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STUDIES ON CURRENT TOPICS IN THE MANAGEMENT OF PRIMARY HYPERPARATHYROIDISM

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine, University of Helsinki, for public examination in Auditorium 4, Meilahti Hospital, on December 16th 2016, at 12 noon.

Helsinki 2016
To my family
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List of original publications

This thesis is based on the following publications:


The publications are referred to in the text by their roman numerals. These articles have been reprinted with the permission of their copyright holders.
Abstract

The aim of this thesis on primary hyperparathyroidism (PHPT) was to improve preoperative imaging, to evaluate the effect of parathyroidectomy on health-related quality of life, and to investigate parathyroid carcinoma and its incidence in Finland.

PHPT is due to a parathyroid adenoma (in 80%), hyperplasia in two or more glands (15–20%) or, rarely, to parathyroid carcinoma. The only definitive treatment is an operation, which is indicated if surgical criteria are met. Preoperative imaging localizing the pathological gland(s) in the neck allows 70% of parathyroidectomies to be targeted. Otherwise, all four glands are explored. In our retrospective study of 269 PHPT patients who have undergone primary operation, the planar $^{123}$iodine/$^{99m}$Tc-sestamibi scintigraphy and $^{99m}$Tc-sestamibi scintigraphies were accurate in 61% and 34% of patients, respectively. The cure rate was 93%, but 61% in those with multigland disease (16% of the cohort). The gland size, serum calcium and PTH concentrations correlated to the proportion of scintigraphy findings.

In the reoperative setting, preoperative imaging has a crucial role, as the risk of surgery complications is higher. In our prospective study of 21 PHPT patients planned for reoperation, the imaging results were accurate in 59% of $^{123}$iodine/$^{99m}$Tc-sestamibi scintigraphies, in 19% of $^{99m}$Tc-sestamibi-SPECT/CT, in 65% of $^{11}$C-methionine-PET/CT, and in 40% of selective venous sampling studies (SVS). False positives were present in nearly half (9 out of 20) of SVSs but only in one PET/CT study.

In our prospective study of 124 PHPT patients, the preoperative health-related quality of life (HRQoL) studied with the 15D- instrument was lower than in a comparable sample of the general Finnish population (n=4295). It increased after surgery and was sustained in a one-year follow-up. The change in HRQoL was clinically significant in 77.4% of patients. Serum calcium and parathormone concentrations did not correlate with the preoperative level or the postoperative change of HRQoL.

Parathyroid carcinoma (PC) often presents with more severe PHPT than in the benign disease. We noticed that the incidence of PC has markedly increased in recent decades, with one case in 1 000 000 persons per year between 2010 and 2013. With our national research group, we collected and analyzed all the 32 PC cases and their tissue specimen diagnosed in Finland between 2000 and 2011. We compared these to 28 atypical adenoma and 72 age- and gender-adjusted parathyroid adenoma cases. Tissue Micro Array (TMA) analysis was performed on all tissue samples. Mutation analysis of the CDC73 gene related to PC was performed on 56% and 57% PC and atypical adenomas respectively, and was positive in 6% in both groups. PC
patients had higher serum calcium and PTH concentrations, and more often both bone and kidney manifestations.

The diagnosis of PC is based on metastasis or capsular, vascular or neural invasion, which can be challenging to diagnose. An atypical adenoma lacks the signs of invasion but has other features concordant with PC. In our study, the presence of lymph node metastasis at diagnosis, negative parafibromin staining, and a proliferation index of over 5% seemed to be related to a more aggressive disease. All recurrent tumors had a vascular invasion. PC has been reported to recur in 40–60% of patients. Therefore, it is recommended that the primary operation is more radical than a routine parathyroidectomy. At the seven-year follow-up, 21% had a recurrence of PC, and half of the patients were operated on at least twice. The mortality of the PC group did not differ from other subgroups, although in the PC group four died of the disease. One of the atypical adenoma patients had a recurrence.

In conclusion, the use of a thyroid-specific tracer like $^{123}$Iodine improves the accuracy of planar $^{99m}$Tc-MIBI scintigraphy. In multigland disease, representing 16% of the cases, the accuracy of $^{123}$Iodine/$^{99m}$Tc-sestamibi scintigraphy is markedly lower compared to single gland disease. Before reoperation, if ultrasound and scintigraphy findings are discordant or negative, $^{11}$C-methionine-PET/CT is recommended. The HRQoL in PHPT patients is reduced compared to healthy controls, but it improves significantly after operation. The incidence of parathyroid carcinoma is increased and it should be suspected if serum ionized calcium exceeds 1.70 mmol/l. PC patients often need reoperations, but the recurrence rate is lower than previously reported.
Väitöskirjatyöni tavoitteena oli kehittää primaarin hyperparatyreoosin (PHPT) preoperatiivisia paikantamismenetelmiä, arvioida lisäkilpirauhasleikkauksen vaikutusta terveyteen liittyvään elämänlaatuun sekä lisäkilpirauhassyövän yleisyyttä ja taudinkulkua Suomessa. Tutkimukset tehtiin vuosina 2009-2016.


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AP2S1</td>
<td>Adaptor-related protein complex 2σ 1 subunit</td>
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<td>APA</td>
<td>Atypical adenoma</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<td>BNE</td>
<td>Bilateral neck exploration</td>
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<td>CaSR</td>
<td>Calcium-sensing receptor</td>
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<td>CCR</td>
<td>Urinary calcium/creatinine ratio</td>
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<td>CDC73</td>
<td>Cell Division Cycle 73 gene</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>EANM</td>
<td>European Association of Nuclear Medicine</td>
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<td>EMG</td>
<td>Electromyogram</td>
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<tr>
<td>ECF</td>
<td>Extracellular fluid</td>
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<tr>
<td>ESES</td>
<td>European Society of Endocrine Surgeons</td>
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<tr>
<td>FCH</td>
<td>18F-fluorocholine</td>
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<td>FHH</td>
<td>Familial hypocalciuric hypocalcemia</td>
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<td>FIHP</td>
<td>Familial isolated HPT</td>
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<tr>
<td>18F-FDG</td>
<td>18F-Fluorodeoxyglucose</td>
</tr>
<tr>
<td>FU</td>
<td>Follow-up time</td>
</tr>
<tr>
<td>GNA11</td>
<td>G protein subunit α11</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HPT</td>
<td>Hyperparathyroidism</td>
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<td>HPT-JT</td>
<td>Hyperparathyroidism-jaw tumor syndrome</td>
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<tr>
<td>HRpQCT</td>
<td>High-resolution peripheral quantitative</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>HUS</td>
<td>Hospital District of Helsinki and Uusimaa</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases 10</td>
</tr>
<tr>
<td>ICF</td>
<td>International Classification of Functioning, Disability and Health</td>
</tr>
<tr>
<td>ioPTH</td>
<td>Intraoperative PTH measurement</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MEN</td>
<td>Multiple endocrine neoplasia</td>
</tr>
<tr>
<td>MGD</td>
<td>Multiglandular disease</td>
</tr>
<tr>
<td>MBq</td>
<td>Megabecquerel</td>
</tr>
<tr>
<td>MIP</td>
<td>Minimal invasive parathyroidectomy</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MTC</td>
<td>Medullary thyroid carcinoma</td>
</tr>
<tr>
<td>NS-PHPT</td>
<td>Neonatal severe PHPT</td>
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<td>NPHPT</td>
<td>Normocalcemic PHPT</td>
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<td>NPV</td>
<td>Negative predictive value</td>
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<tr>
<td>PA</td>
<td>Parathyroid adenoma</td>
</tr>
<tr>
<td>PAS</td>
<td>Pasieka’s Assessment Score</td>
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<tr>
<td>PC</td>
<td>Parathyroid carcinoma</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PF</td>
<td>Parafibromin</td>
</tr>
<tr>
<td>PHPT</td>
<td>Primary hyperparathyroidism</td>
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<tr>
<td>PHPQoL-16</td>
<td>Disease-specific HRQoL questionnaire for PHPT</td>
</tr>
<tr>
<td>PI</td>
<td>Proliferation index</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>PRUNE2</td>
<td>Prune homolog 2 [Drosophila] gene</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
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<tr>
<td>PTX</td>
<td>Parathyroidectomy</td>
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<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Forms-36</td>
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<tr>
<td>SVS</td>
<td>Selective venous sampling</td>
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<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
</tr>
<tr>
<td>S-PINP</td>
<td>Serum procollagen type I N-propeptide</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>TBS</td>
<td>Trabecular Bone Score</td>
</tr>
<tr>
<td>99mTc-MIBI</td>
<td>Technetium-multiplex ion-beam imaging</td>
</tr>
<tr>
<td>TMA</td>
<td>Tissue Micro Array</td>
</tr>
<tr>
<td>TTF1</td>
<td>Thyroid transcription factor 1</td>
</tr>
<tr>
<td>UNE</td>
<td>Unilateral neck exploration</td>
</tr>
<tr>
<td>U-hCG</td>
<td>Urinary human chorionic gonadotropin</td>
</tr>
<tr>
<td>U-NTX</td>
<td>Urinary N-telopeptide of type 1 collagen</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>VFA</td>
<td>Vertebrae fracture assessment</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>4D-CT</td>
<td>Four-dimensional computed tomography</td>
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Primary hyperparathyroidism (PHPT) is the most common cause for hypercalcemia (Marcocci, Cetani 2011) in which parathormone (PTH) is produced excessively from one or more of the four parathyroid glands (Bilezikian et al. 2016). The prevalence is 1–4 per 1000 and is highest among elderly women. PHPT is due to a parathyroid adenoma (80%), two or more hyperplastic parathyroid glands (15–20%) or, rarely, parathyroid carcinoma. In 5–10% of cases, PHPT is part of a genetic syndrome such as multiple endocrine neoplasia (MEN) syndrome, hyperparathyroidism-jaw tumor (HPT-JT) syndrome, or familial hypocalciuric hypercalcemia (FHH) (Thakker 2016).

Surgery is the only possible definitive treatment for PHPT. At diagnosis, patients are guided either to surgery or lifelong annual surveillance. The operation, bilateral exploration, includes the visualization of all four parathyroids and the removal of the enlarged one. However, multiglandular disease, present in 15–20% of patients, is more difficult to locate and complicates the choice of operation technique (Norman, Lopez & Politz 2012). Surgical techniques and especially the use of imaging to preoperatively locate the pathological gland have evolved (Bergenfelz et al. 2009). This enables focused parathyroidectomies with lower complication risks and shorter hospital stays. Patients with persistent or recurrent disease sometimes need reoperation, which is related to higher complication rates and require two concordant results in preoperative imaging studies (Hindie et al. 2009, Hindie et al. 2015). While the most commonly used methods, ultrasound and scintigraphy, remain discordant or negative, selective venous sampling (SVS) has long been the gold standard in the localization of an over-functioning parathyroid gland (Udelsman et al. 2009a).

