A strategy change in the treatment of end-stage renal disease related hyperparathyroidism after the introduction of calcimimetics: a retrospective observational study

Figure 1. Posterior view of the parathyroid glands

Final report for the Research Clerkship of:
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**Summery**

Hyperparathyroidism (HPT), both secondary and tertiary, is a common abnormality in patients with end stage renal disease (ESRD). It is characterized by calcium-phosphate imbalances and elevated serum parathormone (PTH) levels and has been associated with severe bone disorders, cardiovascular complications and increased mortality. Since the introduction of calcimimetics in 2004, treatment of renal HPT has dramatically shifted from surgery to predominantly medical therapy. The aim of this study was to evaluate the impact of this change of management on the renal HPT patient population before undergoing (sub)total parathyroidectomy (PTx).

A retrospective cohort study was conducted. All patients with secondary or tertiary HPT undergoing PTx between 1991-2015 were included. Patient characteristics prior to surgery as well as pre- and postoperative laboratory values, postoperative complications and weight of the resected parathyroid glands were recorded and collected in a database. Two groups of patients were compared: Group A, who underwent PTx before January 2005 and group B, who underwent PTx after 2005, since Cinacalcet was first prescribed in the UMCG in 2005. We found a 22-month delay of surgery in group B compared to group A. Also, patients of group B still presented with continuously elevated preoperative PTH values, despite medical treatment. Furthermore, postoperative complication rates were very low and we demonstrated that after PTx, PTH levels decreased drastically. In conclusion, the introduction of calcimimetics is associated with a 22-month delay of surgery with continuously elevated preoperative PTH levels whilst parathyroid surgery, even in a fragile population, is considered a safe and effective procedure.

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**Samenvatting**

Zowel secundaire als tertiaire hyperparathyroïdie (HPT) is een veelvoorkomende aandoening bij patiënten met een chronische nierinsufficiëntie. HPT wordt gekarakteriseerd door een disbalans in de calcium-fosfaat huishouding en verhoogde parathormoon (PTH) spiegels en gaat gepaard met stoornissen in het botmetabolisme, cardiovasculaire aandoeningen en verhoogde mortaliteit. Sinds de introductie van calcimimetica in 2004 is de behandeling van renale HPT drastisch veranderd van een chirurgische benadering naar voornamelijk medicamenteuze therapie. Onze studie tracht deze verandering in behandeling van de HPT-patiëntenpopulatie te evalueren voordat ze een (sub)totale parathyroïdectomie (PTx) ondergaat.

We hebben een retrospectieve cohortstudie uitgevoerd. Alle patiënten die een PTx hebben ondergaan met als indicatie secundaire of tertiaire HPT tussen 1991 en 2015 zijn geïncludeerd. Informatie over patiëntkarakteristieken voorafgaand aan de operatie, pre- en postoperatieve labwaarden, postoperatieve complicaties en het gewicht van de verwijderde bijzchildklieren is verzameld in een database. Vervolgens hebben we twee groepen vergeleken: Groep A, patiënten die voor januari 2015 zijn geopereerd en groep B, patiënten die na januari 2015 zijn geopereerd, aangezien Cinacalcet in het UMCG voor het eerst in 2005 is voorgeschreven. Uit de resultaten bleek dat de patiënten uit groep B 22 maanden later werden geopereerd dan de patiënten uit groep A. Ook bleek dat de patiënten uit groep B ondanks het gebruik van Cinacalcet nog steeds zeer hoge PTH-waarden hadden bij aanvang van PTx. Verder vonden we dat de postoperatieve complicaties minimaal waren en niet verschillend in beide groepen. Ten slotte is PTx een zeer effectieve procedure; de PTH-waarden daalden drastisch. Concluderend stellen we
dat de introductie van calcimimetica in 2004 gepaard gaat met een 22 maanden vertraging van operatieve behandeling met bovendien zeer hoge preoperatieve PTH-waarden. Ondanks de zeer fragiele patiëntenpopulatie, bleek PTx wel een zeer veilige en effectieve chirurgische procedure.
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Introduction

Anatomy of the parathyroid gland
Posterior of the thyroid, four parathyroid glands are found normally in the superior and inferior regions of both sides of the thyroid (Figure 1), although their localization varies widely. Other than being close neighbors, the thyroid and parathyroid are not related. The beanlike shaped soft glands are usually 4-9 mm long, 2-4 mm wide and 0.5-2 mm thick. Normally, the weight of a single parathyroid gland is 30 to 40 milligrams. Most people have 4 parathyroid glands, although in 5% of subjects additional glands are found. The parathyroid glands generally receive their blood supply by the inferior thyroid arteries. The parathyroid glands are, like other endocrine organs, surrounded by a wide capillary framework. The cervical sympathetic ganglia provide the parathyroid glands with nerve supply. The parathyroid glands consist mainly of parenchymal cells and fat cells with a 50 / 50 parenchymal cell / fat cell ratio. The parenchymal cells can be subdivided in oxyphil cells and chief cells. The latter produces parathyroid hormone (PTH)*, which function is discussed later. The exact role of oxyphil cells is unknown.

Parathyroid hormone
With the secretion of PTH by chief cells, the main function of the parathyroid glands is to regulate calcium and phosphate homeostasis. Calcium levels are controlled by the effects of PTH on bones, kidneys and the intestinal tract. PTH binds to its receptor on osteoblasts, which, via a complex ligand dependent pathway stimulate osteoclasts. In turn, osteoclasts enhance bone resorption through which calcium is released into the bloodstream. In the kidneys, PTH stimulates active reabsorption of calcium in the distal tubuli, but has the opposite effect to phosphate. It inhibits the absorption of phosphate in the proximal tubuli. Lastly, the calcium absorption is regulated by PTH via 1,25-dihydroxycholecalciferol in the intestinal tract. PTH enhances the activation of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D. Thus, the net effect of PTH is lowering serum phosphate levels, while increasing the serum calcium level (Figure 2). The secretion of PTH by the chief parathyroid cells is strictly regulated and can alternate very

*A complete list of abbreviations is added in attachment 1

Figure 2. Effects of PTH in reaction on a low serum calcium level
rapidly. The parathyroid gland is able to sense extracellular levels of calcium via the calcium-sensing receptor (CaSR) on the parathyroid cells. Via multiple transduction pathways, high extracellular calcium levels result in the inhibition of the chief cells to release secretary granules with PTH. This negative feedback loop maintains consistent levels of serum calcium. The rapid changes in serum PTH concentration are also caused by the extremely short half-time of PTH. In less than 2 minutes half of the PTH concentration is disappeared, this makes the circulating PTH level a reliable surrogate for parathyroid function in vivo. Therefore, PTH assays are often performed during parathyroid gland removal surgery, in order to help in surgical decision making.

