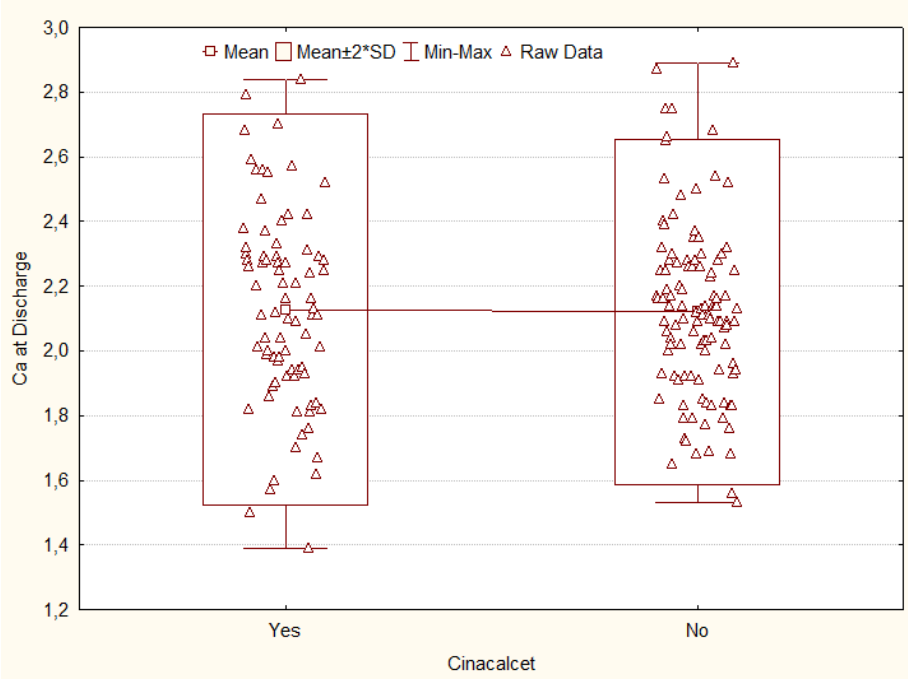
Graph 14: Lowest postoperative serum Ca levels related to cinacalcet therapy.

A mean number of 2-4 patients per year had symptomatic hypocalcemia after the operation with serum Ca < 1.6mmol/l (no statistical significance in Ca levels, K-S test p>0.10)



Graph 15: Number of patients with symptomatic hypocalcemia in both study groups by years.

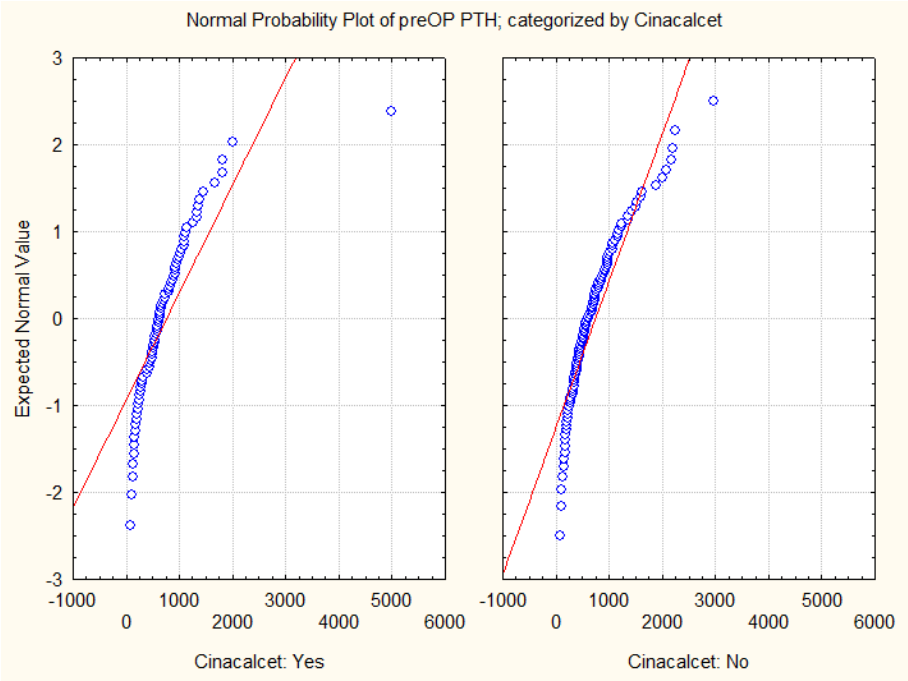
Ca levels at discharge did not differ in the two study groups, 2.12±0.30 mmol/l with cinacalcet and 2.12 ±0.27 mmol/l without it (p=0.90, t-test).



Graph 16: Serum Ca levels at discharge related to cinacalcet therapy.

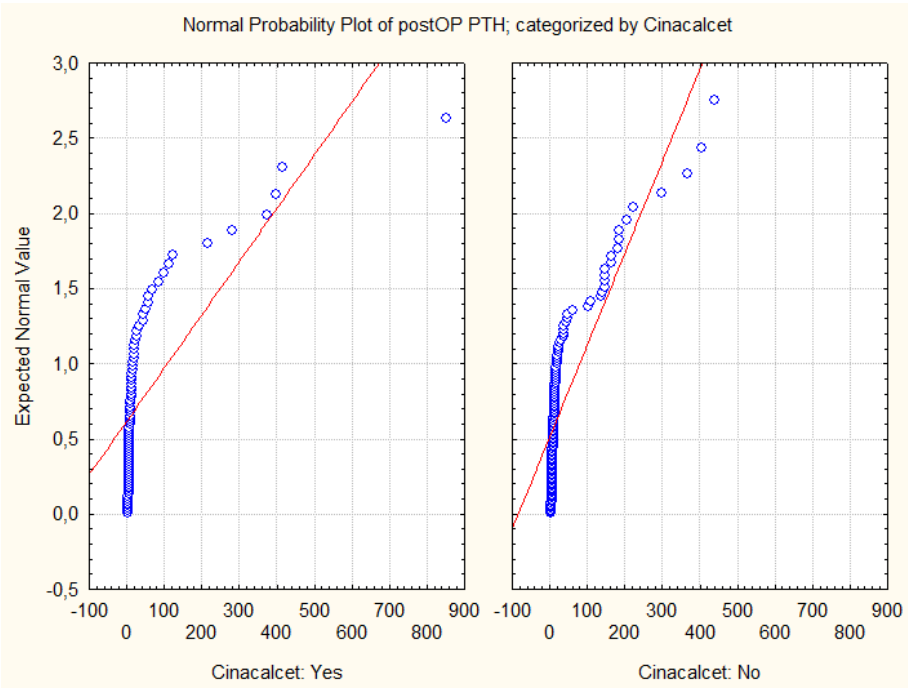
10.8. Perioperative PTH levels

The study groups did not differ regarding preoperative PTH levels, having mean values of 755 and 742ng/l with and without cinacalcet respectively (p>0.10 K-S test). The values are presented as a normal probability plot for better visualization, although normal distribution is not confirmed (K-S test for normality p<0.01).



Graph 17: Preoperative PTH levels related to cinacalcet therapy.

Controls of PTH on the 1-st postoperative day showed no significant difference between groups, with mean values of 49.8 and 42.2ng/l with and without cinacalcet respectively ($p>0.10$ K-S test). The values are presented as a normal probability plot (K-S test for normality is $p<0.01$).



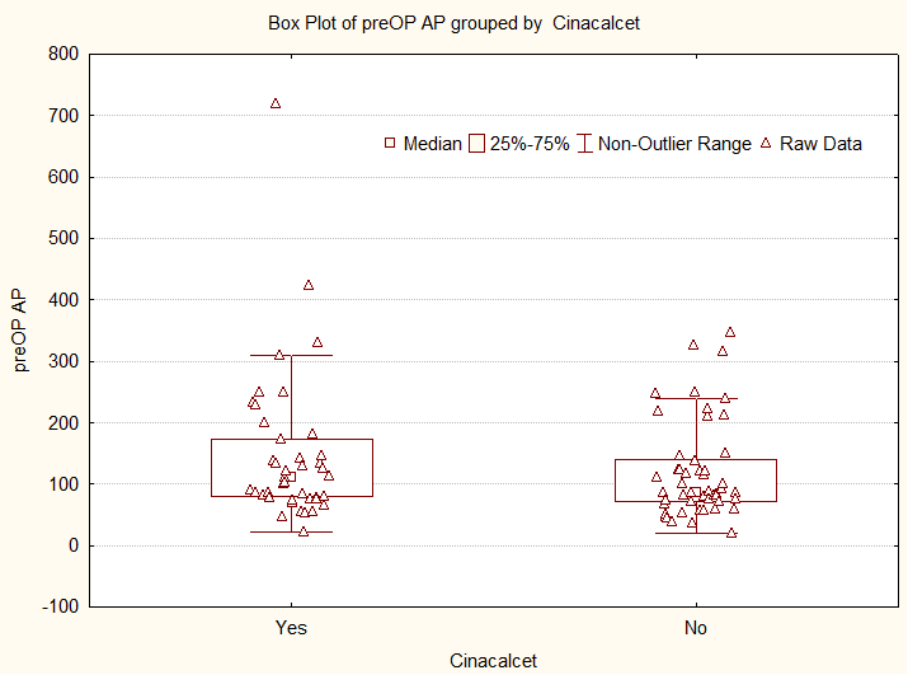
Graph 18: Postoperative PTH levels related to cinacalcet therapy.