PHPT has been known as a disease which presents severe bone and renal changes as well as abdominal and psychiatric symptoms. In recent decades, the better availability of serum calcium measurement has led to earlier diagnosis of PHPT. Consequently, the clinical profile has shifted from an advanced to a mild disease. To date, up to 80% of patients have none or only subtle symptoms of PHPT at diagnosis (Marcocci, Cetani 2011). However, the most recent studies show that these asymptomatic patients still suffer from neuropsychological and cognitive symptoms as well as other non-specific symptoms. PHPT is associated with impaired health-related quality of life, but it is still unclear as to whether the symptoms ameliorate and HRQoL improves after surgery, and if and when these symptoms justify surgery (Grant, Velusamy 2014).

Parathyroid carcinoma (PC) is a rare endocrine cancer, causing 1–3% of PHPT cases (Cetani, Pardi & Marcocci 2016). In Finland, the proportion of diagnosed PC among parathyroid tumors seems to have increased during the last two decades. PC has a more severe clinical presentation than benign parathyroid tumors with symptoms due to hypercalcemia, not to tumor mass itself. PC patients suffer from successive recurrences (in 40–60% of cases), multiple reoperations and surgery complications (Harari et al. 2011). A third of patients die of the disease during six-year follow-up periods (Talat, Schulte 2010). Distinguishing PC from benign or
atypical adenomas (APA) is often challenging. APAs are borderline tumors with features of PC but without invasion. PC patients need en bloc resection to provide the most effective chance of cure, and a closer post-operative follow-up (Schulte et al. 2012).

The aim of this study was to investigate these current topics in the management of PHPT. We compared preoperative imaging methods and analyzed the effect of preoperative localization on surgical techniques and results of 269 patients who had undergone primary operation and reoperation, respectively, at Helsinki University Hospital. We followed the health-related quality of life (HRQoL) in 125 PHPT patients referred to surgery for one year postoperatively. We collected all 32 parathyroid carcinomas diagnosed in Finland between 2000 and 2011 to assess the incidence, clinical and histological features of PC, and compared these to 28 atypical and 72 benign parathyroid adenomas.
2 REVIEW OF THE LITERATURE

2.1 CALCIUM METABOLISM

2.1.1 ROLE AND DISTRIBUTION OF CALCIUM

Calcium is indispensable for life. Calcium and phosphorus are the main elements of the bone, constituting two-thirds of the weight of bone. Nearly all, 99%, of total body calcium is in bone, and 99% of that is within the crystal structure of the mineral phase. In bone, the concentrations of the remaining 1% of calcium are equal in the extra- and intracellular fluids. This soluble portion of calcium is important for bone and cartilage mineralization and a cofactor for many enzymes, for instance in the coagulation cascade.

In blood, 50% of the calcium is bound to proteins, such as albumin and globulins. The ionized calcium concentration is 1.2 mmol/liter (5 mg/dl) on average. This biologically active form is tightly controlled. However, the intracellular calcium concentration is only 100 nmol/l, and there is a large chemical gradient (10000:1) with the extracellular fluid. This gradient provides rapid transition of calcium through calcium channels. Most of the intracellular calcium is bound to intracellular membranes and its release is tightly regulated.

Calcium homeostasis is essential because of the key role of calcium in extra- and intracellular compartments. In extracellular fluid (ECF) (Figure 1), calcium functions in membrane excitability, in bone mineralization, and as an important cofactor in proteins (adhesion molecules, clotting factors, enzymes). The intracellular functions of calcium include muscle contraction, activating endocytosis, hormone secretion and neuron activation (Brown 2013).

Figure 1. Distribution of different forms of calcium in blood plasma (adapted from Guyton and Hall, Textbook of Physiology 13th Edition)
2.1.2 REGULATION OF CALCIUM HOMEOSTASIS

Serum concentration and total body balance of calcium is kept within a narrow range by the interaction of calcium-sensing receptors and hormones (parathormone, vitamin D, calcitonin and FGF23). The organs taking part to the calcium homeostasis are parathyroid chief cells, thyroidal C-cells, and specific cell types in kidney, intestine, and bone. These mechanisms of calcium homeostasis are explained in the following sections and in Figure 2.

Figure 2. Summary of the effects of parathyroid hormone on bone, the kidneys, and the intestine in response to decreased serum calcium concentration (adapted from Guyton and Hall, Textbook of Physiology 13th Edition)

2.1.2.1 Parathormone

Parathormone (PTH) is a peptide hormone which can rapidly regulate the calcium concentration in blood and extracellular fluid. The effect of PTH is mediated by PTH receptors expressed in bone, the kidneys, and the brain. The PTH receptors are found in both in osteoblasts and their precursors, but not in osteoclasts. PTH is first synthetized as a pre-pro-PTH. Mature PTH of 84 amino acids requires cleavage of 25 amino acid pre- or signal sequence residues and of the six amino acid pro-sequence residues. The mature PTH is packed into vesicles in the parathyroid chief cells and either secreted from the cell or sequestered in the cell. This carboxyterminal pro-PTH fragment, unlike the aminoterminal PTH fragments, is also secreted from the cell but does not activate PTH receptors. The half-life of PTH is two minutes, and it is degraded in the liver (70%) and kidneys (20%) (Marcocci,

The serum calcium level is the main regulator of PTH secretion, and its effect is mediated by the calcium-sensing receptors on parathyroid chief cells. Hypocalcemia leads to an increase in PTH secretion. PTH stimulates osteoclast resorption to release skeletal calcium, although this is mediated through osteoblasts. PTH also enhances calcium reabsorption from distal tubules and increases the turnover of 25-hydroxyvitamin D to 1,25(OH)₂D₃. PTH also strongly inhibits phosphate and also renal sodium, water, and bicarbonate reabsorptions. PTH is a central regulation of bone formation and resorption (Brown 2013, Välimäki, Mäkitie 2009).

2.1.2.2 Calcitonin, 1,25(OH)₂D₃ and FGF23
Calcitonin is produced by the C-cells of the thyroid gland. This is stimulated by high serum calcium and is mediated by calcium-sensing receptors. Calcitonin reduces serum calcium by inhibiting osteoclasts and reduces calcium and phosphate release from bones (Fraser 2009).

The active form of vitamin D is the 1,25(OH)₂D₃. Its main function is to provide the main minerals for bone by increasing the intestinal absorption of calcium and phosphate. The precursors of this form are either synthetized in the skin or received in the diet, especially in fish, margarine, and milk with vitamin D supplementation. The liver metabolizes these precursor forms to 25(OH)D₃ which is converted later to 1,25(OH)₂D₃ by 1α-hydroxylase in the kidneys. This latter step can be stimulated by PTH and hypophosphatemia. This active vitamin D increases the absorption of dietary calcium and phosphate in the gut, and decreases PTH formation (Figure 2). When dietary calcium is limited, PTH increases 1,25(OH)₂D₃ production and intestinal calcium absorption and mobilizes skeletal calcium (Brown 2013). Vitamin D is also important for muscle function (Välimäki, Mäkitie 2009).

Fibroblast growth factor 23 (FGF23) is an important regulator of phosphate homeostasis. Its concentration in blood is increased when serum phosphate, serum calcium, or serum vitamin D concentrations or dietary intake of phosphate are high. FGF23 leads to hyperphosphaturia and a decrease in the production of 1,25(OH)₂D₃ in the kidneys. When kidney function is impaired, FGF23 concentrations are higher. FGF23 is released at least from osteocytes, and the effect is mediated by its own receptor (Brown 2013, Välimäki, Mäkitie 2009).

2.1.2.3 Calcium-sensing receptors
Due to its critical role in the optimal functioning of the body, plasma calcium concentration is kept in a narrow range. It is monitored minute-to-minute and is closely regulated by calcium-sensing receptors (CaSR), which are G protein coupled receptors expressed in many tissues (Alfadda et al. 2014). CaSR senses small perturbations in plasma-ionized calcium from its normal level (Brown 2013). CaSRs mediate the alterations of calcium: in hypercalcemia, the secretion of PTH and 1,25
vitamin D is decreased and that of calcitonin is increased. CaSRs can also directly modulate the calcium reabsorption in kidneys to preserve normocalcemia. Some studies have found CaSRs on osteoclasts and osteoblasts (Brown 2013). In the stomach, CaSR stimulation by elevated ECF calcium concentration leads to increased gastrin secretion. CaSR influences fluid transport and motility in the colon, as well as keratinocyte proliferation and growth in the skin (Figure 3) (Alfadda et al. 2014).

![Figure 3. Effects of calcium-sensing receptors in different organs, adopted from Alfadda et al. 2014](Alfadda et al. 2014)

### 2.1.3 EMBRYOGENESIS AND ANATOMY OF PARATHYROID GLANDS

Healthy individuals usually have four parathyroid glands, two superior and two inferior, but supernumerary parathyroid glands can occur in 2–13% of the population. Approximately 1–3% have only three parathyroid glands. The superior parathyroids develop from the fourth pharyngeal pouch. The inferior glands develop from the third pouch and migrate a longer distance in conjunction with thymic tissue. Thus, these glands are more likely to be in ectopic sites (Duan, Gomez Hernandez & Mete 2015).

The superior parathyroid glands can locate under the pseudocapsule of the thyroid gland or within the thyroid gland. A normal parathyroid gland appears brown, round-to-ovoid, small (often <6–8 mm), and can weigh up to 40–60 mg each (Duan, Gomez Hernandez & Mete 2015). Each gland has a thin fibrous capsule surrounding a network of adipose tissue, blood vessels, and glandular tissue. The parathyroid gland is composed predominantly of chief cells, as well as oncocytic cells, which are mitochondria rich, and rarely of clear cells (Carlson 2010, Bondeson et al. 2004).
2.2 HISTORY AND EPIDEMIOLOGY OF PRIMARY HYPERPARATHYROIDISM

2.2.1 HISTORY

Primary hyperparathyroidism is an ancient disease with a 7000-year-old case, one of the earliest documented, described in a woman aged 25–35 discovered in an early Neolithic cemetery in Germany (Zink et al. 2005). The disease was confirmed by radiologic imaging showing changes consistent with HPT, including significant demineralization of the skeleton with a “salt and pepper” appearance of the skull. In 1880, Swedish medical student Ivar Sandström was the first to describe the human parathyroid glands, whose function was unknown at that time, and he suggested the name “glandulae parathyroideae” (Carlson 2010). The first parathyroidectomy was performed by Dr. Felix Mandl in 1925 (Lee et al. 2016).