**Aetiology and pathogenesis of secondary and tertiary hyperparathyroidism**

In end-stage renal disease (ESRD), due to decreased renal mass and function, the kidney is not able to maintain appropriate calcium and phosphate homeostasis. Hyperphosphatemia, hypocalcaemia and vitamin D deficiency develops. These changes promote the synthesis and secretion of PTH, to correct the disturbances in blood levels. A long-term increased activity of the parathyroid gland will eventually lead to parathyroid hyperplasia with or without hyperplastic nodules and secondary hyperparathyroidism (HPT). By definition, secondary HPT is associated with high levels of PTH and low levels of serum calcium. Secondary HPT rarely evolves into parathyroid carcinoma.

The severity of secondary HPT is inversely related to the glomerular filtration rate (GFR) (Figure 3). In early stages of secondary HPT, the parathyroid glands stop with the overproduction of PTH after successful kidney transplantation (KTx). The enlarged parathyroid cells regress slowly and thus the calcium phosphate homeostasis normalizes. However, when pre-existing HPT does not resolve after successful KTx and PTH levels continue to rise, the parathyroid becomes insensitive to serum calcium levels due to a reduction of CaSRs, resulting in the autonomous development of hypercalcaemia. This phenomenon is known as tertiary HPT. Henceforth, secondary and tertiary HPT will be referred to as renal HPT.

![Figure 3. Relationship between kidney filtration rate and PTH](image-url)
Epidemiology of secondary and tertiary hyperparathyroidism
Renal hyperparathyroidism, both secondary and tertiary, is a common complication among patients with ESRD. Incidence rates of secondary HPT vary from 28% in India to 54% in the United States of America. Incidence of tertiary HPT ranges from 6 to 30%.

Clinical manifestations of secondary and tertiary hyperparathyroidism
Symptoms directly related to hypercalcaemia include pruritus, bone pain, calciphylaxis, pathologic fractures and muscle weakness. On top of that, the PTH-mediated elevation of free calcium is responsible for much of the generalized organ dysfunction in ESRD. Clinical manifestations vary from progressive bone loss due to increased bone turnover, to an increased risk of cardiovascular disease and mortality due to accelerated cardiovascular calcification. Data on the effects of long-term elevated PTH levels on future kidney graft function are limited. However a large post hoc analysis did show a significant association between tertiary HPT and adverse renal graft outcome. Lastly, both secondary and tertiary HPT have been associated with increased all-cause mortality.

Treatment options of renal hyperparathyroidism
In the management of renal HPT, different treatment modalities are at our availability, from medical therapy to surgical treatment.

Medical treatment
Three classes of drugs are available: phosphate binders, vitamin D analogs, and calcimimetics. Phosphate binders reduce the net absorption of phosphate by binding to it in the gastrointestinal tract. Phosphate binders are in addition to a low-phosphorus diet, the first step in the treatment of renal hyperparathyroidism. Vitamin D derivatives are initially being prescribed for patients with low serum calcium levels. Calcitriol, the active metabolite of vitamin D, stimulates the absorption of calcium and thus suppresses the secretion of PTH. Lastly, the calcimimetic agent Cinacalcet can be used in the treatment algorithm of renal HPT. Cinacalcet binds to the CaSR of the parathyroid gland, inhibits the release of PTH and hence the calcium-phosphorus homeostasis improves.

Parathyroidectomy
In contrast to primary HPT, in which mostly only one parathyroid gland is enlarged, all four glands are frequently hyperplastic in secondary and tertiary HPT. Consequently, patients with renal HPT, when referred for surgery, undergo four-gland exploration and (sub)total parathyroidectomy (PTx). Over the years, different surgical approaches were reported. The two most frequently used in the university medical center Groningen (UMCG) and recommended as standard procedures are here discussed. (1) Subtotal PTx and (2) total PTx with autotransplantation (AT). In subtotal PTx, 3.5 parathyroid glands are resected, leaving half of the most normal-appearing gland in situ. When less than 3.5 gland is removed, the risk of persistence or recurrence emerges. On the other side, in attempt to prevent hypocalcaemia, at least half a gland is left in place. In total PTx + AT all four parathyroid glands are identified and resected. Then, the most normal-appearing gland is halved and cut into 1-2 mm pieces for reimplantation. This minced
parathyroid tissue is then placed into the sternocleidomastoid muscle or sometimes in the forearm muscle pockets. After 4 to 6 weeks, the autografted gland will develop new blood supply and will produce small amounts of PTH again. Both sPTx and tPTx + AT are proved to be safe and effective.\textsuperscript{18} In tertiary HPT, PTx is considered to be the only definite treatment option, because the autonomous production of PTH can no longer be suppressed by medical therapy.\textsuperscript{14}

\textit{Strategy change in the management of renal HPT}

Previously, PTx played a dominant role in the treatment algorithm of renal HPT, together with calcium salts and vitamin D sterols.\textsuperscript{36} However since its introduction in 2004, the calcimimetic agent Cinacalcet is initially being used to correct the hyperfunctioning parathyroid glands and PTx is only recommended in patients with severe renal HPT who fail to respond to medical treatment.\textsuperscript{32} The effectiveness of Cinacalcet is initially shown in several observational studies: they prove a significant reduction of levels of serum calcium and thus a reduction in hypercalcaemia related morbidity.\textsuperscript{37-39} Despite the lack of randomized studies that compare Cinacalcet with surgical treatment, Cinacalcet seems to have contributed to a change in clinicians’ strategy and parathyroidectomies are less often performed.\textsuperscript{31} Nonetheless, several questions are being raised with respect to the effectiveness, the adverse events and the costs of Cinacalcet. Brunaud et al. showed that Cinacalcet did not impact mean PTH values in a prospective study.\textsuperscript{40} While a long-term elevated PTH level is thought to have negative effects on cardiovascular status and mortality, the most recent Cochrane review concluded that there is no evidence that Cinacalcet reduces the risk of death or major cardiovascular events.\textsuperscript{31,41} Furthermore, the EVOLVE trial reported that Cinacalcet is associated with multiple adverse events, 45.9% of the patients reported nausea, vomiting, diarrhea and/or other serious side events effects (versus 18.9% in placebo group).\textsuperscript{42} Lastly, a cost-utility analysis showed that PTx is less expensive and more cost-effective at 7.25 months in comparison to Cinacalcet-based medical therapy.\textsuperscript{43} This suggests that PTx is preferred over Cinacalcet in long-term hemodialysis patients. Despite these conclusions, with the advent of Cinacalcet, the global prescription patterns have dramatically shifted from surgery towards predominantly medical therapy.

\textit{Aim}

It is currently not known what the effects are of this worldwide strategy change in management on the patient population that still undergoes PTx. Therefore, the aim of this observational retrospective study is to evaluate the impact of the change of management on the HPT patient population before undergoing (sub)total PTx.
Material and Methods

Study design and population
A retrospective cohort study was undertaken at the department of endocrine surgery of the UMCG. The study population consisted of end stage renal disease patients with secondary or tertiary hyperparathyroidism who underwent parathyroidectomy in the UMCG from 1991 to 2015. During this 25-year period, 484 patients parathyroidectomies were performed in the UMCG. Inclusion criteria comprised at least 18 years of age and a positive diagnosis of secondary or tertiary HPT. Patients were excluded if they had (para)thyroid malignancy in medical history and/or previous surgery in neck-area. After applying inclusion and exclusion criteria, a total of 119 (24.6%) patients were included (Figure 4). Six patients underwent re-exploration(s), however, only their first parathyroidectomy was taking into account. The Medical Ethical Committee (METC) of the UMCG was obtained for approval to conduct this study (attachment 2).