In patients with high postoperative PTH levels additional PTH control at the time of hospital discharge was performed. There were four patients with PTH levels >300ng/l (K/DOQI cut-off

level), three of them (1.5%) received cinacalcet preoperatively. In these patients, persistent HPT was confirmed.

10.9. Alkaline phosphatase preoperative data

Alkaline phosphatase levels were measured once before the operation, alkaline phosphatase level at discharge was not documented. In groups of patients with and without cinacalcet alkaline phosphatase levels did not significantly differ ($p>0.10$, K-S test). Data is presented as box and whiskers plot for a better visualization.



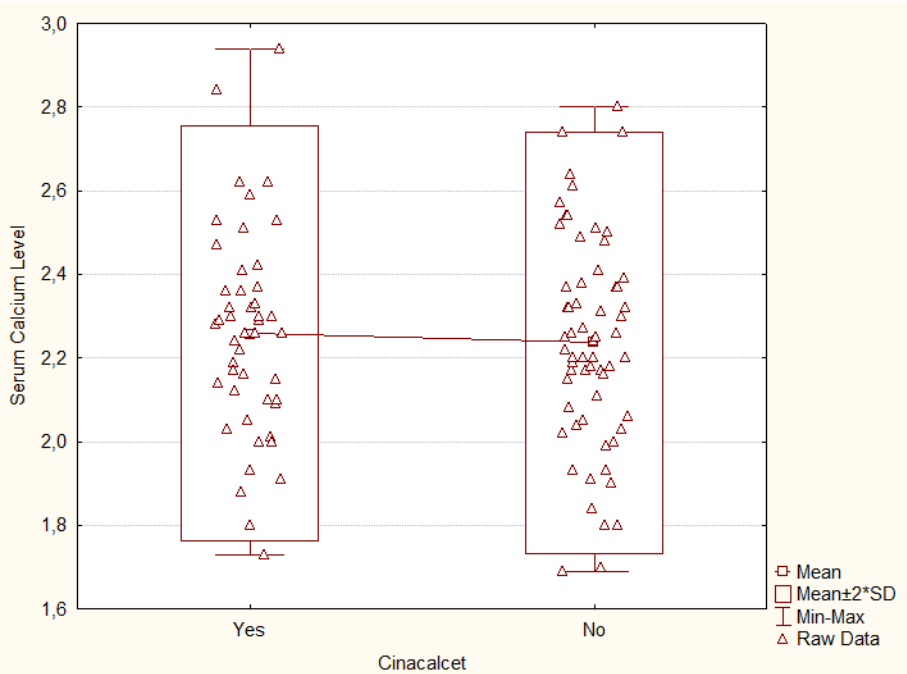
Graph 19: Alkaline phosphatase levels preoperatively related to cinacalcet therapy.

10.10. One-year follow-up data

Mean follow-up time was 48.4±25.2 months (4 to 88), 39.7±22.6 (4 to 86) with cinacalcet and 54.4±25.3 (4 to 88) without cinacalcet. Therefore, it was significantly shorter in the cinacalcet group ($p<0.001$, K-S test).

10.10.1. Ca levels at 1-year controls

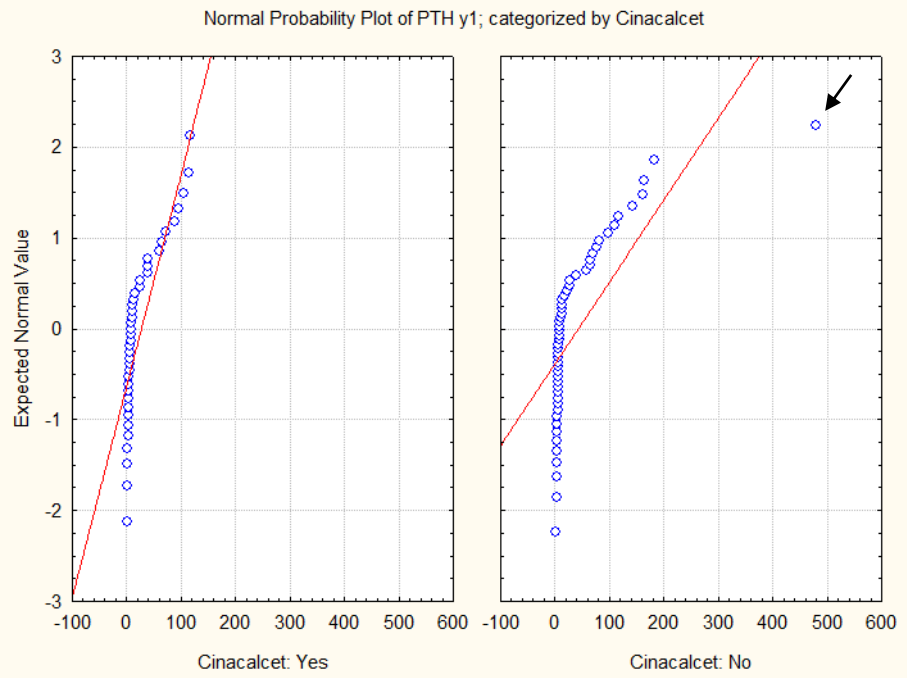
Ca control one year after the operation showed no significant differences in the two study groups, 2.26±0.25 in the group receiving cinacalcet preoperatively and 2.24±0.25 in the other one ($p=0.67$, t-test).



Graph 20: Ca levels at 1-year controls related to preoperative cinacalcet therapy.

10.10.2. PTH levels at 1-year controls

PTH one year after the operation showed no significant differences in the two study groups, mean values were 26.9 ng/l in the group receiving cinacalcet preoperatively and 42.1 ng/l in the other group ($p>0.10$, K-S test). Values are presented as a normal probability plot (K-S test for normality is $p<0.01$). The marked case (↙) will be discussed separately (female patient W.).



Graph 21: PTH levels at 1-year controls related to preoperative cinacalcet therapy.

We separately observed the PTH levels in patients with extremely high PTH levels before the operation (>2000), because a high risk of recurrence was assumed. It was noticed that the PTH levels were decreasing to normal or acceptable ranges in all patients.

Patient No. /sex/ age by operation	Year of operation	preoperative PTH	Postoperative PTH	PTH at discharge	PTH 1 year after operation	Death as to 05.2015
1/w/69	2013	2017	124	124	24	No
2/m/26	2009	2085	39	39	No data	unknown
3/w/64	2012	2164	13	3	No data	unknown
4/w/43	2011	2204	10	10	56	No
5/w/51	2009	2255	24	12	6	No
6/m/36	2010	2967	9	9	7	No
7/w/47	2011	5000	281	196	No data	Yes

Table 12: Data on patients with extremely high preoperative PTH levels.

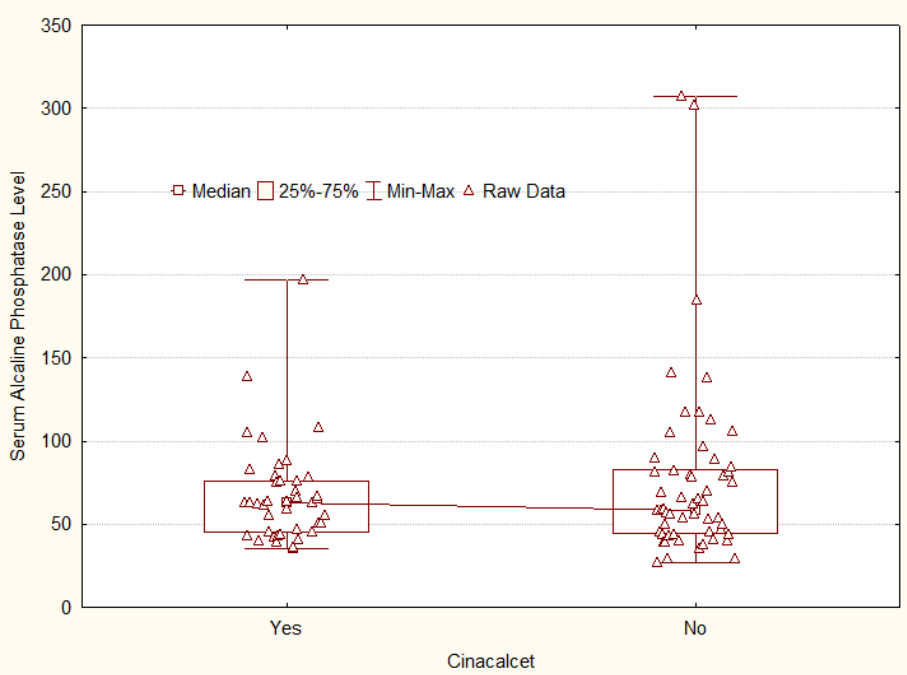
The single patient, who had undergone a hemithyroidectomy and one-sided PTx in 2011 with acceptable levels of PTH at discharge, had high PTH levels one year after operation. A recurrent HPT was diagnosed and a reoperation was performed in 2012 with complete remission.