2.2.2 EPIDEMIOLOGY

The prevalence of PHPT is 1–4 cases in 1000 persons (Christensson et al. 1976, Boonstra, Jackson 1971), and it is most common among 55- to 75-year-old women (21 cases in 1000 persons) (Lundgren et al. 1997). According to a recent study, which included 3.5 million adults from the United States, the prevalence of PHPT tripled from 1995 to 2010, increasing from 76 to 233 per 100 000 women and from 30 to 85 per 100 000 men (Yeh et al. 2013). The increase in prevalence is related to
conservatively treating patients with mild PHPT (Yeh et al. 2013). The reported incidence of PHPT has also increased in recent decades and is partly related to the introduction of the multichannel autoanalyzer in clinical laboratories (Bilezikian et al. 2016). In the United States, the incidence of PHPT is highest among blacks, followed by whites, Asians, and Hispanics (Yeh et al. 2013).

### 2.3 PATHOGENESIS AND ETIOLOGICAL FACTORS OF THE PARATHYROID TUMORIGENESIS

Abnormal parathyroid glands are associated with hypercalcemia in three settings: In PHPT, in familial hypocalciuric hypercalcemia (FHH), and in drug-induced hypercalcemia. Parathyroid adenoma causes 80–85%, multiglandular hyperplasia or double adenoma 10–15%, and parathyroid carcinoma 1–3% of PHPT cases (Bringhurst, F.R., Demay M.B., Kronenberg H.M 2008). It is very rare for PHPT to be caused by ectopic PTH secretion (Bilezikian et al. 2016).

### 2.3.1 HEREDITARY SYNDROMIC FORMS OF PHPT

Hereditary syndromic forms of PHPT include hyperparathyroidism-jaw tumor syndrome (HPT-JT), multiple endocrine neoplasia syndromes (MEN types 1 - 4), familial hypocalciuric hypercalcemia (FHH), and familial isolated HPT (FIHP). Recent data suggests that as many as 10% of younger patients (< 45 year of age) with apparent sporadic PHPT have a germline mutation in one of the genes associated with familial PHPT (Starker et al. 2012). A family history of nephrolithiasis or premature osteoporosis may be the first sign of a genetic basis for PHPT. Guidelines on genetic testing are presented in section 6.1.

#### 2.3.1.1 Hyperparathyroidism-jaw tumor syndrome (HPT-JT)

HPT-JT is a rare, autosomal-dominant cancer syndrome caused by inactivating germline mutation of the tumor suppressor gene Cell Division Cycle 73 (CDC73), alternatively known as HRPT2, located on chromosome 1q25-32 (Newey et al. 2010). Of the 17 exons in CDC73 gene, the most mutations are found from exons 1, 2 and 7. It encodes a ubiquitously expressed protein, parafibromin, that is a transcriptional regulator as part of an RNA polymerase complex. CDC73 mutation leads to total absence of its protein product, parafibromin, which can be used as a diagnostic tool. More than a hundred CDC73 mutations have been found, two-thirds of them germline and other somatic mutations (Newey et al. 2010, Korpi-Hyovalti et al. 2014). CDC73 has an important role in the molecular pathogenesis of parathyroid carcinomas (PC) and a germline mutation is found in one-third of all PCs (Cetani, Pardi & Marcocci 2016).

Because of the incomplete penetrance and variable expression of the CDC73 mutation, patients with a germline CDC73 mutation (Bradley et al. 2006) present a
wide spectrum of phenotypes. The most common manifestation of HPT-JT is PHPT varying from familial isolated hyperparathyroidism (FIHP) to parathyroid cancer (in 15% of PHPT in HPT-JT) including occasionally tumors in other organs (Korpi-Hyovalti et al. 2014, Sharretts, Simonds 2010). These can be silent or clinically evident fibro-osseous tumors of the maxilla or mandible (histologically classified as cemento-ossifying fibromas), kidney tumors, such as Wilms tumor or cysts, and uterine lesions (Li, Simonds 2016). HPT-JT has no ethnic preference (Li, Simonds 2016).

### 2.3.1.2 Multiple endocrine neoplasia (MEN) syndromes

MEN1 is a rare condition, with a prevalence of 2–3 per 100 000, but the most common of hereditary cause of PHPT accounting for 2% of all cases (Sharretts, Simonds 2010). Loss-of-function mutation in the tumor suppressor gene MEN1 producing menin is responsible for autosomal-dominantly inherited MEN type 1. PHPT is the most common component of MEN1 with a 90% penetrance by the age of 50, typically presenting in the second to fourth decades of life. The disease is usually due to multiglandular hyperplasia and thus has a high rate of recurrence following apparent surgical cure. Malignant parathyroid tumors in MEN1 are rare (1–2% of all MEN1-related PHPT cases) (Christakis et al. 2016). MEN1 is also associated with pituitary and gastroenteropancreatic tumors, and less frequently with other tumors.

Multiple endocrine neoplasia type 2 (MEN2) has three clinical variants: MEN2a, MEN2b (or MEN3) and MTC-only. Each type is associated with specific, autosomal-dominant, germline mutation in the RET (rearranged during transfection), a proto-oncogene that normally positively regulates cell growth and/or proliferation, but when activated by mutation can induce neoplasia. Patients with MEN2a, the most common, have medullary thyroid carcinoma (MTC) (99%), pheochromosytoma (50%) and parathyroid tumors (20%) of patients. PHPT is usually mild resembling a sporadic PHPT in its clinical presentation and is usually due to benign tumors (single or multigland disease). MEN2b is not associated with parathyroid tumors (Thakker 2016).

Rarely, in 3%, patients with MEN1-associated tumors lack MEN1 mutation but have a mutation in CDKN1B. This gene encodes p27, a protein involved in cell cycle controlling (Marinoni, Pellegata 2011). This form is called multiple endocrine neoplasia type 4 (MEN4). These patients present with PHPT, pituitary, renal, or adrenal gland tumors, or with gastrointestinal neuroendocrine tumors, and the inheritance is autosomal dominant (Thakker 2016).
2.3.2 NON-SYNDROMIC FORMS OF PHPT

2.3.2.1 Familial isolated hyperparathyroidism (FIHP)
Familial isolated hyperparathyroidism (FIHP) is a clinically defined syndrome in relatives with HPT but which lacks the specific manifestations of other organs as in MEN1, HPT-JT or FHH. Some FIHP patients also have a germline mutation of MEN1, CDC73 or CaSR, suggesting incomplete penetrance (Simonds et al. 2004).

2.3.2.2 Familial hypocalciuric hypercalcemia (FHH)
FHH is an autosomal-dominant disorder with three subtypes with specific gene mutations, all leading to decreased sensitivity of CaSR to extracellular calcium concentration. Therefore, an increased level of ionized calcium is needed to suppress PTH secretion (Costa-Guda, Arnold 2014). FHH presents with a lifelong elevation in serum calcium concentration, normal PTH concentration, and in 80% of patients a low urinary calcium concentration (urinary calcium/creatinine ratio (CCR) < 0.01), and sometimes hypermagnesemia (Gorvin et al. 2016). These patients can be misdiagnosed as having PHPT, as 20% have elevated serum calcium and 20% may have CCR > 0.01. PHPT patients with vitamin D deficiency or renal insufficiency may also have low CCR. It is critical to diagnose FHH, as hypercalcemia is generally benign without skeletal or renal complication (Thakker 2016), and it parathyroidectomy does not correct hypercalcemia. Mutational analysis helps to distinguish FHH patients from those with PHPT.

Patients with FHH1 have a heterozygous loss-of-function of the extracellular calcium-sensing receptor (CaSR) located in chromosome 3 (Hannan, Thakker 2013). FHH2 is related to the mutation of G protein subunit α11 (GNA11) (Gorvin et al. 2016) and FHH3 to adaptor-related protein complex 2σ1 subunit (AP2S1) (Nesbit et al. 2013). Both FHH2 and FHH3 are loss-of-function mutations in chromosome 19 and represent on average 5% of FHH patients (Thakker 2016).

Severe neonatal PHPT (NS-PHPT) is defined as symptomatic hypercalcemia with severe skeletal manifestations in the first six months of life (Thakker 2016). Homozygous CaSR mutations or the inheritance of two inactive CaSR alleles classically results in NS-PHPT (Costa-Guda, Arnold 2014, Gorvin et al. 2016). These children have life-threatening hypercalcemia during their first days or weeks of life and require urgent parathyroidectomy.

2.3.3 TUMORIGENESIS IN SPORADIC ADENOMAS
Parathyroid adenomas are monoclonal, caused by sequential mutations in the DNA of a parathyroid cell. It is now recognized that somatic mutations in the CCND1 (PRADI) oncogene, encoding cyclin D1 protein, and MEN1 tumor suppressor gene, encoding menin, are frequently found in sporadic parathyroid adenomas (Sharretts,
Simonds 2010). Acquired, inactivating mutation of both alleles of the MEN1 gene has been reported in 12–35% of sporadic parathyroid adenomas (Farnebo et al. 1998). A pericentromeric inversion of chromosome 11 leads to the activation of transcription in \(CCND1\) (\(PRAD1\)), and Cyclin D1 is overexpressed in 20–40% of sporadic adenomas. \(CCND1\) mutations are found in 8% of cases (Costa-Guda, Arnold 2014). However, hyperplastic parathyroid glands are of polyclonal origin and are related to hereditary forms of PHPT (see section 4.1) (Costa-Guda, Arnold 2014). Somatic inactivation of CaSR has not been found in sporadic parathyroid adenomas (Hosokawa et al. 1995), and inactivating germline mutations of CaSR in sporadic adenoma patients are very rare, detected in <1% of patients (Guarnieri et al. 2010).

The incidence of PHPT among those who received radiation to tonsils before the age of 16 was 18.7 per 100,000 person-years below the age of 40 and 171 per 100,000 person-years in the age range of 40 to 60 years, representing a 2.9-fold and 2.5-fold increase compared with that among the general population (Cohen, Gierlowski & Schneider 1990).