Study groups
Two subgroups were defined. As Cinacalcet was in the UMCG first prescribed in 2005, January 2005 was chosen as cut-off date to form two groups. The first group consisted of all patients who underwent PTx before January 2005 and will be referred to as ‘group A’ and the second group comprised of patients who underwent PTx after January 2005 and will be referred to as ‘group B’.

Figure 4. Cohort patient selection flow diagram
Data collection
Data of the included patients was extracted from the electronic patient record system of the UMCG (PoliPlus) and collected in a database. Furthermore, the electronic record system of the Dialysis Center Groningen (Diamant) was used to collect data.

Study endpoints
Primary endpoints
Primary outcome measures were patient characteristics prior to surgery and time from renal HPT diagnosis to PTx. The following baseline characteristics were taken into account: age at time of PTx, gender, ASA-score, BMI, history of diabetes mellitus, time on dialysis, type of PTx, kidney transplantation in medical history and finally use of Cinacalcet and other calcium regulating medication.

The American Society of Anesthesiologists (ASA) established a grading system to score preoperative health status of surgical patients. From only a few cases we could extract ASA-scores from anesthesiology reports. For the rest of the patients we calculated the ASA-scores using patient’s medical history and current definition according the American Society of Anesthesiologists physical status classification. The ASA physical status classification is added in attachment 3.

From only a few patients body mass indices (BMI) were reported in the anesthesiology reports, for the rest of the cases we calculated the BMI using the reported height and weight of the patient.

Time on dialysis was defined as the moment the patient first started with dialysis until the date of PTx.

In the included 25-year period, different surgical approaches were reported, which were subdivided into three categories: (1) total PTx with autotransplantation (AT) of parathyroid tissue in the sternocleidomastoid muscle, (2) subtotal PTx (3.5 parathyroid gland resection) and (3) all other types of PTx.

Calcium regulating medication other than Cinacalcet comprised of calcium based phosphate binders (such as, but not limited to: Renvela, Renagel, Fosrenol and OsvaRen), calcium supplements, vitamin D analogues (including: Colecalciferol, Alfacalcidol, Calcitriol and Paricalcitol).

Date of renal HPT diagnosis was difficult to determine in this retrospective study, because this was not well recorded in the electronic medical record systems. Therefore, with the agreement of the nephrologists, the moment vitamin D derivatives were first prescribed was defined as the date of diagnosis of renal HPT.

Secondary endpoints
Secondary outcome measures were laboratory values, postoperative complications, and parathyroid gland weight.

Laboratory values were recorded preoperatively (at day of admission), 3 months and 6 months after PTx. The following laboratory values were included: calcium (mmol/l), phosphorus (mmol/l), alkaline phosphatase (U/l), albumin (g/l) and PTH (pg/ml). Beside 3 and 6 months, PTH levels of 1 year, 2 years and 5 years after PTx were also included.
From 1991 till 2006, PTH analysis was performed using PTH-intact assays from Nichols Institute Diagnostics. In this period several assays have been deployed, using the same antibodies with different detection methods (radioimmunoassay and chemiluminescent immunoassays). Since February 2006 PTH has been analyzed using PTH-intact assays using the Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA) and the Cobas e601 (Roche Diagnostics, Mannheim, Germany). In-house comparison of consecutive PTH assays showed only significant deviation between the Nichols Advantage ILMA and the Siemens Immulite 2500. To compare data before and after the method conversion, the data before 2006 were recalculated using the following conversion factor:

\[ \text{Immulite (pmol/L)} = 1.27 \times \text{Advantage (pmol/L)} + 0.5. \]

The conversion factor was established according to CSLI EP9 protocol by Passing-Bablok regression analysis, as analyzed with Analyse-IT and Clinical Laboratory version 1.71.

In order to interpret serum calcium levels correctly, measured calcium levels should be adjusted for the serum albumin concentration. This is required because 35-40% of serum calcium is bound to albumin. In 1973, Payne described how the corrected calcium is calculated:

\[ \text{Total calcium} = \text{measured calcium} + (0.025 \times (40 - [\text{albumin}]). \]

Postoperative morbidity was expressed based on complications presented within 30 days after surgery, including surgical site problems (SSP) (including hematoma, infection, skin tethering and keloid formation), recurrent laryngeal nerve damage, hypocalcaemia, pneumonia and transfer to the intensive care unit (ICU).

Two different methods were used to define hypocalcaemia. First, we recorded whether ‘hypocalcaemia’ was mentioned in the discharge letter by the surgeon. However, with agreement of the nephrologists, we decided that this method would not be reliable because hypocalcaemia occurs in almost every patient directly after PTx. Therefore, we recorded the use of calcium supplements 6 months after parathyroidectomy. This would indicate that the parathyroid is not able to maintain or reestablish normal calcium levels by itself.

Information about weight and size of the removed parathyroid glands was extracted from pathology reports. Weight of the largest removed parathyroid gland was used in statistical analysis.

**Literature search**

In order to compare our outcomes with previous study results, a literature search was conducted using PubMed. This free accessible database comprises over 25 million biomedical research publications from scientific journals. To identify relevant articles the Medical Subject Headings (MeSH) and “Title and Abstract (TiAb) terms “parathyroidectomy”, “secondary hyperparathyroidism” and “PTH” were combined. A
complete description of the search strategy is added in attachment 4. In addition, we checked references of selected papers for supplementary studies.

**Statistical analysis**
Descriptive tests were used to express continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR) and categorical variables were described as count (n) and percentage (%). Statistical analysis was performed using SPSS Statistics version 22.0 (IBM Corp. Armonk, NY, USA.) and involved the following aspects. To compare patient characteristics, distribution was assessed with the Shapiro-Wilk normality test. In case of normal distribution, the independent sample T-test was used to compare continuous variables. The Mann Whitney U-test was performed to assess in-between group differences of abnormal distributed and ordinal variables. Differences between nominal variables were determined by using Pearson chi-square test. Correlation analysis was performed by using Spearman Rank correlation. P-values less than 0.05 were considered statistically significant.
Results

Patient characteristics

Baseline characteristics of the 119 included patients are described in Table 1. 70 patients (58.8%) underwent PTx before the introduction of Cinacalcet (group A) and 49 (41.2%) patients after the introduction of Cinacalcet (group B). Mean age was 53 years (range 18-79 years) and the male/female ratio was 1.0/1.64. A vast majority of all patients (81.5%) were classified as ASA III. 30 (61.2% of group B) patients used Cinacalcet in the period prior to PTx. 77.9% of all patients received conservative medications including vitamin D analogues and phosphate binders. 63.7% of all patients were receiving vitamin D supplements and 61.9% phosphate binders at enrollment. On average, patients were 58.7 months on dialysis. The mean time between diagnosis of HPT and PTx was 42.8 months (range 0-208 months).