Name/ sex	age at operation	Year of operation	Preoperative PTH	Postoperative PTH	PTH at discharge	PTH 1 year after operation	Death as to 05.2015
W., female	72	01.2011	209	146	196	480.8	No
	74	11.2012	587	10	10	39.6	

Table 13: Detailed description of the patient with persistent HPT one year after the initial operation.

10.11. AP levels at 1-year controls

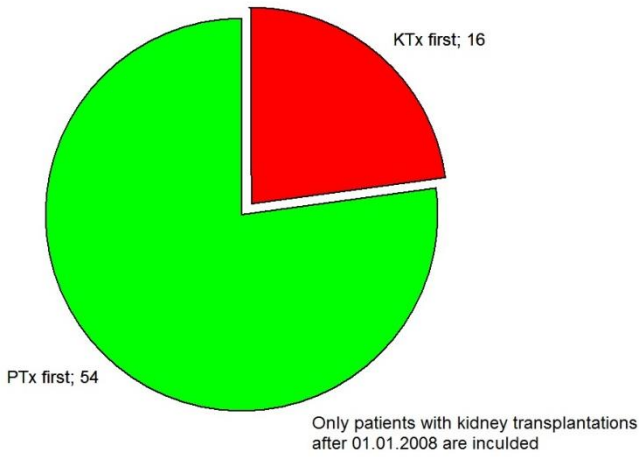
AP levels of patients in the two study groups at 1-year controls did not show a statistically significant difference ($p>0.10$, K-S test), a box plot is presented below.



Graph 22: Alkaline phosphatase levels at 1-year controls related to preoperative cinacalcet therapy.

10.11.1. Graft function one year after PTx

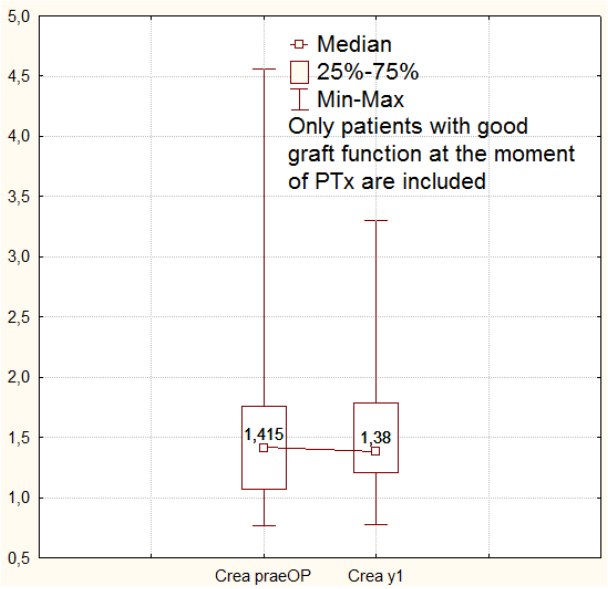
Nephrologists in the Charité clinic recommend performing PTx before KTx to avoid possible deterioration of kidney graft function. The proportion of patients in whom the parathyroidectomy was performed before kidney transplantation, or vice versa is shown in the figure below.



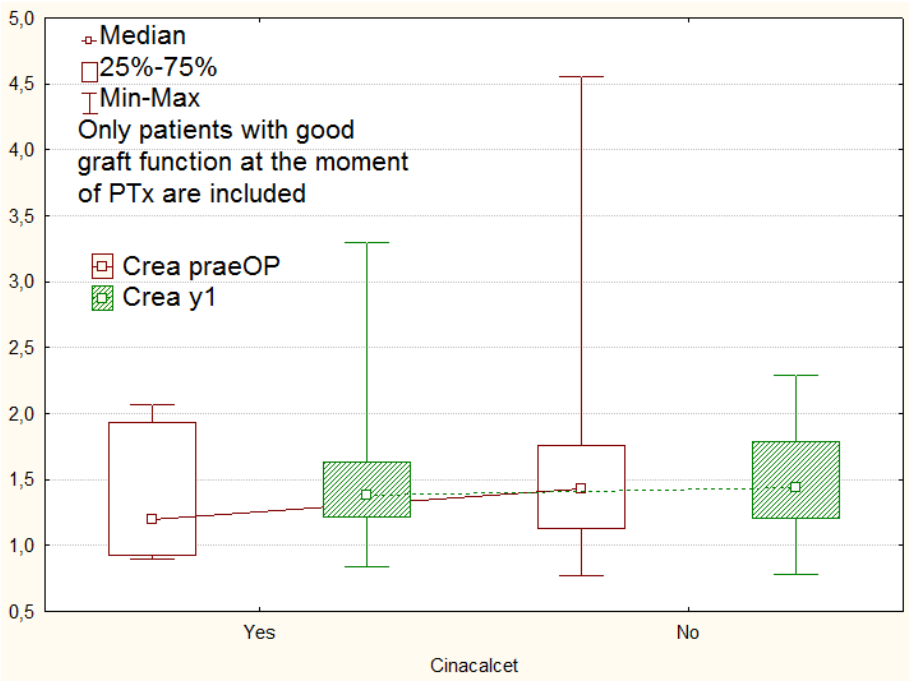
Graph 23: Proportion of patients undergoing PTx before and after KTx during the study period

Prevalence of preoperative cinacalcet therapy between these groups did not differ significantly (χ^2 test, p=0.7725).

Some of the patients with a kidney graft (KTx before PTx) had a good graft function and CKD stages I, II, III at the time of the PTx (22/47 transplanted patients). Creatinin levels before the PTx and at one-year control were compared in patients with kidney grafts and compensated kidney function at the moment of operation. There were no statistically significant differences in creatinine levels one year after the PTx neither in the whole group nor in the subgroups with/without cinacalcet (Wilcoxon test p=0.11 for whole cohort, p=0.14 with cinacalcet, p=0.33 without cinacalcet).



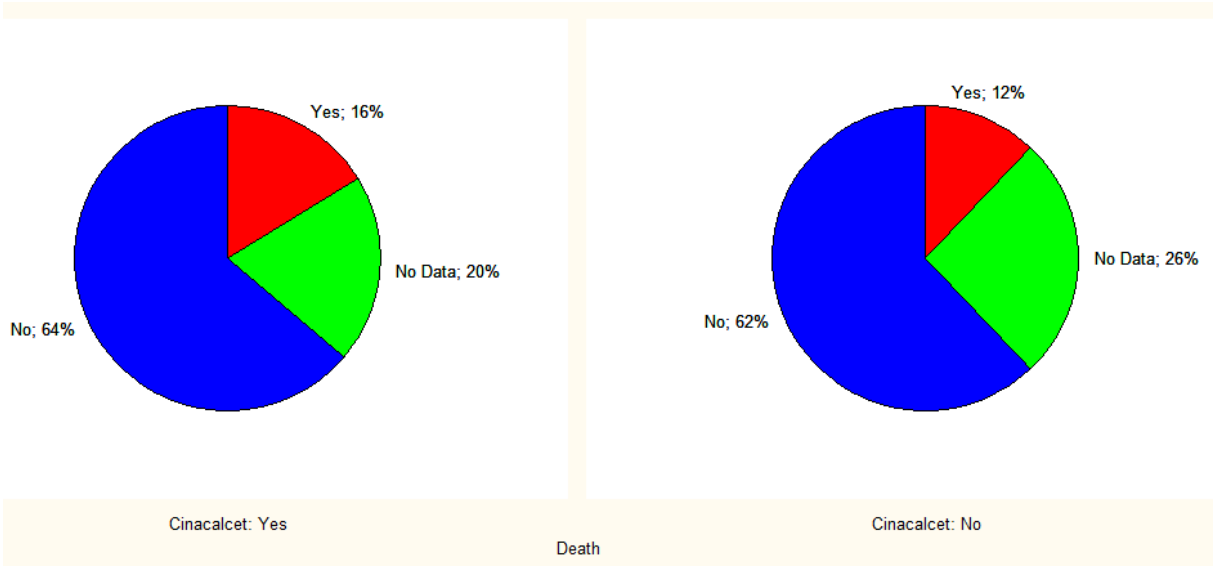
Graph 24: Creatinine levels in patients with kidney grafts and good graft function by the time of PTx and at one year controls.