2.3.4 LITHIUM-INDUCED PHPT

On average, 10% of patients on lithium therapy, serum calcium and PTH concentrations are elevated (McKnight et al. 2012). Lithium inactivates the CaSR, leading to an increased release of PTH (McKnight et al. 2012). Hypercalcemia is often reversible within several months after stopping lithium therapy, but occasionally hypercalcemia persists. In these cases, surgery reveals a parathyroid adenoma (in 92% of cases) or a four-gland hyperplasia (Awad, Miskulin & Thompson 2003, Szalat, Mazeh & Freund 2009). Of all lithium users, the risk for hypercalcemia was highest in women over the age of 60 and lowest in young men (Shine et al. 2015). Serum calcium should be measured when starting lithium therapy and it should be checked annually during the treatment.

2.4 HISTOPATHOLOGY OF PARATHYROID TUMORS

2.4.1 PARATHYROID ADENOMA

The average weight of adenomas weight 1 g, whereas the normal parathyroid gland weight is approximately 40–60 mg (DeLellis 2011). Parathyroid adenomas are benign neoplasms composed of varying proportions of chief, oncosytic, transitional oncocyctic, and clear cells (Duan, Gomez Hernandez & Mete 2015). Adenomas are encapsulated and often have a rim of normal parathyroid in the periphery. The cells are arranged in different proportions of cords, nests, sheets, and follicles mimicking thyroid tissue (Duan, Gomez Hernandez & Mete 2015). Cystic changes are relatively common in large adenomas (DeLellis 2011). A mitotic figure can be present, but the
proliferation index (PI) is usually < 4% (Duan, Gomez Hernandez & Mete 2015, Abbona et al. 1995). The parathyroid adenoma cells stain positively for cytokeratins, PTH, and chromogranin A, while staining for thyroglobulin and thyroid transcription factor-1 (TTF1) is negative (DeLellis 2011). Immunohistochemical stainings are used to distinguish parathyroid from thyroid tissue. PTH staining is positive in parathyroid tissue, and thyreoglobulin or TTF1 are positives in thyroid tissue (Grimelius et al. 2004).

2.4.2 PARATHYROID HYPERPLASIA

Parathyroid hyperplasia is a multiglandular disorder with morphological variants of diffuse, nodular hyperplasia (with one or more nodules) and a mixture of these (Duan, Gomez Hernandez & Mete 2015). In PHPT caused by hyperplasia, 25% of cases are heritable (as with MEN types 1–4). In hyperplastic glands, chief cells dominate, the ratio of parenchymal cells to fat is increased and, as in adenomas, a rim of normocellular parathyroid tissue can be found at the periphery.

When two or more parathyroid glands are enlarged, parathyroid hyperplasia should be considered in differential diagnosis. Diagnosis cannot solely be based on histological criteria, as parathyroid glands in chief cell hyperplasia may have a similar appearance to that of small adenomas. The examination of associated glands left in situ is important to distinguish hyperplastic glands from adenomas. Strong nuclear pleomorphism suggests a parathyroid adenoma instead of hyperplasia. The glands are symmetrically enlarged in ~50% of the cases (DeLellis 2011, Grimelius et al. 2004).

2.4.3 ATYPICAL PARATHYROID ADENOMA

Atypical parathyroid adenomas (APA) are borderline neoplasms and often larger than adenomas but smaller than PCs. They share some features of PC such as fibrosis, hemosiderin deposits, and mitoses, but, importantly, they lack definitive evidence of invasive growth (Duan, Gomez Hernandez & Mete 2015, Bondeson et al. 2004). Adherence to surrounding tissue is not as common as in PC (Schneider et al. 2015, Quinn et al. 2015).

2.4.4 PARATHYROID CARCINOMA

Malignant parathyroid tumors present as larger masses that are often adherent to adjacent structures. Compared to adenomas, carcinomas are gray-white and have a firmer consistency. The World Health Organization (WHO) criteria for parathyroid carcinoma include vascular invasion, invasion to perineural space, capsular penetration with growth to adjacent tissue, and/or metastases (Bondeson et al. 2004).
Vascular invasion should be present in the tumor capsule or in the surrounding tissue rather than within the tumor. The frozen section is of little value in distinguishing benign from malignant disease, and thin-needle biopsy that can cause tumor cell seeding is strongly discouraged and gives little information on possible tumor invasion (Cetani, Pardi & Marcocci 2016). Parathyroid carcinoma is characterized by recurrent local disease and typically metastases to cervical and mediastinal lymph nodes. Local recurrences are highly suspicious for malignancy, but local seeding from intraoperatively ruptured adenoma can implant and mimic malignant growth (parathyreomatosi) (Bondeson et al. 2004, Fernandez-Ranvier et al. 2007). Distant metastases are found most commonly in lungs, but also in bone and liver. Bone metastases should be distinguished from Brown tumors related to severe PHPT and cemento-ossifying fibromas in mandible and maxilla related to hereditary parathyroidism-jaw tumor syndrome (HPT-JT) (Cetani, Pardi & Marcocci 2016).

In carcinomas, chief cells predominate, but oncocytic tumors occur, and mixtures of the cells are seen. Oncocytic carcinomas seem to share similar clinical behavior with carcinomas composed of chief cells. Band-forming fibrosis and hemosiderin deposits are common but not pathognomonic findings in PC (Bondeson et al. 2004, Fernandez-Ranvier et al. 2007). The triad of coagulative necrosis, macronucleoli, and Ki-67 over 10% strongly suggest malignant parathyroid tumors (Bondeson et al. 2004, Fernandez-Ranvier et al. 2007).

2.4.5 IMMUNOHISTOCHEMISTRY IN PARATHYROID TUMORS

Differentiating benign and malignant parathyroid tumors is often challenging, as invasive growth is not always unequivocal and tumors are enucleated with very small margins. Many immunohistochemical markers, such as parafibromin, retinoblastoma protein, PGP9.5, Ki-67, cyclin D1, and galectin-3 have been studied to distinguish between benign and malignant parathyroid tumors. Parafibromin (PF), the protein product of \( CDC73 \), is present in nearly all adenomas, absent in 31–38% of PCs, and in 21% of atypical adenomas (Quinn et al. 2015, Fernandez-Ranvier et al. 2007). The mutation in \( CDC73 \) leads to the absence of PF in parathyroid tissue. A recent study reported that PF-negative APAs did recur in 10% of cases in contrast to PF-positive APAs, none of which recurred (Kruijff et al. 2014). The proliferation marker Ki-67 levels may be increased both in benign and malignant tumors, and do not have diagnostic value in this respect. However, indices greater than 5% should lead to a closer and prolonged follow-up of the patients due to increased risk of malignancy and recurrence (Bondeson et al. 2004). Quinn et al. reported PI of 6.8% vs 3.9% for PCs vs APAs (Quinn et al. 2015). Some studies suggest immunohistochemical panels to be superior compared to any single marker (Fernandez-Ranvier et al. 2007, Truran et al. 2014). It has been suggested that E-cadherin distinguishes PC from APAs (Schneider et al. 2015).
2.5 CLINICAL PRESENTATION

2.5.1 THE CHANGING PRESENTATION OF PHPT

The classical presentation of PHPT, also described as “painful bones, renal stones, abdominal groans and psychic moans” includes skeletal and renal involvements as well as symptoms related to hypercalcemia (Bilezikian et al. 2016). PHPT is also associated with hypertension and with other cardiovascular changes. In Western countries, the detection of serum calcium levels as part of many routine screenings has increased diagnoses of PHPT and especially of the mild forms of the disease. In developing countries, the classic PHPT still dominates: in Beijing, China, the mean age of PHPT patients is 37 years, 60% having the bone involvement of the disease (Bilezikian et al. 2000).

The primary abnormality of parathyroid tissue leads to inappropriate secretion of PTH. This is succeeded by excessive tubular calcium reabsorption and phosphaturia, 1,25(OH)₂ D synthesis in kidneys, and increased bone resorption, resulting in hypercalcemia and hypophosphatemia and cortical bone loss (Bringhurst, F.R., Demay M.B., Kronenberg H.M 2008). However, when PHPT patients develop hypercalciuria, the amount of urinary calcium exceeds the ability of PTH to enhance tubular calcium reabsorption (Bilezikian et al. 2016).

2.5.2 SKELETAL INVOLVEMENT OF PHPT

Specific skeletal manifestations of PHPT, called osteitis fibrosa cystica, are seen in advanced forms of PHPT. The symptoms include bone pain, skeletal deformities, and pathological fractures (Bilezikian et al. 2016), and are due to the generalized increase in bone resorption and osteoblastic activity (Bringhurst, F.R., Demay M.B., Kronenberg H.M 2008). Generalized demineralization of bone is evident as subperiosteal bone resorption, especially in the phalanges of the hands, and as bone cysts and brown tumors, composed of multinucleated osteoclasts, stromal cells and matrix, most often found in trabecular parts of the jaw, the long bones and the ribs. The skull often presents with a salt and pepper appearance in radiologic imaging (Bringhurst, F.R., Demay M.B., Kronenberg H.M 2008).

In mild PHPT, the bone involvement is typically seen only as a decrease in bone mineral density assessed by Dual X-ray Absorptiometry (DXA). It is known that the cortical bone compartment is especially involved. In an Italian cohort of consecutively diagnosed PHPT patients, 63% had a T-score < -2.5 SD at any site in DXA and 35% had a vertebral fracture (> 25% in height of a vertebra) according to X-rays (Cipriani et al. 2015). Vestergaard et al. noticed an increase in the bone fracture risk as early as 10 years before parathyroidectomy in PHPT patients (Vestergaard et al. 2000). According to a recent study (Castellano et al. 2016), 11% of patients with no symptoms, bone or renal signs of PHPT had osteoporosis (T-score ≤ -2.5 SD), and half of these met the criteria for parathyroidectomy.
However, bone mineral density accounts for only approximately 60–80% of the reduction in bone strength. The Trabecular Bone Score (TBS) assessment and high-resolution peripheral quantitative CT (HRpQCT) have been used to assess bone quality in PHPT (Silva et al. 2013, Stein et al. 2013). Measuring bone density in the hip, lumbar spine, and the distal third of the radius is recommended in the evaluation of PHPT. A vertebral fracture in an X-ray or computed tomography (CT) (regardless of bone mineral density) or an osteoporotic value (T-score < -2.5 SD) in the lumbar spine, total hip, or distal third of the radius in DXA are considered to be criteria for parathyroidectomy (Bilezikian et al. 2014). After surgery, fracture risk seems to return to the same level as in age- and gender-matched controls (Vestergaard et al. 2000). The fracture risk of those not operated on remains increased (Vestergaard, Mosekilde 2003a).