Table 1. Patient characteristics at parathyroidectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N=119)</th>
<th>Group A Before the introduction of Cinacalcet (N=70)</th>
<th>Group B After the introduction of Cinacalcet (N=49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at surgery, years</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>53.0</td>
<td>52.5</td>
<td>54.0</td>
<td>0.81</td>
</tr>
<tr>
<td>25th to 75th percentile</td>
<td>40.0-60.0</td>
<td>40.8-60.0</td>
<td>38.5-59.5</td>
<td></td>
</tr>
<tr>
<td>Number of females, n (%)</td>
<td>74 (62.2)</td>
<td>47 (67.1)</td>
<td>27 (55.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of females, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>24.3</td>
<td>23.4</td>
<td>25.3</td>
<td>0.05</td>
</tr>
<tr>
<td>25th to 75th percentile</td>
<td>21.4-27.1</td>
<td>20.7-25.8</td>
<td>23.3-27.3</td>
<td></td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Type I</td>
<td>3 (2.5)</td>
<td>1 (1.4)</td>
<td>2 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>11 (9.2)</td>
<td>8 (11.4)</td>
<td>3 (6.1)</td>
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<tr>
<td>Steroid-induced diabetes</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
<td>2 (4.1)</td>
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<td>ASA-classification, n (%)</td>
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<tr>
<td>II</td>
<td>21 (17.6)</td>
<td>9 (12.9)</td>
<td>12 (24.5)</td>
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<tr>
<td>III</td>
<td>97 (81.5)</td>
<td>61 (87.1)</td>
<td>36 (73.5)</td>
<td></td>
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<tr>
<td>IV</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>KTx in medical history (%)</td>
<td>21 (17.6)</td>
<td>11 (15.7)</td>
<td>10 (21.3)</td>
<td>0.44</td>
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<tr>
<td>Duration of dialysis, months</td>
<td></td>
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<tr>
<td>Median</td>
<td>46.0</td>
<td>46.0</td>
<td>48.5</td>
<td>0.67</td>
</tr>
<tr>
<td>25th to 75th percentile</td>
<td>24.0-76.0</td>
<td>28.0-87.0</td>
<td>21.5-76.0</td>
<td></td>
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<tr>
<td>Use of vitamin D analogues, n (%)</td>
<td></td>
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<tr>
<td>Median</td>
<td>72 (63.7)</td>
<td>38 (59.4)</td>
<td>34 (69.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>25th to 75th percentile</td>
<td>16.8-56.3</td>
<td>12.5-48.0</td>
<td>21.0-75.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Use of phosphate binders, n (%)</td>
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<td></td>
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<tr>
<td>Median</td>
<td>30.0 (25.2)</td>
<td>0 (0.0)</td>
<td>30 (61.2)</td>
<td></td>
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<tr>
<td>25th to 75th percentile</td>
<td></td>
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<td></td>
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<tr>
<td>Use of Cinacalcet, n (%)</td>
<td></td>
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</tr>
<tr>
<td>Median</td>
<td>33.5</td>
<td>27.0</td>
<td>49.0</td>
<td></td>
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<tr>
<td>25th to 75th percentile</td>
<td>16.8-56.3</td>
<td>12.5-48.0</td>
<td>21.0-75.0</td>
<td></td>
</tr>
<tr>
<td>Time interval from HPT diagnosis to PTx, months</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33.5</td>
<td>27.0</td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td>25th to 75th percentile</td>
<td>16.8-56.3</td>
<td>12.5-48.0</td>
<td>21.0-75.0</td>
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</tbody>
</table>
Baseline characteristics were comparable across both groups. There was no significant difference with respect to age, gender, BMI-index, ASA-classification, diabetes and kidney transplantation history and time on dialysis. In group B, phosphate binders were significantly more frequently prescribed (p=0.027). Median interval between diagnosis and PTx was 27 months (IQR, 12.5-48.0) and 49 months (IQR, 21.0-75.0) respectively for group A and group B (p=0.007).

**Biochemical measures**

Preoperative laboratory values are listed in Table 2. A list of normal ranges of relevant laboratory values is added (Attachment 5). PTH levels were increased in both groups (median [IQR], 936.4 [600.0-1272.7] pg/ml and 1091.0 [482.2-1372.8] pg/ml for group A and B respectively, p=0.38). Calcium levels corrected for albumin varied from 1.60 to 3.68 mmol/l (mean ± SD, 2.60 ± 0.34 mmol/l) and were not significantly different between the two groups. Calculated calcium-phosphorus product ranged from 1.20 to 8.69 (median [IQR], 4.06 [2.98-5.19]). In group B, the calcium-phosphorus product was significantly lower than in group A at time of PTx (median [IQR], 4.34 [3.27-5.82] mmol²/l² vs. 3.47 [2.55-4.74] mmol²/l², p=0.012).

![Table 2. Preoperative laboratory variables](attachment:5)

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=119)</th>
<th>Group A Before the introduction of Cinacalcet (N=70)</th>
<th>Group B After the introduction of Cinacalcet (N=49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH, pg/mlᵃ</td>
<td>963.3 [527.3-1300.0]</td>
<td>936.4 [600.0-1272.7]</td>
<td>1091.0 [482.2-1372.8]</td>
<td>0.38</td>
</tr>
<tr>
<td>Calcium, mmol/l</td>
<td>2.60 ± 0.31</td>
<td>2.63 ± 0.34</td>
<td>2.56 ± 0.25</td>
<td>0.21</td>
</tr>
<tr>
<td>Corrected calcium, mmol/l</td>
<td>2.610 ± 0.34</td>
<td>2.67 ± 0.36</td>
<td>2.50 ± 0.28</td>
<td>0.008</td>
</tr>
<tr>
<td>Phosphorus, mmol/l</td>
<td>1.59 ± 0.58</td>
<td>1.67 ± 0.56</td>
<td>1.49 ± 0.60</td>
<td>0.09</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/lᵃ</td>
<td>147.5 [99.25-203.75]</td>
<td>150.5 [100.5-226.0]</td>
<td>137.0 [94.0-194.5]</td>
<td>0.48</td>
</tr>
<tr>
<td>Calcium-phosphorus product, mmol²/l²</td>
<td>4.06 [2.98-5.19]</td>
<td>4.34 [3.27-5.82]</td>
<td>3.47 [2.55-4.74]</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are shown in mean ± SD
ᵃMedian [interquartile range

Laboratory measurements 3 months after surgery are listed in Table 3. Postoperative corrected calcium levels decreased significant compared to before PTx (mean [SD], 2.61 [0.35] vs. 2.30 [0.31] (p=0.000). After PTx, the mean level of corrected calcium was within the normal value range (2.18-2.58 mmol/l). Furthermore, mean postoperative phosphate level reached its value within the reference range (0.80-1.50 mmol/l). This was also a statistically significant difference (p=0.004). All laboratory values were not statistically different in between the two study groups.
Mean preoperative, intraoperative and postoperative PTH levels ± SD are shown in Figure 5. PTH levels decreased significantly: 3 months after PTx the median PTH drop from baseline was 95.82% (IQR, 84.27-99.03). 78.8% of all patients had PTH levels 3 months after PTx below 150 pg/ml. This dramatic PTH reduction was also seen in long-term follow up. Although PTH levels slightly elevated 5 years after PTx (37.3 [6.8-107.7] pg/ml vs. 80.5 [19.7-193.2] pg/ml, p=0.036), 62.1% of all patients still had PTH levels below 150pg/ml.