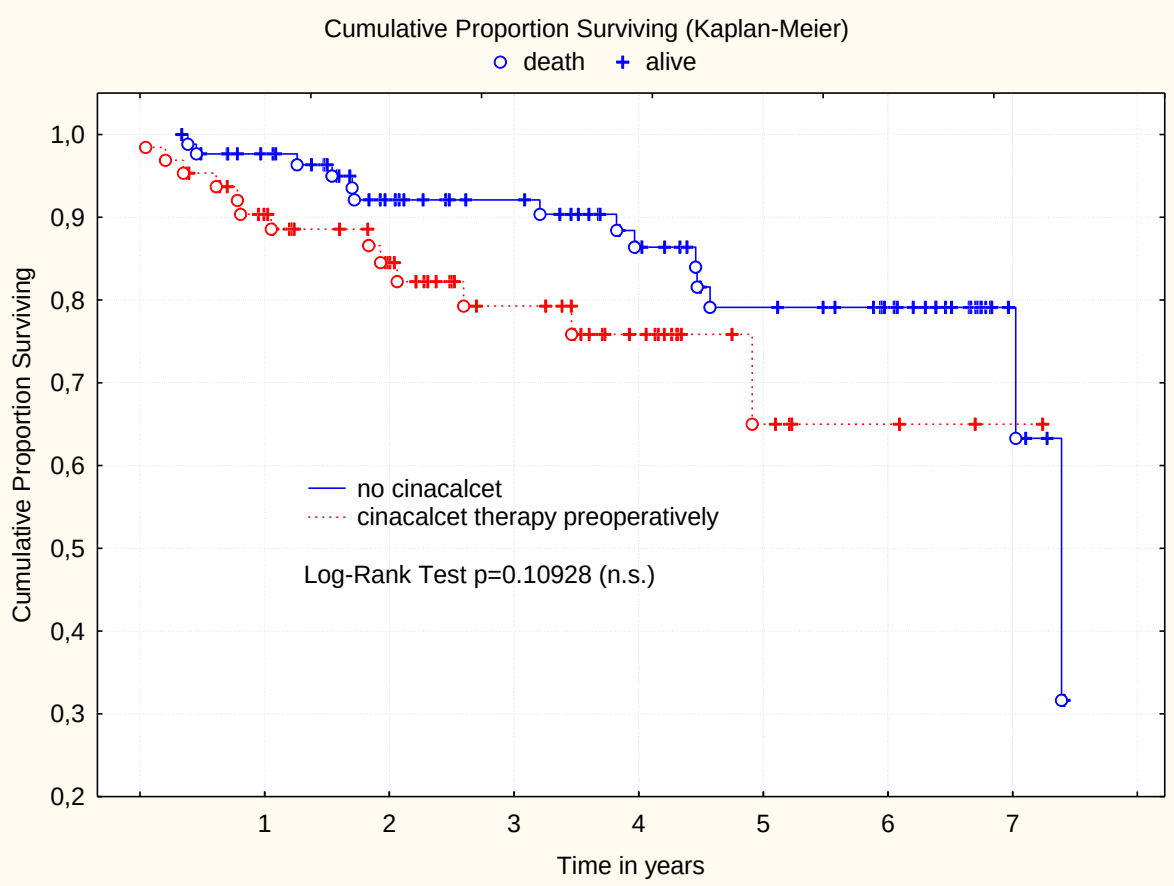
Graph 25: Creatinine levels in patients with kidney graft and good graft function by the time of PTx and at one year controls related to cinacalcet therapy preoperatively.

10.12. Mortality rates (as to 31.05.2015).

The follow-up data for the present study were obtained in close cooperation with the referring physicians. Nevertheless a significant number of patients (46 of 191 i.e. 24%) were lost to follow up. They were international patients with missing contact data, patients who relocated and/or changed the referring physicians, and those who didn't show up for the termed controls due to unknown reasons.



Graph 26: Diagram of mortality rates as to 05.2015 related to cinacalcet therapy preoperatively. Mortality rates did not differ in the two study groups (12/52 vs. 14/72 with vs. without cinacalcet; p=0.68, χ^2 test).



Graph 27: Kaplan-Meier survival analysis for the two study groups.

A Kaplan-Meier survival analysis with Log-Rank test comparing the two study groups did not show a statistical significance (p= 0.10928).

10.13. Cardiovascular events (as to 31.05.2015)

The following table shows the prevalence of cardiovascular events after PTx in both study groups. The precise moment of each event was not limited to the time of observation, but the cut-off point was the end of the study. The comparison has shown no significant statistical difference between the groups.

	With cinacalcet	Without cinacalcet	Statistical significance (χ^2-test)
Myocardial infarction	13%	18%	Non significant
PTA/Bypass	13%	22%	Non significant
Peripheral Bypass	9%	12%	Non significant
Stroke	13%	10%	Non significant

Table 14: Cardiovascular events as to 05.2015 related to cinacalcet therapy.

11. Discussion

Cinacalcet is a relatively new drug, introduced to market in 2004, but to date there is a substantial amount of experience of using it in specialized clinics and nephrological centers. Most of the publications regarding therapy with cinacalcet are focused on the changes in treatment of renal HPT in patients on chronic dialysis after the introduction of a completely new active agent. The present study is focused on patients who received cinacalcet and underwent surgical treatment for renal HPT.

Published data suggests that cinacalcet effect in renal HPT is limited in time, and HPT recurrence also happens in patients receiving medical treatment preoperatively [33, 59]. In our study all patients in the cinacalcet group had high levels of HPT and indications for PTx. Ten out of 20 patients undergoing surgical treatment for recurrent disease were treated with cinacalcet preoperatively.

The main result of the undertaken retrospective study is that no significant differences in the intra- and postoperative period in patients with and without cinacalcet therapy have been detected. That implies a similar risk/benefit ratio for patients undergoing surgical treatment of renal HPT both after prior treatment with cinacalcet and without it.

The rate of cardiovascular events and mortality by the end of the surveillance period was not significantly different in the study groups.

There were no perioperative deaths and no life-threatening complications.

The rate of recurrent HPT was 5/196=2.6% within the study period and was similar in both groups. The rate of persistent HPT was 4/196=2.0% with nearly all patients in the cinacalcet group (3/196= 1.5%).

Kidney transplanted patients with good graft function at the time of PTx showed no significant differences in creatinine levels one year postoperatively.
The study has revealed practically equivalent retrospective outcomes of surgical treatment for renal HPT, either after the therapy with cinacalcet or without it.
There are currently only few other publications comparing perioperative data on patients with and without cinacalcet undergoing surgical treatment.
Oltmann et al. studied the perioperative course of 36 patients with end stage renal disease treated by parathyroidectomy. [72] Many preoperative parameters (Ca, P, PTH, pre- and postOP, surveillance, all-cause survival) were observed to have influence on the outcome of patients with sHPT undergoing PTx. 50% of patients were treated with cinacalcet preoperatively but there was no analysis of the outcome related to cinacalcet therapy.
In a second report from Coulston et al. [73] cinacalcet therapy was applied to 16.5% of patients receiving parathyroidectomy, but again, no separate analysis of this parameter was performed either.
In a recent retrospective research [74] a decrease in numbers of parathyroidectomy for tHPT since 2004 is stated, which coincides with the introduction of cinacalcet to the market.

11.1. Characteristics of the study group

The retrospective analysis was performed using a single-centre database. The observed time range was 2008 - 2015, whereas cinacalcet has been available since 2004. This made it possible to include patients who were treated with cinacalcet and showed refractory high PTH levels. They were compared to the patients who received no cinacalcet but were operated on at the same period of time.
The study population comprises patients who were operated on for renal HPT. We included patients either with sHPT, or with tHPT. Mean age (51.4±12.9, range 12 to 81 years) and number of comorbidities in the study group differ much from the general population of chronic dialysis patients, thus, the rate of diabetic nephropathy alone was 16% compared to 35% in the combined group of German chronic dialysis patients [26]. The overall rate of KTx in the study group was 60%, which can be regarded as an indirect sign for younger age and overall better ASA risk class.
The two study cohorts were comparable in basic demographic data - age, sex and rate of comorbidities (Table 5, table 8). The number of patients in the group receiving cinacalcet was smaller (80 vs. 116), although the histogram (Graph 6) shows a rising number of patients in the

cinacalcet group. There are correlating published data: in a study from 2010 [73] the rate of patients receiving cinacalcet was 16.5%, in 2015 [72] 50%.
The study groups had similar proportions of primary operations for renal HPT and operations for recurrent renal HPT, the rate of recurrent operations was 13% vs. 9% (Graph 5).
The patient population represents a multimorbid group, most of them receiving chronic dialysis for a long period of time. At the time of operation most patients had terminal CKD and were on dialysis. In the group without cinacalcet there were more patients with sufficient renal function (16% vs. 9%), which can be accounted for two reasons: first, cinacalcet is not allowed in CKD III-IV; second, ($p>0.10$ K-S test)

in patients with transplanted kidney and good graft function cinacalcet can be prescribed for treatment of HPT only after individual clinical evaluation and confirmation from the insurance company.