2.5.3 RENAL INVOLVEMENT OF PHPT

In the kidneys, PTH stimulates the renal tubular reabsorption of calcium. However, in spite of this, total renal calcium excretion is typically increased due to the augmented filtered calcium load (Starup-Linde et al. 2012). Renal stones can be asymptomatic or may cause acute, intermittent flank pain radiating to the lower abdominal groin, as well as hematuria and nausea.

Renal manifestations in severe PHPT include recurrent renal stones (stones in the urinary tract), nephrocalcinosis, and renal function abnormalities ranging from impaired renal concentration capacity to end-stage renal failure (Bilezikian et al. 2016). Fifty years ago, the prevalence of renal stones was 60%, but is estimated to now be around 7–20% (Bilezikian et al. 2016, Mollerup et al. 2002). The prevalence of PHPT among patients presenting with nephrolithiasis is 2–8% (Mollerup et al. 2002). In a Danish cohort of operated PHPT patients, the prevalence of renal calcification was 25.4% (15.3% having renal stones and/or 10.3% renal calcifications) in CT imaging (Starup-Linde et al. 2012).

Hypercalciuria is generally considered to be a contributor to the pathophysiology of nephrolithiasis, but the precise relationship between PHPT and nephrolithiasis is incompletely understood (Rejnmark, Vestergaard & Mosekilde 2011). Calcium phosphate stones predominate, but calcium oxalate and mixed calcium stones are also common, whereas uric-acid stones are less common (Rejnmark, Vestergaard & Mosekilde 2011). Most studies (Starup-Linde et al. 2012, Mollerup et al. 2002, Rejnmark, Vestergaard & Mosekilde 2011, Berger et al. 2009) have not found any correlation between renal calcium excretion and kidney stones. There were no significant differences in urine analysis between PHPT patients with and without kidney stones (Berger et al. 2009). According to a large meta-analysis by Mollerup et al. (Mollerup et al. 2002), the risk of renal stones is increased in males and at young onset age of PHPT, whereas the risk is not increased in users of oral calcium supplements. The risk of nephrolithiasis has been shown to decrease after curative parathyroidectomy (PTX), although the risk remains slightly increased compared
with the background population (Rejmark, Vestergaard & Mosekilde 2011). The risk decreases to near-normal after a 10-year follow-up (Mollerup et al. 2002).

PHPT associates with renal impairment in severe forms of PHPT but, according to a large recent review of the literature (Hendrickson, Castro Pereira & Comi 2014), it is not commonly observed in mild PHPT. Patients with concomitant renal disease or any renal impairment are thought to be more prone to PHPT-mediated kidney damage and nephrocalcinosis (Hendrickson, Castro Pereira & Comi 2014). Older studies (Kristoffersson et al. 1990) have reported an improvement in renal concentration capacity, but no change in GFR after a one-year follow-up. A study of 109 consecutive patients operated on for PHPT, including 14 subjects with reduced GFR, demonstrated no change in GFR after parathyroidectomy (Tassone et al. 2015). In the three randomized studies comparing observed and surgically-treated mild PHPT patients not fulfilling the current surgical criteria (Ambrogini et al. 2007, Bollerslev et al. 2007, Rao et al. 2004), there were no changes in pre- and postoperative creatinine levels at 1–2-year follow-up. Accordingly, the surgical criteria recommending operations for all with GFR < 60ml/min/1.73 m² have been also criticized (Hendrickson, Castro Pereira & Comi 2014, Tassone et al. 2015, Walker et al. 2014).

### 2.5.4 MUSCULAR AND NEUROLOGICAL MANIFESTATIONS IN PHPT

Non-specific symptoms associated with PHPT include reduced muscle strength, neurocognitive symptoms (fatigue, depression, and memory loss), reduced well-being, polydipsia, abdominal pain, nausea and constipation, as well as non-specific pain in the back and extremities.

Classical, severe PHPT has been associated with weakness and easy fatigability of muscles. Muscle biopsies showed atrophy of both type I and type II muscle fibers, and electromyogram (EMG) was abnormal, especially in lower extremities in PHPT patients whose symptoms ameliorated after parathyroidectomy (Patten et al. 1974). In mild PHPT, neuromuscular disease is rare and neurological examination remains normal, but weakness and easy fatigability are common complaints (Bilezikian et al. 2016). PHPT patients demonstrated alterations in EMG with a subclinical sensory-motor peripheral polyneuropathy compared to healthy persons (Diniz et al. 2013). Mechanisms of action accounting for muscle weakness and neurocognitive symptoms seem to include increased plasma Ca²⁺ hampering muscle contraction (Rolighed et al. 2014b). PTH receptors are also found in brain and muscle tissues, which can be related to the mechanisms in neurological and muscle symptoms (Reppe et al. 2007). In PHPT, the reduced muscle function improves to the level of the control group after surgery (Deutch et al. 2000). In addition, asymptomatic patients have reduced muscle function (Rolighed et al. 2014a).

Neurocognitive skills, such as concentration, nonverbal learning, and memory, are also impaired in PHPT, and neuropsychiatric alterations (anxiety and mood) are evident in PHPT (Babinska et al. 2012, Walker et al. 2009, Roman et al. 2011b). Improvement in these symptoms have been reported after parathyroidectomy in

2.5.5 CARDIOVASCULAR HEALTH IN PHPT

Hypertension, premature atherosclerosis, valve calcification, left ventricular hypertrophy, and arrhythmias have been associated with PHPT (Iwata et al. 2012). A large meta-analysis (van Ballegooijen et al. 2013) demonstrates that higher PTH concentration is associated with increased risk of fatal and non-fatal cardiovascular events. PTH receptors have been found in cardiomyocytes, and left ventricular dysfunction is related to PHPT. According to another large meta-analysis, parathyroidectomy has a beneficial effect on cardiovascular events, while the magnitude of the effect depends on the preoperative PTH level (Walker et al. 2012). Mild PHPT is also associated with aortic valve calcification, and PTH is an important predictor of the valve calcification (Iwata et al. 2012).

There is also growing evidence of a bidirectional relationship between the renin-angiotensin-aldosterone system (RAAS) and PTH. Both serum aldosterone and PTH concentrations has been reported to decrease during RAAS inhibitor treatment (Brown et al. 2015). Patients with primary hyperaldosteronism have higher PTH levels than those with essential hypertension, and both adrenalectomy or spironolactone decreases PTH concentrations (Pilz et al. 2012). The aldosterone-renin ratio is independently associated with nocturnal blood pressure in PHPT patients and is related to the severity of the disease (Verheyen et al. 2016). Primary aldosterone is associated with lower BMD and a higher fracture risk (Vaidya, Brown & Williams 2015).

2.5.6 QUALITY OF LIFE IN PHPT

2.5.6.1 Assessing health-related quality of life

The concept of health-related quality of life (HRQoL) has evolved since the 1980s. The World Health Organization’s (WHO) definition of health includes mental, physical, and social aspects. The WHO’s International Classification of Functioning, Disability and Health (ICF), a classification of health and health-related domains, describes the different aspects related to HRQoL (Sintonen 2013). HRQoL also includes the patient’s perception of his/her physical and mental health. There is no gold standard or reference ranges for HRQoL, thus the results need to be compared to pretreatment values or a control group (Sintonen 2001).

HRQoL can be measured by disease-specific or generic methods. Disease-specific instruments are designed for specific patient populations. Of these, the PAS (Pasieka’s Assessment Score) (Pasieka et al. 2002) and the disease-specific HRQoL questionnaire for PHPT patients called the PHPQoL-16 (Webb et al. 2016) have
been designed for PHPT. Generic methods measure HRQoL and its changes, and are appropriate to all patients regardless of the disease. Generic instruments provide a comparison between different patient groups. HRQoL is affected by patients’ gender and age distribution (Sintonen 2013). In PHPT patients, Short Forms (SF)-36 has been most commonly used.

An HRQoL instrument can give one score and/or a profile. The Finnish 15-dimensional questionnaire (the 15-D instrument) is a well-validated, generic, self-administered measure for HRQoL. It can be used as a single score or as a profile of 15 different dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity) presented as a graph. It consists of 15 questions and it is completed in four minutes on average (see Appendix 1 and 2) (Sintonen 2001). The 15D covers 80% of the domains of ICF, and the sensitivity in reacting to changes after an intervention is among the best of all the HRQoL instruments (Saarni et al. 2006, Kontodimopoulos et al. 2012).

Short Form-36 (SF-36) is a generic general health survey (Jenkinson, Coulter & Wright 1993). The questionnaire assesses 36 items and consists of eight dimensions: Social and physical functioning, mental health, physical and mental role limitation, vitality/energy, pain, and general health perception. It provides two scores: One for mental and one for physical components, as well as scores for all dimensions. It has been widely used in HRQoL of PHPT.

2.5.6.2 Health-related quality of life in PHPT

Health-related quality of life is often reduced by chronic diseases such as PHPT. Adequate tools are needed for assessment of the prevalence of neurocognitive symptoms and their impact on daily life in PHPT. The transition of PHPT toward mild or even asymptomatic disease has led to a need to re-evaluate the effects of the disease on patients, as well as the surgical criteria (Grant, Velusamy 2014).

There is a consensus that HRQoL is reduced in PHPT (Pasieka et al. 2002, Burney et al. 1999), and in mild PHPT patients not fulfilling the international criteria for surgery when compared to controls (Bollerslev et al. 2007) or to thyroid-operated patients (Weber et al. 2013, Pasieka et al. 2002).

In patients operated on because of PHPT according to the prevailing surgical criteria, an improvement in HRQoL was observed (Burney et al. 1999, Blanchard et al. 2014, Caillard et al. 2007, Gopinath, Sadler & Mihai 2010, Sheldon et al. 2002). Of three prospective, randomized studies evaluating mild PHPT patients not fulfilling the surgical criteria, a significant improvement in HRQoL was reported: Two cohorts of patients aged 53–56(Ambrogini et al. 2007, Rao et al. 2004) reported significant changes as assessed by the SF-36. The largest study of 191 patients by Bollerslev et al. (Bollerslev et al. 2007) demonstrated reduced preoperative HRQoL, but failed to find a significant increase in HRQoL after parathyroidectomy. However, there were some patients who did not accept the result of randomization and changed group from the surgery to the follow-up group. A recent meta-analysis
(Cheng et al. 2015) concluded that HRQoL might improve in patients with asymptomatic PHPT after parathyroidectomy. Some (Weber et al. 2013, Blanchard et al. 2014) but not all (Burney et al. 1999, Blanchard et al. 2014, Caillard et al. 2007, Gopinath, Sadler & Mihai 2010, Sheldon et al. 2002) studies found a correlation between serum calcium levels and postoperative improvement of HRQoL. The Fourth International Workshop on PHPT in 2014 (Silverberg et al. 2014) concluded that PHPT is associated with reduced HRQoL but that the data from randomized controlled trials is inconsistent regarding the benefits of parathyroidectomy on neurocognitive symptoms in mild PHPT.