### Table 3. Postoperative laboratory variables

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=119)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH, pg/ml</td>
<td>109.78 ± 198.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Corrected calcium, mmol/l</td>
<td>2.30 ± 0.31</td>
<td>0.000</td>
</tr>
<tr>
<td>Phosphorus, mmol/l</td>
<td>1.39 ± 0.52</td>
<td>0.004</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>96.0 (71.8-133.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Calcium-phosphorus product, mmol²/P²</td>
<td>3.17 ± 1.31</td>
<td>0.000</td>
</tr>
</tbody>
</table>

¶ Plus-minus values are means ± SD  
* Median (interquartile range)  
* P-values of preoperative compared to preoperative laboratory measurements

**Figure 5.** Median preoperative, intraoperative and postoperative PTH levels
Parathyroid gland weight
To compare resected parathyroid gland weight, weight of the largest parathyroid gland was used. Median weight of the largest removed parathyroid was 1.16 (IQR, 0.70-1.86) grams. There was no significant difference in parathyroid gland weight between the two groups (median [IQR], 1.11 [0.63-1.82] grams vs. 1.28 [0.72-1.90] grams, p=0.506). Correlation analysis with preoperative PTH levels and weight of the largest parathyroid gland showed a significant positive correlation (R=0.293, p=0.005).

Re-exploration
Six patients (5.0%) required re-exploration. In 4 cases indication for re-explorations was persistent hyperparathyroidism, 2 patients suffered from recurrent hyperparathyroidism. Five of the patients who underwent reoperation had subtotal PTx, 1 patient underwent total PTx + autotransplantation. In the study group before the introduction of Cinacalcet, re-exploration was required in 5 (7.1%) cases. 1 (2.0%) patient after the introduction of Cinacalcet underwent reoperation. There was no significant difference in re-exploration rate between the two groups (p=0.211). Mean time from initial PTx to re-exploration was 27.2 ± 23.7 months.

Postoperative complications
Postoperative complications are listed in Table 4. In all patients, the number of complications including mortality, recurrent laryngeal nerve damage, SSP, pneumonia and intensive care unit (ICU) admission was 10 (8.8%). There was no significant difference in number of complications between the two groups (p=0.657).

<table>
<thead>
<tr>
<th>Table 4, Postoperative complications</th>
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</thead>
<tbody>
<tr>
<td>Overall (N=119)</td>
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<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve damage, n (%)</td>
</tr>
<tr>
<td>Surgical site problems, n (%)</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
</tr>
<tr>
<td>Intensive Care admission, n (%)</td>
</tr>
<tr>
<td>Calcium supplements 6 mo post-op, n (%)</td>
</tr>
</tbody>
</table>

30 day mortality
Of all 119 patients, only 1 (0.8%) patient died within 30 days post surgery. This patient was a 66 year old female who underwent total parathyroidectomy in 2012. She was admitted to the intensive care unit with an extensive medical history of ESRD, lung bleeding and cardiac arrest. Amongst several other conditions, this patient suffered from refractory hypercalcaemia, which did not respond to Cinacalcet. Therefore, she underwent an uncomplicated total PTx with AT. Nevertheless, she remained hemodynamically unstable and died seven days after PTx due to general poor condition. Her death cannot directly be blamed on the parathyroidectomy.
**Recurrent laryngeal nerve damage**
Damage of the recurrent laryngeal nerve was defined as unilateral or bilateral vocal cord paralysis. Diagnosis was confirmed by an otolaryngologist, based on laryngoscopy. Seven patients complained of hoarseness and or inability to speak loudly. However, in only two patients vocal cord paralysis was confirmed by laryngoscopy.

**Wound problems**
In 4 cases wound problems were reported. One (0.8%) patient developed a bleeding for which reoperation was required. Another patient developed minute bleeding next to the drain, which was controlled with extra stitches. The other two patients developed wound infection for which antibiotics were prescribed.

**Pneumonia**
Two (1.8%) patients developed pneumonia post-PTx. Both patients were successfully treated with antibiotics.

**Intensive care admission**
Only one patient was admitted to the ICU within 30 days after total PTx + AT. Reason of admission was symptomatic hypocalcaemia; the patient presented with confusion, muscle cramps, ECG changes and hypophosphatemia. Patient was treated with high doses of calcium, administered intravenously and magnesium. Serum electrolyte levels improved rapidly after treatment and the patients were discharged after three days and sent home with, amongst other medication, vitamin D sterols and calcium supplements.

**Hypoparathyroidism / hypocalcaemia**
In 44 cases hypocalcaemia was reported as complication in the discharge letter, 23 (35.7%) in the group before the introduction of Cinacalcet, 21 (42.0%) in the study group after the introduction of Cinacalcet (p=0.455). As explained in the Material and Methods section, we eventually decided to use another definition of hypocalcaemia. In the 6 months after surgery, 42.2% patients of the group before the introduction of Cinacalcet and 36.7% patients of the group after the introduction of Cinacalcet required calcium supplements (p=0.557). Patients, who still needed calcium supplements 6 months post-PTx, had higher preoperative PTH levels compared to patients who did not develop postoperative hypocalcaemia (mean ± SD, 862.20 ± 452.87 pg/ml vs. 1228.91 ± 566.91 pg/ml, p=0.001).
Discussion

In end stage renal disease (ESRD), hyperparathyroidism (HPT) is a common. Main findings are calcium-phosphate imbalances and elevated levels of parathormone (PTH). Bone disease, cardiovascular events and increased mortality are recognized consequences of renal HPT. Over the last decade, the treatment algorithm has changed drastically with the advent of calcimimetics. The effects and consequences of this change of management on the renal HPT patient population that undergoes parathyroidectomy (PTx) are currently unknown. Therefore, we aimed to assess the selected PTx population and PTx outcomes before and after the introduction of calcimimetics.

We conducted a retrospective observational cohort study. Main outcome measures were time interval between renal HPT diagnosis and surgery, laboratory values and 30-day mortality and morbidity.