11.2. Operative data

11.2.1. Types of operations

There were two types of operations for renal HPT in our study population: sPTx being a standard procedure (n=138) and tPTx without AT (n=38) performed in patients with high risk of recurrent disease and due to anatomical reasons. Although in the K/DOQI guidelines [34] the three operations, tPTx, sPTx, and tPTx with AT are described as equally effective in view of the outcome, the choice of the operation can be left to the surgeon. In a retrospective study (n=606) by R. Schneider et al. [40] different types of operations for renal HPT were compared. The most common operation in that study was a tPTx with AT (504 of 606) as the standard procedure in the institution. The sPTx was performed in 21/606 cases as the equivalent procedure before 1991. The rate of persistant HPT requiring reoperation was not significant as well no autotransplantation of cryopreserved parathyroid tissue was necessary. A tPTx without AT was performed in 32/606 cases, and there were no reimplantations in that subgroup, as well as no adynamic bone disease. The authors conclude that tPTx without AT may be accepted as a routine operation and the existing practice of routine cryopreservation should be critically evaluated, although the risk of adynamic bone disease should be kept in mind.
There was a study comparing tPTx with tPTx+AT+thymectomy by K.Schlosser [75]. None of the patients with tPTx only received a delayed AT. The need for routine cryopreservation of parathyroid tissue was put under the question, and further studies were anticipated.

In our study groups special parameters of renal bone disease could not be analyzed, but no clinical symptoms, like bone pain and fractures, were reported from the referring physicians and alkaline phosphatase levels were not elevated during the follow-up (Graph 22).
In a previous retrospective study performed at our clinic 33 kidney transplanted patients with tHPT have undergone either sPTX or tPTX without AT. A relatively high rate of HPT persistence or recurrence (5/16=31%) was observed in the sPTx group compared to 0/17 in the tPTx group. No symptomatic hypoparathyroidism or hypocalcemia was observed under medical treatment in both groups [45].
A meta-analysis was performed to compare the efficacy of sPTX and tPTX with AT related to rate of recurrent HPT, both retrospective and prospective studies were included [76]. Authors state both procedures to be equally effective and to have similar recurrence rates. Neither of the studies included in this meta-analysis, nor in any other publication have compared outcomes of different operations related to cinacalcet therapy preoperatively.
Based on our study results and on published data, the two operative procedures (sPTX and tPTX) are comparable regarding outcomes, complications and recurrence.
There was a similar proportion of operations for recurrent HPT in the study groups, 5% and 6% with/without cinacalcet respectively (Graph 7). Operations for recurrent disease are technically more challenging, due to postoperative scarring with fibrosis, abnormal anatomy and difficulties in both preoperative imaging and intraoperative localization of parathyroid tissue. In addition to cervical operations, two thoracoscopic removals of ectopic PT glands were performed (both in the group without cinacalcet).

11.2.2. Operating time

The operating time did not differ significantly between the study groups (means 126 and 136 minutes), but was significantly longer in case of simultaneous thyroid operation (156.3 vs.109.5 min). Simultaneous thyroid operations were performed in 47% of the cases (Graph 10, graph 11).
A report by L.Kuo [48] with 898 retrospectively reviewed operations shows a mean operative time of 133 and 120 min in groups of tPTx and sPTx respectively. The rate of simultaneous thyroid operations was 9.2% but the operating time in those cases was not separately analyzed. So overall, the operation time was within the expected range compared to the literature.
The overall high rate of thyroid disease [71] is one reason for the high rate of simultaneous thyroid operations. An additional indication for thyroid resection is presumed intrathyroidal parathyroid gland in case of a missing gland. In 12 of 196 (6%) of cases one of the PTG could not be found, so in 7/12 of these cases a simultaneous thyroid operation was performed.

11.2.3. Surgical complications

The rate of complications was 2.6% (5/196) for recurrent laryngeal nerve palsies, 0.5% (1 case) was permanent (Table 10). This patient had a redo operation for recurrent rHPT. In literature the overall reported rate of temporary laryngeal nerve palsy in operations for rHPT was 5.4% by Schneider et al. [40], 11.6% by Schlosser et al. [38], with 1.1% and 0% of permanent palsies respectively. Probably, the use of intraoperative neuromonitoring and the fact that only few and very experienced surgeons performed the operations led to the relatively low rate of recurrent laryngeal nerve palsies. Notably, 1% of patients had preoperative laryngeal nerve palsies detected on the preoperative ENT check. This underlines the importance of thorough examination of the vocal cords routinely before and after the operation.

A study by Shih [46] reports 14.9% (14/94) postoperative complications: combined neck hematomas and vocal cord palsy, unfortunately without further specification. In this study ENT assessment either before or after operation was not performed as a routine procedure, only a clinical assessment was stated.

In addition, 1.5% wound complications were recorded, 1% of them being hematomas and 0.5% wound infections requiring revision. Again, there were no significant differences between the study groups. No previous reports on that issue have been published so far.

The rate of postoperative bleeding was reported to be 0.45% by L.Kuo [48]. Schneider et al. [40] report 1% of bleeding rate, 1.3% of wound infection, our data being similar to both studies; the overall complication rate in the latter retrospective analysis [40] was 7.9% (including cardiac, neurologic and other).

11.2.4. Duration of hospital stay

In recent years a tight cooperation of outpatient nephrologists and dialysis centers has allowed earlier discharge of patients once the Ca levels were defined as stable (not decreasing in two consequent blood tests) under oral Calcium- and Vitamin D_3 supply (Graph 12). The preoperative use of cinacalcet had no influence on the hospital stay in our patients.

Compared to the study by L.Kuo [48] with a mean of four days of in-hospital stay, our study has shown a longer in-hospital stay, discharge conditions were not documented by Kuo. The study by Shih [46] reports a mean duration of in-hospital stay of 6 and 9 days in tPTx and sPTx groups respectively, discharge conditions were defined as stabilized normal serum Ca levels. These numbers were comparable to the results at the first years of this study.

11.3. Perioperative PTH and Ca homeostasis

The two study groups had similar preoperative PTH levels with means of 755 and 742 ng/ml (Graph 17). At the same time the preoperative serum Ca levels differed significantly, being lower in the cinacalcet group, 2.28±0.23 vs. 2.41±0.23 mmol/l (p=0.0002, t-test) presumably reflecting the efficacy of cinacalcet on Ca homeostasis, but not on PTH levels (Graph 13). The study of medically treated patients with renal HPT has shown significantly lower Ca levels compared to placebo-controls [53].

The postoperative minimal Ca levels and Ca levels at discharge did not differ significantly between the groups (Graph 14, graph 16). The use of cinacalcet did not affect Ca homeostasis in postoperative patients.

There was no statistical significance in postoperative PTH levels between the groups (Graph 18). High PTH levels were recorded in some patients directly after the operation, and an additional laboratory control was performed before discharge. There were four cases (2%) with persistent HPT (PTH>300 ng/l) at discharge. In published studies with comparable groups of patients a similar rate of persistent HPT was reported with 0.83% and 1.4% [38, 40]. A higher rate of 3% and 3.1% [44, 72] was reported in a relatively small group of patients n=36 [72] published in 2002 and including less radical operation types (removal of only 1, 2 or 3 parathyroid glands) [44]. At present, no study has separately compared Ca and PTH levels before and after operation related to preoperative cinacalcet therapy.

11.4. PTH and Ca one year postoperatively, recurrent HPT

The levels of Ca and PTH did not differ significantly between the study groups at 1-year control. Within 1 year after the operation only one patient (1/196 = 0.51%) had a reoperation in Charité Clinic due to high PTH and Ca levels (Table 13). The cumulative recurrence rate is increasing with a longer follow-up. There were a total of five (2.6%) reoperations for recurrent HPT in the clinic.

In studies reporting surgical treatment of renal HPT the following recurrence rates can be encountered: 3.5% (tPTx without AT) [73], 5.3% (tPTX+AT), 9.5% (sPTX) 6.1% (incomplete PTx) [40], 5.8% (sPTx and tPTx with AT) [44], 11.7% (tPTx without AT) [46], 0% (tPTx), 31% (sPTx) [45]. These rates are difficult to compare due to differences in study conditions like kidney function, different types of operations, follow-up time and others.