2.5.7 MORTALITY IN PHPT

A Danish study reported higher mortality for conservatively-treated compared to surgically-treated PHPT patients with a mortality of 37% and 31%, respectively, in a 6-year follow-up (Vestergaard, Mosekilde 2003b).

2.5.8 NORMOCALCEMIC PHPT

Before the diagnosis of normocalcemic PHPT (NPHPT) can be made, secondary hyperparathyroidism should be excluded, and calcium and PTH concentrations should be measured on several occasions (Eastell et al. 2014). Causes of secondary hyperparathyroidism include vitamin D deficiency (minimal 25OH D level > 50 nmol/l), low calcium intake related to bariatric surgery or malabsorptive conditions such as untreated celiac disease, hypercalciuria or renal failure, or drugs known to increase PTH concentration (hydrochlorothiazides, anticonvulsants, lithium, and bone resorption inhibitors (denosumab or bisphosphonates). After successful surgery for PHPT, normocalcemia with transiently elevated PTH can be seen in patients with skeletal involvement (Bilezikian et al. 2016). It has been proposed that NPHPT is an early phase preceding PHPT (Eastell et al. 2014). A recent study comparing the change in bone mineral density (BMD) after parathyroidectomy in normo- and hypercalcemic patients with PHPT also reported a significant increase in the NPHPT group (Koumakis et al. 2013).

2.6 EVALUATION

The evaluation of hypercalcemic patients starts with a carefully performed medical history and physical examination. The history must include previous neck operations and exposure to radiation, family history regarding calcium metabolism and tumors in endocrine or other organs, previous bone fractures or symptoms of renal stones, and medication. Neurocognitive and other symptoms should be evaluated. On
physical examination, attention should be paid to palpation of the neck and to assessing possible problems with the voice (Marcocci, Cetani 2011).

2.6.1 BIOCHEMISTRY

The diagnostic criteria of PHPT include hypercalcemia that has sustained for 3–6 months in combination with increased PTH concentration. Calcium can be measured in serum either as albumin-adjusted calcium or ionized calcium concentration. Second-generation PTH assays measure with two antibodies (1-84) PTH and also 7–84 fragments, but there are also third-generation assays recognizing the extreme N-terminal fragment (1-4) of PTH, the measurement of which is recommended. In some rare cases, hypercalcemia is due to PHPT, although PTH concentrations remain within normal range (Marcocci, Cetani 2011, Bilezikian et al. 2016).

In the evaluation of a patient with PHPT, serum 25-hydroxy-vitamin D, often decreased in PHPT, and renal function should be measured. In addition, the 24-hour urine calcium and creatinine levels should be investigated and the calcium/creatinine clearance ratio < 0.01 suggests FHH. Serum phosphate is often decreased in PHPT. The bone turnover marker, urinary N-telopeptide of type I collagen (U-NTX), and the bone formation markers serum alkaline phosphatase and serum procollagen type I N-propeptide (S-PINP) may be increased in patients with skeletal involvement (Marcocci, Cetani 2011, Bilezikian et al. 2016, Fraser 2009, Bringhurst, F.R., Demay M.B., Kronenberg H.M 2008). Genetic screening for CDC73, MEN1, and RET genes, for instance, is indicated in high-risk patients (Udelsman et al. 2014); these are those with PHPT occurring before the age of 45, with multigland disease, with atypical adenoma or parathyroid carcinoma, the first degree relatives of mutation carriers, and patients with at least two MEN-syndrome-associated endocrine tumors (Thakker 2016).

2.6.2 IMAGING

DXA from the lumbar spine, hip and distal third of the radius site and an X-ray of the spine or vertebrae fracture assessment (VFA) are recommended in order to evaluate the skeletal involvement of PHPT. If available, other methods such as the Trabecular Bone Score by DXA can give additional information on bone quality. If 24-hour urinary calcium exceeds 10 mmol (400 mg), further imaging with ultrasound, X-ray, or CT should be performed to assess renal involvement (Marcocci, Cetani 2011, Bilezikian et al. 2016).
2.6.3 CRITERIA FOR SURGERY

The international guidelines in PHPT for parathyroidectomy were re-evaluated and reported by the Fourth International Workshop on the Management of Asymptomatic PHPT in 2014 (Udelsman et al. 2014). According to these guidelines, surgery is recommended for all patients under 50 years of age, or when serum calcium is $\geq 0.25$ mmol/l above normal. The presence of a vertebrae fracture detected by DXA, X-ray, or VFA, or osteoporosis (T-score (Z-score in men and premenopausal women) < -2.5 SD in the lumbar spine, total hip, femoral neck, or distal third of radius in DXA) is an indication for parathyroidectomy. Renal changes requiring surgical care are creatinine clearance < 60 ml/min and presence of nephrocalcinosis or nephrolithiasis in an ultrasound, X-ray or CT. In addition, patients planning a pregnancy are guided to operation. Patients with NPHPT and osteoporosis, kidney stones, and nephrocalcinosis need parathyroidectomy, and for those not operated on, annual calcium and PTH measurements are recommended (Bilezikian et al. 2014). The surgical criteria of the Third International Workshop on the Management of Asymptomatic PHPT that were in use between 2008 and 2014 also included hypercalciuria ( $> 10$ mmol/ 24 h) (Udelsman et al. 2009b). In the Helsinki and Uusimaa Hospital District, parathyroidectomy is recommended to individuals with PHPT and one of following criteria: age < 50 years, serum ionized calcium over 1.50 mmol/l, serum ionized calcium over 1.40 mmol/l, impaired renal function, or a decrease of >30% in the glomerular filtration rate or a history of renal stones, osteoporosis, or an osteoporotic fracture, and an unquestionable PHPT with a 1–2 year history of neuropsychiatric symptoms (Välimäki, Mäkitie 2009).

2.7 PREOPERATIVE IMAGING

In PHPT, preoperative imaging should not be used as a diagnostic procedure, and should be performed only on patients scheduled for surgery (Udelsman et al. 2014). Neck ultrasound and parathyroid scintigraphy are the most commonly used preoperative imaging techniques (Udelsman et al. 2014). Preoperative imaging may identify ectopically located abnormal parathyroid glands, and will guide the surgeon in terms of the type of surgery that should be chosen (bilateral neck exploration or minimally invasive surgery) (Schildt et al. 2015). It has been estimated that 60–70% of parathyroidectomies for PHPT could be unilateral or targeted operations, but this requires an unequivocal finding from preoperative imaging. Imaging methods tend to be false negative in multiglandular disease (MGD), the rate of which has been estimated at 15% of PHPT cases (Berber et al. 2008).

2.7.1 ULTRASOUND

Ultrasound (US) is one of the most commonly used imaging methods before parathyroidectomy in PHPT. Most surgeons appreciate US as it evaluates the size of
the thyroid gland in general, and is good for identifying thyroid nodules (Schildt et al. 2015). Ultrasound is a low-cost, noninvasive method, and it does not expose the patient to ionizing radiation (Udelsman et al. 2014).

A meta-analysis by Cheung et al. (Cheung et al. 2012) of selected imaging studies published between 1997 and 2009 reported a mean preoperative US sensitivity of 76% (range 43% - 96%), and positive predictive value (PPV) of 93% in PHPT patients operated on for the first time. In a review of studies including all together 20,000 PHPT patients, the sensitivity of US for MGD was 35% (Ruda, Hollenbeak & Stack 2005). Another review for studies published between 1995 - 2003, including also reoperated patients, reported a sensitivity of 78% for US and only 5.7% for patients having multiglandular disease (Ruda, Hollenbeak & Stack 2005). Multiglandular disease and concomitant thyroid disease, such as goiter and thyroid nodules, also reduce the sensitivity of US (Medas et al. 2016). Ultrasound is of limited value in evaluating retroesophageal lesions as it can not penetrate the clavicles or sternum. The evaluation of mediastinal parathyroid glands is therefore quite limited. US is also highly performer-dependent (Schildt et al. 2015).

2.7.2 SCINTIGRAPHY

2.7.2.1 Planar single- and double-tracer $^{99m}$Technetium-scintigraphies

$^{99m}$Technetium-multiplex ion-beam imaging ($^{99m}$Tc-MIBI) was first introduced by Coakley et al. in 1989 (Coakley et al. 1989). Sestamibi is a lipophilic cation that accumulates in the mitochondria due to the transmembrane electrical potential. Normal parathyroid glands are not visible in sestamibi images. $^{99m}$Technetium-sestamibi is sequestered into mitochondria in the thyroid and parathyroid glands as well as in salivary glands and cardiac cell muscle.

**Dual-phase $^{99m}$Tc-MIBI scintigraphy**, where imaging is performed twice every few minutes as well as two hours after the injection of the tracer, is based on different washout times in the tissues taking up $^{99m}$Technetium. Maximum thyroid activity is reached within five minutes after the injection. In contrast, washout in the parathyroid tissue is delayed, which allows parathyroid imaging two hours later (Greenspan et al. 2012). A disadvantage of this protocol is false positives due to thyroid nodules, and some parathyroid tumors may show a rapid washout and give a false negative result (Jorna et al. 2007). Imaging performed with a gamma camera is 2-dimensional. Parallel, pinhole, or all-purpose collimators can be used for this imaging, and pinhole collimators are considered to be superior to parallel collimators (Klingensmith et al. 2013, Tunninen et al. 2013).