We found a 22-month delay of parathyroid surgery in the UMCG since the introduction of Cinacalcet in January 2005. It seems that the increase in the use of mainly medical treatment has led to a delay in referring the renal HPT patient for PTx, possibly withholding the patient from an effective solution. On top of this we observed that, even after the introduction of Cinacalcet, mean preoperative PTH levels after the introduction of Cinacalcet maintained to be elevated. Questions about the effects of this change in clinician’s decision-making remain unanswered.

With these data we did not only describe the strategy change in management of renal HPT, but we also evaluated the efficacy and short-term outcome of parathyroid surgery. PTx turned out to be very effective: 78.9% of all patients had PTH levels below 150 pg/ml 3 months after surgery. These dramatic reductions of PTH were also seen in long-term follow-up. Besides, biochemical measurements improved significantly after PTx. On top of that, despite the fragile patient population, PTx remained a very safe procedure. Apparently, this kind of surgery in the head and neck area, can be very forgiving and is associated with a very low complication rate.

To our knowledge this is the first study documenting the difference in time interval between renal HPT diagnosis and parathyroid surgery since Cinacalcet became available. Previous studies show various effects of the use of Cinacalcet on PTH levels. While initial studies showed a significant reduction of PTH, calcium and phosphate levels due to Cinacalcet, more recent studies show unsatisfactory results of the management of renal HPT and its complications with medical therapy.\textsuperscript{37,40,41} In our study, 61.2% of the patients of the study group after January 2005 is using Cinacalcet. However, despite medical treatment, preoperative PTH levels were as high as before the use of calcimimetics. Our data also show that even when patients were not treated with a calcimimeticum, they were referred for PTx in a later phase.
The effectiveness of PTx has been proven in several previous studies: reduction of PTH levels vary from 75-98%. In table 5, a literature review of relevant studies on PTx efficacy in ESRD patients is incorporated. Our results with an overall reduction of PTH levels of 86% replicate these findings.

Table 5. Review literature efficacy parathyroidectomy in ESRD patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of patients</th>
<th>Follow-up (months, mean)</th>
<th>Preop PTH (pmol/L)</th>
<th>Postop PTH (pmol/L)</th>
<th>PTH reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal PTx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cruzado</td>
<td>2015</td>
<td>15</td>
<td>12</td>
<td>336.4 ± 163.6</td>
<td>54.5 ± 45.5</td>
<td>83.8</td>
</tr>
<tr>
<td>Girotto</td>
<td>2001</td>
<td>6</td>
<td>60</td>
<td>357.3 ± 100.9</td>
<td>25.5 ± 29.1</td>
<td>94.0</td>
</tr>
<tr>
<td>Liang</td>
<td>2015</td>
<td>21</td>
<td>6</td>
<td>1895.4 ± 542.3</td>
<td>225.8 ± 90.2</td>
<td>88.1</td>
</tr>
<tr>
<td>Milas</td>
<td>2004</td>
<td>142</td>
<td>23</td>
<td>1459.0 ± 1190.0</td>
<td>137.0 ± 189.0</td>
<td>90.6</td>
</tr>
<tr>
<td>Schneider</td>
<td>2011</td>
<td>21</td>
<td>57.6</td>
<td>2377.9 ± 412.8</td>
<td>61.4 ± 12.6</td>
<td>97.4</td>
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<tr>
<td>Total PTx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liang</td>
<td>2015</td>
<td>21</td>
<td>6</td>
<td>1798.3 ± 785.4</td>
<td>85.1 ± 26.4</td>
<td>95.2</td>
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<tr>
<td>Schneider</td>
<td>2011</td>
<td>504</td>
<td>57.6</td>
<td>1371.4 ± 52.5</td>
<td>28.8 ± 3.1</td>
<td>97.9</td>
</tr>
<tr>
<td>Subtotal PTx and total PTx</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng</td>
<td>2013</td>
<td>49</td>
<td>12</td>
<td>1416.0 ± 449.0</td>
<td>146.0 ± 228.0</td>
<td>89.7</td>
</tr>
<tr>
<td>Kievit</td>
<td>2010</td>
<td>43</td>
<td>12</td>
<td>1090.9 ± 781.8</td>
<td>272.7 ± 481.8</td>
<td>75.0</td>
</tr>
<tr>
<td>Moldovan</td>
<td>2015</td>
<td>26</td>
<td>24</td>
<td>2464.8 ± 1239.3</td>
<td>746.1 ± 1141.0</td>
<td>73.5</td>
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<tr>
<td>Seehofer</td>
<td>2004</td>
<td>153</td>
<td>0.5</td>
<td>869.0 ± 57.0</td>
<td>42.0 ± 9.0</td>
<td>95.1</td>
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<td>Miscellaneous</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coen</td>
<td>2001</td>
<td>45</td>
<td>39.6</td>
<td>1313.4 ± 1004.1</td>
<td>214.2 ± 301.7</td>
<td>83.7</td>
</tr>
<tr>
<td>Ghani</td>
<td>2012</td>
<td>20</td>
<td>18.6</td>
<td>1537.0 ± 243.5</td>
<td>55.4 ± 26.0</td>
<td>97.0</td>
</tr>
<tr>
<td>Jofré</td>
<td>2003</td>
<td>148</td>
<td>12</td>
<td>1401.0 ± 497.0</td>
<td>154.0 ± 246.0</td>
<td>89.0</td>
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<tr>
<td>UMCG</td>
<td>2015</td>
<td>119</td>
<td>3</td>
<td>991.2 ± 530.7</td>
<td>109.8 ± 198.5</td>
<td>86.0</td>
</tr>
</tbody>
</table>

| Weighted mean PTH reduction (%) | 92.4 |

Normal range parathyroid hormone (PTH): 10 – 55 pg/mL

Looking at the calcium-phosphorus product, we found that this was significant lower after the introduction of Cinacalcet than before. This finding can be explained by the fact that Cinacalcet impacts the calcium-phosphate homeostasis. That is consistent with studies about the effects of Cinacalcet. According to our data complications were rare. This corresponds with other studies with respect to mortality, recurrent laryngeal nerve damage, SSP, and ICU admission. Different definitions of hypocalcaemia were used; nevertheless, our findings of postoperative hypocalcaemia were similar to others.
Hamouda et al. found that in the postoperative hypocalcaemia group, preoperative PTH levels were significantly higher than in the normocalcaemia group, this is comparable to our data.\textsuperscript{64}

A possible reason for 22-month referral delay might be multifactorial. In the past decade, there has been an increasing interest for the medical treatment of renal HPT, in particular for Cinacalcet.\textsuperscript{18} The addition of Cinacalcet to the armamentarium of the nephrologist seems to have contributed to a definite strategy change intending to withhold the patient from surgery as long as the medical condition allows. In general, nephrologists wait for a kidney graft to become available for KTx, hoping to avoid the need for PTx. We find an abundance of literature in which the target was to reduce the risk of PTx. When the aim is not to operate, calcimimetics often help to achieve this. However, whether delaying or obviating surgery with long-term medical therapy is truly beneficial for the patient is very doubtful. Eventually, only when PTH levels keep rising and the renal HPT becomes therapy resistant, the patient seems to be referred for surgery.