In the German guidelines, a remnant of about 60 to 80 mg is recommended, although a correct estimation intraoperatively might be challenging [45]. Experience of the surgeon and correct identification of supernumerary glands are believed to be main factors predisposing to recurrent HPT [28, 42].

In the group of patients without KTx the driving factors of mineral metabolism disturbances are ongoing and a higher rate of recurrent HPT disease is expected [32, 41].
In addition, the definition of recurrent disease differs between studies, so the rate of recurrent HPT in the study by C.Dotzenrath [44] was 12.2%, whereas the reoperation rate was only 3.5%, other studies report only reoperation rates.

11.5. Kidney transplantation status and graft function

11.5.1. KTx status

Both study groups consisted predominantly of patients with terminal CKD, 91% in the group receiving cinacalcet, and 84% in the other. There were 3% of patients with preterminal CKD (stage IV) in the group without cinacalcet – those undergoing elective PTx before KTx from a living donor (Graph 1). Cinacalcet in CKD IV could only be administered as off-label use.
Patients with CKD I-III in both groups were those after KTx with good to moderate graft function, but with persisting renal HPT. Patients of this subgroup receiving cinacalcet underwent individual decisions for treatment after interdisciplinary discussions. As to 2015 there were more transplanted patients in the group without cinacalcet - 64% vs. 54% (Graph 2). There is one explanation for that fact: a surgical-nephrological conference was more likely to select a PTx rather than cinacalcet as treatment for renal HPT in a patient with sHPT resistant to medical treatment, once the chances for receiving a kidney transplant were high.
This statement is further supported by a subgroup analysis of patients with transplanted kidneys: there were 17 patients undergoing PTx before KTx in the cinacalcet group, and 37 patients undergoing PTx before KTx not receiving cinacalcet.
There were similar rates of terminal CKD among patients operated for renal HPT who had KTx in the medical history: in both study groups 14/21 and 11/26 with/without cinacalcet respectively (Graph 3).

11.5.2. Graft function

A literature review (2010) by C.Dotzenrath [37] discusses the risk of decreased graft function following parathyroidectomy: some authors reported worsening of graft function after the operation [32, 77], whereas others didn’t [38]. From previous experience in our own patients, we prefer to perform the parathyroidectomy beforehand. In our study 54 vs. 16 patients have undergone KTx after the PTx operation (Graph 23).
Creatinine levels in patients with tHPT (i.e. those with a functioning kidney transplant, defined as CKD I-III, n=22) were analyzed before PTx and one year after operation. There were no significant differences neither in the whole group, nor in the subgroups related to cinacalcet

therapy (Graph 24, graph 25). We did not analyse immunological markers in all patients. Therefore, we are not able to detect immunological changes. Creatinine is only a gross marker of graft function.

11.6. Cardiovascular events and mortality

The study group had a high rate of comorbidities with an overall high rate of mortality due to cardiovascular and other causes but not the operation itself. Mortality was not a primary end point in the present study.

The observed cumulative rate of cardiovascular events over the whole study period was higher in the group without cinacalcet (Table 11), although not statistically significant.

No perioperative mortality was registered in the study group; all patients were discharged from hospital. These data are comparable with the perioperative mortality reported in a large American retrospective study with a similar patient population being 2/898=0.22% within 30 days after PTx [48].

As to 2015 there was a 15% and 12% mortality rate in the groups with/without cinacalcet (p=0.68), accounting for an overall mortality of app. 3.3% per year of surveillance. At the same time exact data were missing in 26% of the patients (Graph 26, graph 27).

Yearly mortality rate in the cumulative population of chronic dialysis patients in Germany was 18% as to 2005 [37], and up to 40% according to American MediCare data from 1999 [43]. Our data are not comparable due to the relatively better overall condition of our patients. Especially the high proportion of patients undergoing KTx after PTx shows a positive selection for elective surgery combined with younger age.

An American study of chronic dialysis patients undergoing parathyroid surgery reports a mortality rate of 5.3% per year (8/36, mean surveillance 54 months) [72]. A British study by Coulson [73] reports a mortality rate of 7.7% per year in a similar patient population, both studies report 0% perioperative mortality.

12. References

1 Oertli, D. and R. Udelsman, Surgery of the thyroid and parathyroid glands, 2007, Springer,: Berlin ; New York. p. xv, 354 p. ill., ports.

2 Williams, R.H. and S. Melmed, Williams textbook of endocrinology, 2011, Elsevier/Saunders: Philadelphia. p. 1 (1920 p.).

3 Jameson, J.L., L.J. DeGroot, D.M. De Kretser, L. Giudice, A. Grossman, S. Melmed, J.T. Potts, and G.C. Weir Endocrinology : adult & pediatric. 7th edition. ed. 2016. 1 .

4 Hubbard, J.G.H., W.B. Inabnet, and C.-y. Lo, Endocrine surgery principles and practice, in Springer specialist surgery series 2009, Springer,: London. p. 1 (xx, 611 p.) ill.

5 Brown, E.M., G. Gamba, D. Riccardi, M. Lombardi, R. Butters, O. Kifor, A. Sun, M.A. Hediger, J. Lytton, and S.C. Hebert Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. Nature 1993;366:575-80.

6 Schwartz, A.E., D. Pertsemlidis, and M. Gagner Endocrine surgery. 2004, New York: Marcel Dekker. xviii, 711 p.

7 Skandalakis, J.E. and G.L. Colborn, Skandalakis' Surgical anatomy the embryologic and anatomic basis of modern surgery, 2004, PMP ; McGraw-Hill distributor: Athens, Greece London.

8 Gomes, E.M., R.C. Nunes, P.G. Lacativa, M.H. Almeida, F.M. Franco, C.T. Leal, P.J. Patricio Filho, M.L. Farias, and M.D. Goncalves Ectopic and extranumerary parathyroid glands location in patients with hyperparathyroidism secondary to end stage renal disease. Acta Cir Bras 2007;22:105-9.

9 Numano, M., Y. Tominaga, K. Uchida, A. Orihara, Y. Tanaka, and H. Takagi Surgical significance of supernumerary parathyroid glands in renal hyperparathyroidism. World J Surg 1998;22:1098-102; discussion 1103.

10 Hooghe, L., P. Kinnaert, and J. Van Geertruyden Surgical anatomy of hyperparathyroidism. Acta Chir Belg 1992;92:1-9.

11 Akerstrom, G., J. Malmaeus, and R. Bergstrom Surgical anatomy of human parathyroid glands. Surgery 1984;95:14-21.

12 Harrison, T.R. and J.L. Jameson Harrison's endocrinology. 2006, New York: McGraw-Hill Medical Pub. Division. x, 563 p.

13 Robbins, S.L., V. Kumar, and R.S. Cotran Robbins and Cotran pathologic basis of disease. 8th ed. 2010, Philadelphia, PA: Saunders/Elsevier. xiv, 1450 p.

14 Bieglmayer, C., G. Prager, and B. Niederle Kinetic analyses of parathyroid hormone clearance as measured by three rapid immunoassays during parathyroidectomy. Clin Chem 2002;48:1731-8.

15 Slatopolsky, E., A. Brown, and A. Dusso Pathogenesis of secondary hyperparathyroidism. Kidney Int Suppl 1999;73:S14-9.

16 Stubbs, J.R. and J.B. Wetmore Does it matter how parathyroid hormone levels are suppressed in secondary hyperparathyroidism? Semin Dial 2011;24:298-306.

17 Kidney Disease: Improving Global Outcomes, C.K.D.M.B.D.W.G. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2009;S1-130.

18 Parfitt, A.M., M.K. Drezner, F.H. Glorieux, J.A. Kanis, H. Malluche, P.J. Meunier, S.M. Ott, and R.R. Recker Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res 1987;2:595-610.

19 Mettang, T. and A.E. Kremer Uremic pruritus. Kidney Int 2015;87:685-91.

20 Shanahan, C.M., M.H. Crouthamel, A. Kapustin, and C.M. Giachelli Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res 2011;109:697-711.

21 Ohtake, T., K. Ishioka, K. Honda, M. Oka, K. Maesato, T. Mano, R. Ikee, H. Moriya, S. Hidaka, and S. Kobayashi Impact of coronary artery calcification in hemodialysis patients: Risk factors and associations with prognosis. Hemodial Int 2010;14:218-25.

22 Nakamura, S., H. Ishibashi-Ueda, S. Niizuma, F. Yoshihara, T. Horio, and Y. Kawano Coronary calcification in patients with chronic kidney disease and coronary artery disease. Clin J Am Soc Nephrol 2009;4:1892-900.