**In double-tracer scintigraphy**, a thyroid-specific isotope $^{123}$Iodine or $^{99m}$Tc-pertechnetate is used together with $^{99m}$Tc-MIBI. The thyroid images are digitally subtracted from the $^{99m}$Technetium images. This method can be performed as a dual-phase protocol, or with early/late images only. Some studies report that the late phase images do not bring any further information (Caveny et al. 2012, Chen et al.
Review of the literature

Most studies comparing planar dual-phase $^{99m}$Tc-MIBI and $^{99m}$Tc-MIBI-subtraction with iodine or pertechnetate have found the sensitivity of the double-tracer method to be superior to $^{99m}$Tc-MIBI alone (72–94% versus 62–79%) (Caveny et al. 2012, Chen et al. 1997, Hindie et al. 1998, Leslie et al. 2002). However, a study with only 11 cases with a dual-tracer scintigraphy (Jorna et al. 2007) did not report any benefit of adding $^{123}$Iodine-subtraction to $^{99m}$Tc-MIBI scanning. In 2009, the European Association of Nuclear Medicine (EANM) recommended the use of thyroid-specific isotope over $^{99m}$Technetium imaging alone for parathyroid imaging (Hindie et al. 2009), and this was also the conclusion of a recent review (Hindie et al. 2015).

Multiglandular disease. Localizing multiglandular glands is challenging both for $^{99m}$Tc-MIBI and $^{123}$Iodine/$^{99m}$Tc-MIBI scans. Ruda et al. pooled the results for sestamibi scintigraphy from 215 studies and concluded that the sensitivity for a single adenoma is 88%, for MGD 45% and for double adenomas 30% (Ruda, Hollenbeak & Stack 2005). Studied by Jorna et al. (Jorna et al. 2007), in the subgroup of multiglandular disease, $^{99m}$Tc-MIBI scintigraphy had a sensitivity of 47% and a PPV of 95%, $^{99m}$Tc-MIBI SPECT and $^{123}$Iodine/$^{99m}$Tc-MIBI had sensitivities and PPV of 44/10% and 52/92%, respectively.

2.7.2.2 $^{99m}$Technetium-single-photon emission computed tomography/computed tomography (SPECT/CT)

Comparison of planar $^{99m}$Tc-MIBI, $^{99m}$Tc-MIBI SPECT and $^{99m}$Tc-MIBI SPECT/CT. Single-photon emission computed tomography (SPECT) gives a 3-dimensional image of the lesion location, and combining CT with SPECT gives an even more detailed anatomical localization of the parathyroid tumor. Many cohort studies and large meta-analysis studies have confirmed dual-phase $^{99m}$Tc-MIBI SPECT/CT to be superior to planar $^{99m}$Tc-MIBI as well as $^{99m}$Tc-MIBI SPECT scans (Ciappuccini et al. 2012, Garcia-Talavera et al. 2016, Wei et al. 2015). According to the meta-analysis by Wei et al., the sensitivities of $^{99m}$Tc-MIBI SPECT/CT, SPECT, and planar scans were 84, 66, and 63%, respectively, and they had a PPV of 95, 82, and 90%, respectively. According to a recent review (Kunstman et al. 2013), $^{99m}$Tc-MIBI SPECT/CT seems to be the preferred scintigraphy modality at the moment. Compared to planar imaging, dual-phase $^{99m}$Tc-MIBI-SPECT/CT is more expensive (241% of the costs of planar imaging) (Lee et al. 2016) and exposes the patient to more radiation. The radiation doses of a planar $^{99m}$Tc-MIBI scan and $^{99m}$Tc-MIBI SPECT/CT are 3.33 and 7.8 mSv, respectively, while annual natural background radiation is 2.2 mSv (Minisola et al. 2016). Although SPECT/CT locates small adenomas and difficulty located adenomas better than a planar scan, its superiority before routine primary parathyroidectomies is not obvious regarding availability, operation time, and total cost (Hindie et al. 2015, Lee et al. 2016).

Comparison of SPECT/CT to other scintigraphy modalities. SPECT and SPECT/CT can also be combined with thyroid-specific isotopes. Dual-isotope $^{123}$Iodine/$^{99m}$Tc-MIBI SPECT/CT has been found to be more sensitive and specific than planar $^{123}$Iodine/$^{99m}$Tc-MIBI, with a sensitivity of 86 and 75%, and a high
specificity of 100 and 90%, respectively (Hassler et al. 2014). In a study of 360 patients, planar $^{123}$Iodine/$^{99m}$Tc-MIBI had a sensitivity of 86% and an accuracy of 81%, and $^{99m}$Tc-SPECT or $^{99m}$Tc-SPECT/CT did not increase these. In cases where studies were discordant, planar $^{123}$Iodine/$^{99m}$Tc-MIBI performed better (Lee et al. 2016). A Finnish study comparing five different scintigraphy protocols in 24 patients concluded that any dual-tracer protocol with $^{123}$Iodine and $^{99m}$Tc-MIBI is superior to $^{99m}$Tc-MIBI alone (Tunninen et al. 2013). The routine inclusion of SPECT or SPECT/CT before the primary surgery of PHPT added minimal clinical benefit only, but it did increase costs and radiation exposure to the patient (Lee et al. 2016, Minisola et al. 2016). All studies assess the capability of each method to find the correct side on which the abnormal gland resides. This point of view does not, however, take into account the depth assessment of the abnormal gland, which is the strength of SPECT and SPECT/CT (Lee et al. 2016).

Factors contributing to scintigraphy sensitivity. Higher serum calcium, PTH levels and larger tumor size correlate with higher sensitivity in scintigraphy. There is a risk with MGD of negative imaging results (Berber et al. 2008, Ciappuccini et al. 2012). In patients with negative scintigraphy, the parathyroid tumors were predominantly chief cells, whereas those with a positive scan consisted more often of oncocytic cells, known to have more mitochondria (Carlson 2010, Mihai et al. 2006). According to many studies, patients with negative imaging results have higher rates of operative failure. Allendorf et al. reported a cure rate of 92% for those with negative and 99% for those with positive imaging (Allendorf et al. 2003). A Scandinavian multicenter study reported a surgical failure rate of 17% in patients with negative ultrasound and scintigraphy. They had smaller pathological glands and a higher rate of MDG (22%) (Bergenfelz et al. 2011).

2.7.3 OTHER IMAGING MODALITIES

The methods described below are considered second-line imaging modalities and are mostly used in reoperative settings. Localization studies are particularly important before reoperation because of persistent or recurrent HPT, and two concordant imaging studies are recommended before reoperation (Hindie et al. 2009, Hindie et al. 2015). These are scintigraphy and ultrasound, and if the results are not concordant, one of the methods described below is used (Bergenfelz et al. 2009). Patients referred for primary surgery of PHPT who have undergone a non-parathyroid related neck operation (usually due to thyroid carcinoma or goiter) are often considered as reoperations (Traub-Weidinger et al. 2014).

2.7.3.1 Positron Emission Tomography/Computed Tomography

Positron Emission Tomography (PET) imaging has better spatial and time-related resolution compared to SPECT, but the performance of PET depends on the tracer, which should be specifically taken up by the investigated organ (Kluijfhout et al.
2016a). The first tracer used in parathyroid PET imaging was $^{18}$fluoro-d-glucose (18F-FDG) (Neumann et al. 1993) but it was replaced by $^{11}$C-methionine, which has a better sensitivity. In a meta-analysis of 24 studies on $^{11}$C-methionine-PET/CT in PHPT patients, the sensitivity for the detection of a lesion in the correct quadrant had a pooled estimate of 77% (range 44–91%). However, this meta-analysis included only three studies with scintigraphy-negative patients, and two studies of reoperated patients with sensitivities of 54 and 84% (Kluijfhout et al. 2016a). In a study of 15 patients with previous neck surgery and negative $^{99m}$Tc-SPECT/CT, $^{11}$C-methionine-PET/CT was positive in only six (40%) patients. Five of them were reoperated, and in all these cases the surgery confirmed the results of $^{11}$C-methionine-PET/CT to be true positives (Traub-Weidinger et al. 2014).

### 2.7.3.2 Selective venous sampling

This method was introduced for the first time in 1969 for the localization of parathyroid tumors (Reitz et al. 1969). Selective venous sampling (SVS) has been regarded as a gold standard for difficult cases, and is used when noninvasive localization imaging remains negative (Bergenfelz et al. 2009, Udelsman et al. 2003). In SVS, blood sampling is performed from cervical veins after access through the femoral vein. Samples for PTH analyses are drawn from different locations in the superior, mid-cervical, and inferior parts of the right and left internal jugular veins, the right and left brachiocephalic veins, and the superior cava vein. A positive finding in SVS is a twofold increase in PTH in one sample, with an elevated but decreasing concentration in an adjacent sample in the direction of blood flow (Hessman et al. 2008). In the reoperative setting, the sensitivity of SVS has varied from 75 to 100% (Udelsman et al. 2003, Hessman et al. 2008, Jones et al. 2002, Ogilvie et al. 2006) with 12% false positives (Jones et al. 2002).

### 2.7.3.3 Computed tomography and magnetic resonance imaging

Computed tomography, performed as four-dimensional computed tomography (4D-CT) in recent studies, and magnetic resonance imaging (MRI) are second-line modalities used especially in cases of ectopic parathyroid glands (Hindie et al. 2015). The sensitivity and PPV of 4D-CT, $^{99m}$Tc-SPECT/CT, and US in PHPT for a single gland disease were 96, 65, and 58%, respectively (Kukar et al. 2015). In MGD, 4D-CT had sensitivity varying between 14 and 32% (Kukar et al. 2015, Madorin et al. 2013). The benefit of 4D-CT is the shorter duration compared to scintigraphies. In patients with inconclusive or negative $^{99m}$Tc-SPECT and US, the sensitivity and PPV of 4D-CT were 72 and 75%, respectively (Cheung et al. 2012). In a study of 223 patients, including 34 reoperation patients, a conventional, contrast-enhanced neck CT had a sensitivity of 60% and a specificity of 81% (Zald et al. 2008). This method (or MRI) is recommended to confirm thoracic glands found by scintigraphy (Hindie et al. 2015).
MRI does not expose the patient to radiation. The sensitivity has varied between 64 and 82% at 3 Tesla (T) and 1.5 T magnets, respectively, before primary operation, but it can give additional information in most patients (57%) when US and scintigraphy remain negative (Lopez Hanninen et al. 2000, Grayev et al. 2012).

2.8 SURGERY

2.8.1 SURGICAL APPROACHES

2.8.1.1 Bilateral neck exploration

Bilateral neck exploration (BNE) has been the gold standard in parathyroidectomy, but improvements in preoperative imaging and the possibility of intraoperative PTH monitoring have increased the use of minimal invasive approaches (Bilezikian et al. 2016, Udelsman et al. 2014). In bilateral neck exploration (BNE), all four parathyroid glands are examined under general anesthesia. BNE is recommended for patients with a suspicion of multigland disease (10–15% of PHPT cases), especially those with familial PHPT, with previous use of lithium, and for all with discordant or negative imaging. In the hands of an experienced parathyroid surgeon, the cure rate following PHPT is up to 98% by BNE and the complication rate is low (Udelsman et al. 2014).