Also, indications for PTx are broad, but a standardized and specific guideline for surgery is not available.\textsuperscript{18,19} Lastly, the ESRD patient population is considered to be a very fragile population with severe comorbidities and the waiting list for PTx for secondary and tertiary HPT patients sometimes appears to be long.\textsuperscript{18,65,66} All these reasons have resulted in a change of clinical decision making and a reluctance to refer the ESRD patient for PTx.

It should be noted that in this study we did not take into consideration the patients for whom PTx was avoided because of Cinacalcet bridging the period of time until KTx. However, even though Cinacalcet might seem to be effective in treating hypercalcaemia and hyperphosphatemia, PTH levels usually keep elevating. Depending on the perspective of the specialist, the success of this strategy is debatable. While waiting for KTx, renal HPT often becomes refractory leading eventually to the unavoidable PTx.\textsuperscript{18} On top of this around 30\% of renal transplant patients eventually develop tertiary HPT.\textsuperscript{14} Tertiary HPT is characterized by the autonomous production of PTH and thus hypercalcaemia. When the calcium-phosphate homeostasis does not normalize after KTx, treatment often only delays definite surgical intervention.\textsuperscript{19,14} Therefore, predicting factors for developing refractory or tertiary HPT should be investigated to determine in advance which patients are medication refractory and will eventually need PTx anyway.

The change in guidelines in the management of secondary and tertiary HPT might be another explanation for the medicine resistant elevated PTH levels. In 2003 PTH values in ESRD patients with a maximum of 300 pg/ml (3 to 5 times the upper limit) were recommended, while in 2009, guidelines suggested PTH levels 2 to 9 times the upper limit (55 pg/ml), which is up to 495 pg/ml (grade 2C recommendation\textsuperscript{1}).\textsuperscript{32,36} These changes demonstrate the expectant strategy with respect to PTH levels that has developed with the advent of calcimimetics. However, these changes in guidelines lack evidence and the PTH values which patients present with at time of PTx far exceed these recommendations. Treatment algorithm and recommendations of these guidelines are added in attachments 6 and 7.

\textsuperscript{1} Grade 2C recommendation: Strength and grade for quality of evidence: “weak” and “low”\textsuperscript{32}
The delay in PTx to treat renal HPT may have multiple implications. First of all, with the long-term elevated PTH levels in ERSD patients, several problems may arise. Tentori et al. found a positive correlation between higher PTH levels and cardiovascular and all-cause mortality and increased cardiovascular hospitalization. Furthermore, data on the effects of long term elevated PTH levels on future kidney graft function are limited. However a large post hoc analysis did show a significant association between tertiary HPT and adverse renal graft outcome. Additionally, higher preoperative PTH levels were seen in patients who developed postoperative hypocalcaemia. This suggests that it is favorable to operate patients with lower preoperative PTH levels. Secondly, renal HPT patients who are medically controlled use vitamin D derivatives, phosphate binders and calcimimetics, which entail high costs. The EVOLVE trial showed that the use of Cinacalcet is accompanied by several severe adverse effects, which often leads to discontinuation of the drug and Brunaud et al. found that among Cinacalcet users 78% developed hypocalcaemia. Lastly, studies investigating the effectiveness of medical treatment show unsatisfactory results of the management of renal HPT and in practice patients often fail to reach by the KDIGO recommended PTH values. In the last decades the quality of parathyroid surgery has improved with the use of less invasive operations, heat sealing devices and improved imaging for preoperative localization. Our data suggest that surgery in the head and neck area, even in this very fragile population (ASA III or even IV), is accompanied with low complication rates and dramatic decreases in PTH levels.

This study has limitations that should be addressed. First of all, because of its retrospective nature, our data may be biased by multiple different recording methods used in our electronic patient record systems. Furthermore, experience teaches us that the implementation of a new medical therapy in clinical practice takes time and will differ from nephrologist to nephrologist, which makes any date chosen as the Cinacalcet introduction date disputable. Cinacalcet was first prescribed in the UMCG in 2005. For this particular reason, January 2005 was chosen as cut-off date to form two groups. Our study was not designed for comparing PTx with Cinacalcet. A large multicenter randomized control trial (RCT) to compare PTx versus Cinacalcet with long term follow-up from a surgical perspective is urgently required to conclude whether surgery is superior to medical treatment in patients with chronic renal failure. Preparations for this RCT are already being made by the Dutch Hyperparathyroid Study Group (DHSG). Furthermore, evidence based indications for surgery with absolute biochemical criteria should be defined in order to determine which patients should be referred for surgery. Of all patients included in our study, 39.8% developed postoperative hypocalcaemia. Therefore, a strict protocol monitoring serum calcium after surgery and if necessary, the administration of calcium supplements is required to maintain proper calcium levels. In clinical practice, waiting lists for PTx should be shortened in order to optimize the collaboration between nephrologists and the department of surgery.
In conclusion, the introduction of Cinacalcet is associated with a 22-month delay of definite surgical treatment of renal HPT and an overall hesitance to refer ESRD patients for PTx has developed. Despite the extensive use of calcimimetics, in general the renal HPT progressed, leading to continuously high preoperative PTH levels. Nevertheless, PTx remained a very safe and effective surgical procedure in fragile population of ESRD patients. Although in the last decade Cinacalcet has earned an important position in the treatment algorithm of renal HPT, the strategy of purely avoiding a safe and effective surgical treatment as long as possible seems not to be the answer.
Acknowledgments

I would like to express my great appreciation to the department of surgery, for giving me the opportunity to carry out my research clerkship. I would like to offer my special thanks to dr. Schelto Kruijff, who I now know for almost a year. Besides him being a great supervisor, he also stimulated me to get the most out of this internship. He engaged me in other research projects in this specific field of medicine, and introduced me to a lot of his interesting colleagues. With his dedication and constructive way of guidance, he learned me how to always think one step ahead, and how to think like a true researcher. In addition, dr. Kruijff provided me with very valuable knowledge of not only how to conduct high-quality research, but he also enthused me about scientific writing. I would also like to extend my thanks to drs. Akin Ozyilmaz, who guided my way through Diamant, the medical record system of Dialyse Centrum Groningen. Finally, I wish to thank dr. Martin de Borst, nephrologist, for helping me with my statistical questions and for his contributions to this study.
References


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(45) ASA Physical Status Classification System. 2014; Available at: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system. Accessed 10/15.