23 Gwinner, W., S. Suppa, M. Mengel, L. Hoy, H.H. Kreipe, H. Haller, and A. Schwarz Early calcification of renal allografts detected by protocol biopsies: causes and clinical implications. Am J Transplant 2005;5:1934-41.

24 White, R.E., A. Pickering, and G.S. Spathis Mood disorder and chronic hypercalcemia. J Psychosom Res 1996;41:343-7.

25 Cheng, S.P., J.J. Lee, T.P. Liu, T.L. Yang, H.H. Chen, C.J. Wu, and C.L. Liu Parathyroidectomy improves symptomatology and quality of life in patients with secondary hyperparathyroidism. Surgery 2014;155:320-8.

26 Daten und Fakten zur Niere und zu Nierenersatzverfahren. 27.07.2011 2 September, 2015]; (2 September, 2015 at http://www.dgfn.eu/presse/downloadbereich/daten-und-fakten-zur-nephrologie.html).

27 Fassbinder, W., F.P. Brunner, H. Brynger, J.H. Ehrich, W. Geerlings, A.E. Raine, G. Rizzoni, N.H. Selwood, G. Tufveson, and A.J. Wing Combined report on regular dialysis and transplantation in Europe, XX, 1989. Nephrol Dial Transplant 1991;6 Suppl 1:5-35.

28 Triponez, F., O.H. Clark, Y. Vanrenthergem, and P. Evenepoel Surgical treatment of persistent hyperparathyroidism after renal transplantation. Ann Surg 2008;248:18-30.

29 Tentori, F., M. Wang, B.A. Bieber, A. Karaboyas, Y. Li, S.H. Jacobson, V.E. Andreucci, M. Fukagawa, L. Frimat, D.C. Mendelssohn, F.K. Port, R.L. Pisoni, and B.M. Robinson Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. Clin J Am Soc Nephrol 2015;10:98-109.

30 Schneider, R., G. Kolios, B.M. Koch, E.D. Fernandez, D.K. Bartsch, and K. Schlosser An economic comparison of surgical and medical therapy in patients with secondary hyperparathyroidism--the German perspective. Surgery 2010;148:1091-9.

31 Evenepoel, P., K. Claes, D.R. Kuypers, F. Debruyne, and Y. Vanrenterghem Parathyroidectomy after successful kidney transplantation: a single centre study. Nephrol Dial Transplant 2007;22:1730-7.

32 Evenepoel, P., K. Claes, D. Kuypers, B. Maes, B. Bammens, and Y. Vanrenterghem Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. Nephrol Dial Transplant 2004;19:1281-7.

33 Okada, M., Y. Tominaga, K. Izumi, H. Nobata, T. Yamamoto, T. Hiramitsu, M. Tsujita, N. Goto, K. Nanmoku, T. Watarai, and K. Uchida Tertiary hyperparathyroidism resistant to cinacalcet treatment. Ther Apher Dial 2011;15 Suppl 1:33-7.

34 Massry, S.G. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:S1-201.

35 Fishbane, S., W.B. Shapiro, D.B. Corry, S.L. Vicks, M. Roppolo, K. Rappaport, X. Ling, W.G. Goodman, S. Turner, and C. Charytan Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: the ACHIEVE study results. Clin J Am Soc Nephrol 2008;3:1718-25.

36 Nemeth, E.F. The search for calcium receptor antagonists (calcilytics). J Mol Endocrinol 2002;29:15-21.

37 Dotzenrath, C. [Indications for parathyroidectomy in renal hyperparathyroidism: comments on the significance of new therapeutics]. Chirurg 2010;81:902-8.

38 Schlosser, K., N. Endres, I. Celik, V. Fendrich, M. Rothmund, and E.D. Fernandez Surgical treatment of tertiary hyperparathyroidism: the choice of procedure matters! World J Surg 2007;31:1947-53.

39 Cohen, M.S., W.G. Dilley, S.A. Wells, Jr., J.F. Moley, G.M. Doherty, G.A. Sicard, M.A. Skinner, J.A. Norton, M.K. DeBenedetti, and T.C. Lairmore Long-term functionality of cryopreserved parathyroid autografts: a 13-year prospective analysis. Surgery 2005;138:1033-40; discussion 1040-1.

40 Schneider, R., E.P. Slater, E. Karakas, D.K. Bartsch, and K. Schlosser Initial parathyroid surgery in 606 patients with renal hyperparathyroidism. World J Surg 2012;36:318-26.

41 Gasparri, G., M. Camandona, G.C. Abbona, M. Papotti, A. Jeantet, E. Radice, B. Mullineris, and M. Dei Poli Secondary and tertiary hyperparathyroidism: causes of recurrent disease after 446 parathyroidectomies. Ann Surg 2001;233:65-9.

42 Riss, P., R. Asari, C. Scheuba, and B. Niederle Current trends in surgery for renal hyperparathyroidism (RHPT)--an international survey. Langenbecks Arch Surg 2013;398:121-30.

43 Longo, D.L. and T.R. Harrison Harrison's principles of internal medicine. 18th ed. 2012, New York: McGraw-Hill.

44 Dotzenrath, C., K. Cupisti, E. Goretzki, A. Mondry, A. Vossough, B. Grabensee, and H.D. Roher Operative treatment of renal autonomous hyperparathyroidism: cause of persistent or recurrent disease in 304 patients. Langenbecks Arch Surg 2003;387:348-54.

45 Rayes, N., D. Seehofer, R. Schindler, P. Reinke, A. Kahl, F. Ulrich, P. Neuhaus, and N.C. Nussler Long-term results of subtotal vs total parathyroidectomy without autotransplantation in kidney transplant recipients. Arch Surg 2008;143:756-61; discussion 761.

46 Shih, M.L., Q.Y. Duh, C.B. Hsieh, S.H. Lin, H.S. Wu, P.L. Chu, T.Y. Chen, and J.C. Yu Total parathyroidectomy without autotransplantation for secondary hyperparathyroidism. World J Surg 2009;33:248-54.

47 Matsuoka, S., Y. Tominaga, T. Sato, N. Uno, N. Goto, A. Katayama, K. Uchida, and T. Tsuzuki Recurrent renal hyperparathyroidism caused by parathyromatosis. World J Surg 2007;31:299-305.

48 Kuo, L.E., H. Wachtel, G. Karakousis, D. Fraker, and R. Kelz Parathyroidectomy in dialysis patients. J Surg Res 2014;190:554-8.

49 Nemeth, E.F., W.H. Heaton, M. Miller, J. Fox, M.F. Balandrin, B.C. Van Wagenen, M. Colloton, W. Karbon, J. Scherrer, E. Shatzen, G. Rishton, S. Scully, M. Qi, R. Harris, D. Lacey, and D. Martin Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. J Pharmacol Exp Ther 2004;308:627-35.

50 Henley, C., 3rd, Y. Yang, J. Davis, J.Y. Lu, S. Morony, W. Fan, M. Florio, B. Sun, E. Shatzen, J.K. Pretorius, W.G. Richards, D.J. St Jean, Jr., C. Fotsch, and J.D. Reagan Discovery of a calcimimetic with differential effects on parathyroid hormone and calcitonin secretion. J Pharmacol Exp Ther 2011;337:681-91.

51 Nagano, N. Pharmacological and clinical properties of calcimimetics: calcium receptor activators that afford an innovative approach to controlling hyperparathyroidism. Pharmacol Ther 2006;109:339-65.

52 Walter, S., A. Baruch, J. Dong, J.E. Tomlinson, S.T. Alexander, J. Janes, T. Hunter, Q. Yin, D. Maclean, G. Bell, D.B. Mendel, R.M. Johnson, and F. Karim Pharmacology of AMG 416 (Velcalcetide), a novel peptide agonist of the calcium-sensing receptor, for the treatment of secondary hyperparathyroidism in hemodialysis patients. J Pharmacol Exp Ther 2013;346:229-40.

53 Block, G.A., K.J. Martin, A.L. de Francisco, S.A. Turner, M.M. Avram, M.G. Suranyi, G. Hercz, J. Cunningham, A.K. Abu-Alfa, P. Messa, D.W. Coyne, F. Locatelli, R.M. Cohen, P. Evenepoel, S.M. Moe, A. Fournier, J. Braun, L.C. McCary, V.J. Zani, K.A. Olson, T.B. Drueke, and W.G. Goodman Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 2004;350:1516-25.

54 Zitt, E., M. Rix, P. Urena Torres, D. Fouque, S.H. Jacobson, F. Petavy, B. Dehmel, and M. Ryba Effectiveness of cinacalcet in patients with recurrent/persistent secondary hyperparathyroidism following parathyroidectomy: results of the ECHO study. Nephrol Dial Transplant 2011;26:1956-61.

55 Messa, P., F. Macario, M. Yaqoob, K. Bouman, J. Braun, B. von Albertini, H. Brink, F. Maduell, H. Graf, J.M. Frazao, W.J. Bos, V. Torregrosa, H. Saha, H. Reichel, M. Wilkie, V.J. Zani, B. Molemans, D. Carter, and F. Locatelli The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. Clin J Am Soc Nephrol 2008;3:36-45.

56 Sekercioglu, N., J.W. Busse, M.F. Sekercioglu, A. Agarwal, S. Shaikh, L.C. Lopes, R.A. Mustafa, G.H. Guyatt, and L. Thabane Cinacalcet versus standard treatment for chronic kidney disease: a systematic review and meta-analysis. Ren Fail 2016;38:857-74.

57 Komaba, H., S. Nakanishi, A. Fujimori, M. Tanaka, J. Shin, K. Shibuya, M. Nishioka, H. Hasegawa, T. Kurosawa, and M. Fukagawa Cinacalcet effectively reduces parathyroid hormone secretion and gland volume regardless of pretreatment gland size in patients with secondary hyperparathyroidism. Clin J Am Soc Nephrol 2010;5:2305-14.

58 Ichii, M., E. Ishimura, S. Okuno, H. Chou, Y. Kato, N. Tsuboniwa, K. Nagasue, K. Maekawa, T. Yamakawa, M. Inaba, and Y. Nishizawa Decreases in parathyroid gland volume after cinacalcet treatment in hemodialysis patients with secondary hyperparathyroidism. Nephron Clin Pract 2010;115:c195-202.

59 Hirai, T., A. Nakashima, N. Takasugi, and N. Yorioka Association of nodular hyperplasia with resistance to cinacalcet therapy for secondary hyperparathyroidism in hemodialysis patients. Ther Apher Dial 2010;14:577-82.

60 Picazo Sanchez, M., M. Cuxart Perez, R. Sans Lorman, and C. Sarda Borroy Cinacalcet in the treatment of hypercalcaemia and control of hyperparathyroidism due to ectopic parathyroid glands. Nefrologia 2011;31:126-7.

61 Chonchol, M., F. Locatelli, H.E. Abboud, C. Charytan, A.L. de Francisco, S. Jolly, M. Kaplan, S.D. Roger, S. Sarkar, M.B. Albizem, T.C. Mix, Y. Kubo, and G.A. Block A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet HCl in participants with CKD not receiving dialysis. Am J Kidney Dis 2009;53:197-207.

62 Paschoalin, R.P., J.V. Torregrosa, X. Barros, C.E. Duran, and J.M. Campistol Cinacalcet de novo in persistent hypercalcemia after kidney transplantation secondary to hyperparathyroidism: long-term follow-up and effect of withdrawal. Transplant Proc 2012;44:2376-8.

63 Serra, A.L., R. Savoca, A.R. Huber, U. Hepp, A. Delsignore, M. Hersberger, and R.P. Wuthrich Effective control of persistent hyperparathyroidism with cinacalcet in renal allograft recipients. Nephrol Dial Transplant 2007;22:577-83.

64 Evenepoel, P., K. Cooper, H. Holdaas, P. Messa, G. Mourad, K. Olgaard, B. Rutkowski, H. Schaefer, H. Deng, J.V. Torregrosa, R.P. Wuthrich, and S. Yue A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. Am J Transplant 2014;14:2545-55.

65 Mingione, A., C. Verdelli, A. Terranegra, L. Soldati, and S. Corbetta Molecular and Clinical Aspects of the Target Therapy with the Calcimimetic Cinacalcet in the Treatment of Parathyroid Tumors. Curr Cancer Drug Targets 2015;15:563-74.

66 Schwarz, P., J.J. Body, J. Cap, L.C. Hofbauer, M. Farouk, A. Gessl, J.M. Kuhn, C. Marcocci, C. Mattin, M. Munoz Torres, J. Payer, A. Van De Ven, M. Yavropoulou, and P. Selby The PRIMARA study: a prospective, descriptive, observational study to review cinacalcet use in patients with primary hyperparathyroidism in clinical practice. Eur J Endocrinol 2014;171:727-35.

67 Giusti, F., L. Cianferotti, G. Gronchi, F. Cioppi, L. Masi, A. Faggiano, A. Colao, P. Ferolla, and M.L. Brandi Cinacalcet therapy in patients affected by primary hyperparathyroidism associated to Multiple Endocrine Neoplasia Syndrome type 1 (MEN1). Endocrine 2015.

68 Festen-Spanjer, B., C.M. Haring, J.B. Koster, and A.H. Mudde Correction of hypercalcaemia by cinacalcet in familial hypocalciuric hypercalcaemia. Clin Endocrinol (Oxf) 2008;68:324-5.

69 Block, G.A., S. Zeig, J. Sugihara, G.M. Chertow, E.M. Chi, S.A. Turner, D.A. Bushinsky, and T. Investigators Combined therapy with cinacalcet and low doses of vitamin D sterols in patients with moderate to severe secondary hyperparathyroidism. Nephrol Dial Transplant 2008;23:2311-8.

70 Padhi, D. and R. Harris Clinical pharmacokinetic and pharmacodynamic profile of cinacalcet hydrochloride. Clin Pharmacokinet 2009;48:303-11.

71 Rayes, N., D. Seehofer, and P. Neuhaus The surgical treatment of bilateral benign nodular goiter: balancing invasiveness with complications. Dtsch Arztebl Int 2014;111:171-8.

72 Oltmann, S.C., T.M. Madkhali, R.S. Sippel, H. Chen, and D.F. Schneider Kidney Disease Improving Global Outcomes guidelines and parathyroidectomy for renal hyperparathyroidism. J Surg Res 2015.

73 Coulston, J.E., R. Egan, E. Willis, and J.D. Morgan Total parathyroidectomy without autotransplantation for renal hyperparathyroidism. Br J Surg 2010;97:1674-9.

74 Lou, I., D.F. Schneider, G. Leverson, D. Foley, R. Sippel, and H. Chen Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation. Surgery 2016;159:172-80.

75 Schlosser, K., D.K. Bartsch, M.K. Diener, C.M. Seiler, T. Bruckner, C. Nies, M. Meyer, J. Neudecker, P.E. Goretzki, G. Glockzin, R. Konopke, and M. Rothmund Total Parathyroidectomy With Routine Thymectomy and Autotransplantation Versus Total Parathyroidectomy Alone for Secondary Hyperparathyroidism: Results of a Nonconfirmatory Multicenter Prospective Randomized Controlled Pilot Trial. Ann Surg 2016;264:745-753.

76 Chen, J., Q.Y. Zhou, and J.D. Wang Comparison Between Subtotal Parathyroidectomy and Total Parathyroidectomy with Autotransplantation for Secondary Hyperparathyroidism in Patients with Chronic Renal Failure: A Meta-Analysis. Horm Metab Res 2015;47:643-51.

77 Schwarz, A., G. Rustien, S. Merkel, J. Radermacher, and H. Haller Decreased renal transplant function after parathyroidectomy. Nephrol Dial Transplant 2007;22:584-91.

13. Affidavit

“I, Skachko Tatiana certify under penalty of perjury by my own signature that I have submitted the thesis on the topic Effect of Cinacalcet Therapy on Surgical Outcome in Patients with Renal Hyperparathyroidism I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

14. CV

My curriculum vitae is not published for privacy reasons in the electronic version of my work.

15. Acknowledgements

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16. List of abbreviations

$1,25(OH)_2D_3$	1,25-dihydroxy-vitamin D
99mTc	99-Technecium sestamibi
aHT	Arterial hypertony
AP	Alkaline phosphatise
ASA	American society of anesthesiology
AT	Autotransplantation
Ca	Calcium
CaSR	Calcium sensing receptor
CKD	Chronic kidney disease
DM	Diabetes mellitus
DNA	Desoxyribonucleic acid
ENT-specialist	Ear-nose-throat specialist
FDA	Food and drug administration
FGF23	Fibroblast growth factor-23
FGFR	Fibroblast growth factor receptor
HPT	Hyperparathyroidism
pHPT	Primary hyperparathyroidism
sHPT	Secondary hyperparathyroidism
tHPT	Tertiary hyperparathyroidism

IHD	Ischemic heart disease
K/DOQI	Kidney Disease Outcomes Quality Initiative
KTx	Kidney transplantation
MEN syndrome	Multiple endocrinologic neoplasy syndrome
P	Phosphorus
PTx	Parathyroidectomy
sPTx	Subtotal parathyroidectomy
tPTx	Total parathyroidectomy
PTA	Percutaneous transluminal angioplasty
RAAS	Renin-angiothensin-aldostheron system
VDR	Vitamin D receptor

17. List of Figures, Graphs and Illustrations