## Attachments

**Attachment 1 – List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>AT</td>
<td>Autotransplantation</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CaSR</td>
<td>Calcium-sensing receptor</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HPT</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>KTx</td>
<td>Kidney transplantation</td>
</tr>
<tr>
<td>METC</td>
<td>Medical Ethical Committee</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathormone</td>
</tr>
<tr>
<td>PTx</td>
<td>Parathyroidectomy</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized control trial</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SSP</td>
<td>Surgical site problems</td>
</tr>
<tr>
<td>UMCG</td>
<td>University Medical Center Groningen</td>
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</table>
Attachment 2 – METC approval UMCG

Universitair Medisch Centrum Groningen

Medisch Ethische Toetsingscommissie

Amst. W. T. van der Plas
Nieuwe rijn 36, Postbus 130, 9700 AA Groningen

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Belangrijk
Postcode 9713 CJ Groningen

Datum 10 augustus 2015
Onderwerp METC 2015/539
Titel Parathyroid surgery for secondary and tertiary hyperparathyroidism
10 years after the introduction of Cinacalcet

De Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen (METC UMCG) heeft het bovengenoemde onderzoek besproken en beoordeeld op een of meer van de reikwijdte van de Wet medisch-wetenschappelijk onderzoek met mensen (WMO) vol.

Op grond van de ingediende documenten is gesteld dat het onderzoek niet onder de reikwijdte van de WMO valt.

Dit betekent dat er voor de METC UMCG geen taak is weggelegd bij de beoordeling van het onderzoek en dat u geen oordeel nodig heeft van de METC UMCG, doordat u met bovengenoemd onderzoek mag aanvaarden.

Volledigheidshalve melden wij op dat het wetenschappelijke onderzoek mogelijk wel uitgevoerd dient te worden volgens de bepalingen van de overige wet- en regelgeving, waaronder onder andere de Wet geneeskundige behandelingen in toezicht (WGBO), de Wet bescherming persoonsgegevens (WBP) en de grondwettelijke regeleindes van de FEDERA.

Met vriendelijke groet,

namens de Medisch Ethische Toetsingscommissie.

groet,

prof. dr. W.A. Kamps
voorzitter

Dr. G. Draper
ambtelijke secretaris
### Table 6. ASA PS Classifications from the American Society of Anesthesiologists

<table>
<thead>
<tr>
<th>ASA PS Classification</th>
<th>Definition</th>
<th>Examples, including, but not limited to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA I</td>
<td>A normal healthy patient</td>
<td>Healthy, non-smoking, no or minimal alcohol use</td>
</tr>
<tr>
<td>ASA II</td>
<td>A patient with mild systemic disease</td>
<td>Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 &lt; BMI &lt; 40), well-controlled DM/HTN, mild lung disease</td>
</tr>
<tr>
<td>ASA III</td>
<td>A patient with severe systemic disease</td>
<td>Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥ 40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA &lt;60 weeks, history (&gt;3 months) of MI, CVA, TIA, or CAD/stents</td>
</tr>
<tr>
<td>ASA IV</td>
<td>A patient with severe systemic disease that is a constant threat to life</td>
<td>Examples include (but not limited to): recent (&lt;3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis</td>
</tr>
<tr>
<td>ASA V</td>
<td>A moribund patient who is not expected to survive without the operation</td>
<td>Examples include (but not limited to): ruptured abdominal/thoracic aneurism, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction</td>
</tr>
<tr>
<td>ASA VI</td>
<td>A declared brain-dead patient whose organs are being removed for donor purposes</td>
<td></td>
</tr>
</tbody>
</table>
In order to conduct a thorough literature search with respect to the efficacy of parathyroidectomy in end stage renal disease patients, a librarian of the university medical library was consulted. With her agreement we used the following search terms in PubMed:


1047 articles were identified by PubMed. Therefore, we only used papers published in the last 5 years, concerning 195 publications. These were manually screened. When no full text was available and articles written in a non-English language were excluded. In addition, we checked references of selected papers for supplementary studies. Finally, we only selected those papers in which preoperative and postoperative PTH levels were well documented in mean ± standard deviation.
### Table 7. Laboratory reference ranges

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Reference range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected calcium, mmol/l</td>
<td>2.18 – 2.58</td>
</tr>
<tr>
<td>Phosphate, mmol/l</td>
<td>0.80 – 1.50</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>35 – 100</td>
</tr>
<tr>
<td>Calcium-phosphorus product, mmol²/l²</td>
<td>2.10 – 2.37</td>
</tr>
<tr>
<td>PTH, pg/ml</td>
<td>11 – 55</td>
</tr>
</tbody>
</table>

* As indicated in PoliPlus
Attachment 6 – Treatment algorithm of secondary hyperparathyroidism according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines in 2003

Algorithm 11. The Overall Approach to the Management of Bone Metabolism and Disease in CKD Patients (Stages 5 on Dialysis).

1. Measure serum P
   - <3.5 mg/dL (1.10 mmol/L)
     - Assess nutrition
     - Discontinue phosphate binder if being used
   - 3.5-5.5 mg/dL (1.15-1.78 mmol/L)
     - Measure serum Ca
     - <100 µg/mL (11 nmol/L)
       - Stage 5 target: 150-399 µg/mL (165-33 pmol/L)
     - >100 µg/mL (11 nmol/L)
       - Begin dietary counseling and restrict dietary phosphate intake
       - Increase dialysis frequency
       - Start or increase phosphate binder therapy
       - Increase dietary phosphorus (Guidelines 4 & 5)

2. Measure serum PTH
   - <33 pmol/L
     - Begin dietary counseling and restrict dietary phosphate intake
   - 33-150 pmol/L
     - Begin active vitamin D (Guideline VIII)
   - >150 pmol/L
     - Begin short-term Al-based phosphate binder use, then increase non-Al-based phosphate binder
     - Begin dietary counseling and restrict dietary phosphorus
     - Increase dialysis frequency
     - (Guidelines 4 & 5)

3. Measure serum Ca
   - <8.4 mg/dL (2.1 mmol/L)
     - Treat hypocalcemia (Guideline II)
   - 8.4-10.5 mg/dL (2.1-2.6 mmol/L)
     - Continue current therapy
   - 10.6-12.9 mg/dL (2.6-3.4 mmol/L)
     - Decrease vitamin D dose to achieve ideal Ca of 8.4-9.5 mg/dL (2.1-2.4 mmol/L)
     - Decrease Ca-based phosphate binder
   - >12 mg/dL (2.4 mmol/L)
     - Decrease or discontinue vitamin D dose
     - Decrease or discontinue Ca-based phosphate binder
     - Decrease Ca dialysate if still needed (Guideline II)
     - Assess trend in serum PTH as there may be low turnover

4. Measure Ca x P
   - <50
     - Go to #1
   - >50
     - Go to #2

5. Continue trying to lower serum P
   - Serum PTH >650 pg/mL
     - Refer to intervention, and serum Ca >132 mg/dL (3.4 mmol/L)
   - Serum PTH <650 pg/mL
     - Serum PTH refractory to intervention, and serum Ca <132 mg/dL (3.4 mmol/L)

6. If condition persists
   - Go to #1
Attachment 7 – Treatment recommendations of abnormal PTH levels in ESRD patients according to the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines

RECOMMENDATIONS

4.2.1 In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).

It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

4.2.2 In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

4.2.3 In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (2C).

We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

4.2.4 In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

- It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD-MBD (not graded).
- It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise

4.2.5 In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy (2B).