Surgery is the only possible cure for PHPT. The indications for surgery have been described above. A successful operation is followed by a rapid decline of serum calcium to normal level and a >50% decline in serum PTH concentration on the first postoperative day. In 10% of patients, calcium decreases slowly and reaches the upper limit of normal within two weeks following the operation. However, this does not predict a recurrence (Lai et al. 2016).

2.8.1.2 Minimal invasive procedure

Minimal invasive parathyroidectomies (MIP) have gained acceptance during the last two decades. A focused parathyroidectomy is possible when two preoperative localization studies are positive and concordant. In MIP, only the abnormal parathyroid gland and sometimes the ipsilateral gland are visualized. These operations can employ an endoscopic or lateral approach, which leads to a better cosmetic result. In some centers they can be performed under local or regional anesthesia, and in some high-volume centers, patients can be discharged the same day (Kunstman et al. 2013, Rajeev et al. 2013). Focused parathyroidectomy decreases the risk of laryngeal nerve injury, the devascularization of normal parathyroid glands and thus the risk for postoperative hypocalcemia. It also decreases the length of hospital stay and of operation, and, despite obligatory imaging studies, the total costs (Udelsman et al. 2014).
2.8.1.3 Other techniques for parathyroidectomy

Thoracoscopic and mediastinal approaches are rarely needed to resect ectopic mediastinal parathyroid tumors. Efficient localization diagnosis has reduced the need for sternotomies, as most mediastinal ectopic glands can be resected using a cervical approach (Udelsman et al. 2014). In a study of PHPT patients reoperated between 1987–1997 and 1998–2008, 35% and 14% underwent sternotomy, respectively (Karakas et al. 2013). In another study, sternotomy was used in 10% of reoperations (Hessman et al. 2008).

2.8.1.4 Comparison of bilateral exploration and focused parathyroidectomy

According to a retrospective two-center study over the last 23 years (Norlen et al. 2015), 2000 focused and 2500 bilateral primary operations in sporadic PHPT led to persistent disease in 2.7% vs 1.7% of patients, and to long-term recurrence in 0.6% vs 0.4%, respectively. In these focused operations, the ipsilateral gland was revealed or the intraoperative PTH measurement (ioPTH) was used only in some patients. These results are concordant with other studies (Thier et al. 2016, Udelsman, Lin & Donovan 2011, Bergenfelz et al. 2002), and the Swedish prospective study reported a recurrence rate of only 1.1% after MIP at a 15-year follow-up (Thier et al. 2016). Norman et al. criticized MIP for a failure rate of 3–5% and 4–6% in their material at one-year and ten-year follow-up, and returned to do a BNE for 99.5% of the circa 1000 parathyroidectomy patients operated on every year (Norman, Lopez & Politz 2012). Complication rates in BNE and focused parathyroidectomies has varied between 3.1–7.3% and 1.5–3.6%, respectively (Norlen et al. 2015, Udelsman, Lin & Donovan 2011). In a prospective study of nearly 1600 primary operations with sporadic PHPT, MIPs were performed on patients with concordant preoperative localization studies. These operations were converted to BNEs despite an enlarged parathyroid gland being removed and appropriately decreased IoPTH. This revealed an additional pathological parathyroid gland in 15% of cases, but the prevalence of MGD and double adenomas in the study group were 16% and 16%, respectively (Siperstein et al. 2008). The cost of BNE with an intraoperative frozen section but without preoperative imaging equals the cost of MIP with preoperative sestamibi scintigraphy and ioPTH measurement (Bergenfelz et al. 2002). There is still no consensus on the best strategy for choosing the surgical technique in parathyroidectomy for PHPT (Udelsman et al. 2014).

2.8.1.5 Parathyroidectomy for hereditary patients

Parathyroidectomy in patients with some of the hereditary syndromes (MEN1, MEN4 and HPT-JT) is more challenging, because these patients more often have hyperplasia of all four glands. In a Dutch cohort of 73 MEN1 patients, the proportion of recurrent PHPT was 53% in parathyroidectomies of 1–2 glands, 17% in subtotal parathyroidectomy and 10% in those with additional autotransplantation of
parathyroid tissue in a forearm muscle. This study implies that some MEN1 mutations may have a higher recurrence rate (Pieterman et al. 2012). The most commonly recommended technique for the primary operation is subtotal parathyroidectomy removing 3.5 glands (Iacobone et al. 2015). The advantage of autotransplantation of the 0.5 glands is the elimination of recurrent operations to the neck (Udelsman et al. 2014, Stalberg, Carling 2009). In MEN1 there is also a 15% risk of having parathyroid tissue in the thymus. In contrast, MEN2 and MEN3 patients are less likely to develop recurrence, and MIP is recommended. Patients with familial HPT-JT syndrome are at risk of parathyroid carcinoma and recurrent PHPT, but the autotransplantation of 0.5 gland can cause the dissemination of possible cancer cells. In HPT-JT, an operation strategy similar to sporadic PHPT is recommended, combined with a lifelong serum calcium follow-up (Iacobone et al. 2015).

2.8.1.6 Reoperations in PHPT

Patients referred for reoperation consist mostly of those with persistent PHPT after primary surgery. This occurs when the parathyroid adenoma cannot be located or when inadequate resection is performed in patients with multigland disease. Reoperation can be necessary for parathyreomatosis when residual hyperfunctioning parathyroid tissue is left due to tumor rupture. Patients with non-parathyroid-related neck operations, such as thyroidectomy, should also be managed as patients scheduled for reoperation of PHPT when planning preoperative imaging and assessing surgery complications (Udelsman 2011). The critical re-evaluation of the diagnosis and the need for the reoperation are also important before proceeding to preoperative imaging for a new operation (Udelsman 2011).

In a study of reoperations performed between 1982 and 1995 (Jaskowiak et al. 1996), 77% were due to an undetected single adenoma compared to 22% of a more recent study in a tertiary center (Karakas et al. 2013). In 144 reoperations (Hessman et al. 2008) reported, similarly to others (Jaskowiak et al. 1996), the vast majority of enlarged glands were located in normal positions in the parathyroid glands, but concealed by the irregularities of the thyroid or behind it (Figure 5). On average 10% of glands were intrathyroidal, another 10% were para- or retroesophageal, and nearly 10% in the thoracic thymus. Since 1990, sternotomies have been used in reoperations in 10% of patients (Hessman et al. 2008).
Patients who have a planned reoperation are at high risk of postoperative hypocalcemia (up to 20%) and recurrent laryngeal nerve palsy (up to 15%) (Karakas et al. 2013). After primary surgery, scarring is intensive and leads to difficulties in distinguishing the laryngeal nerve, as well as abnormal and normal parathyroid glands. The type of surgery in reoperations between 1998 and 2008 was more often a focused parathyroidectomy than between 1987 and 1997 (23% vs 57%, respectively). Although the proportion of sternotomies has decreased, the cure rate of reoperations is similar to primary operations. When comparing the earlier and the later decades, the rate of laryngeal nerve palsies did not change (9% vs 9%), while the rate of hypocalcemia decreased (9% vs 6%) (Karakas et al. 2013).

### 2.8.2 INTRAOPERATIVE METHODS

Intraoperative PTH measurement (ioPTH) helps the surgeon to evaluate whether all the abnormal parathyroid glands have been removed or not. PTH has a mean circulating half-life of 3.5–4 minutes in patients with normal renal function and therefore the change in PTH concentration can be noticed intraoperatively. Serum PTH is measured before initiation of the operation. The criteria for sufficient PTH decline at 10 minutes after the resection is, first, a fall of ≥50% in PTH concentration during the operation and, secondly, a decline to the normal range of PTH (Yen et al. 2008). Patient characteristics do not affect the half-life of PTH (Leiker et al. 2013). The European Society of Endocrine Surgeons (ESES) allows unilateral primary
operations despite discordant imaging studies if ioPTH is used and requires ioPTH measurement for all reoperations (Bergenfelz et al. 2009). Karakas et al. showed an increased in the cure rate of reoperations (from 91% to 98% in a decade) after the introduction of SPECT/CT and ioPTH (Karakas et al. 2013). Some studies (Siperstein et al. 2008) have shown that a sufficient fall in the intraoperative PTH level does not exclude the possibility of pathological glands remaining in situ. However, the latest guidelines (Udelsman et al. 2014) require measuring IoPTH during mini-invasive procedures as a confirmation of successful operation.

In radio-guided parathyroidectomy, the identification of the hyperplastic parathyroid gland is performed by assessing the uptake of $^{99m}$Tc-sestamibi given intravenously one hour prior to the operation. The gamma probe is handheld and is able to search for the pathological gland both through the skin and from the skin incision. The radioactivity of the adenoma must be over 20% of that of the background (You, Zapas 2007). Thyroid nodules can be false positives. The use of a gamma probe led to a cure rate of 96% in the reoperations (Pitt et al. 2009) and it can be used in a reoperative setting (Bergenfelz et al. 2009, Udelsman et al. 2014). Intraoperative monitoring of the recurrent laryngeal nerve requires an endotracheal tube and can be performed on patients under general anesthesia. In 75 parathyroidectomies including 10 reoperations, the incidences of transient and permanent laryngeal nerve palsy were 3.8% and 1.3%, respectively. In this material, the nerve monitoring had a PPV of 97.4% and a negative predictive value (NPV) of 50.0% (Eid et al. 2013). The recent international workshop on PHPT does not recommend this monitoring as a routine method in all parathyroidectomies (Udelsman et al. 2014). A frozen section is recommended when the surgeon is in doubt as to whether a nodule is parathyroid tissue (Bergenfelz et al. 2009).

2.8.3 SURGICAL COMPLICATIONS

Mortality in parathyroid surgery is near to 0%, but can be as high as 10% in elderly patients with other comorbidities (Morris et al. 2010).

Postoperative hypocalcemia results from local trauma or devascularization of the parathyroid glands during operation of the thyroid bed. In addition, a slow PTH-secreting response of the remaining glands due to long-term suppression of the removed hyperfunctioning gland exposes the patient to hypocalcemia. Within 12 to 48 hours after surgery, hypocalcemia becomes symptomatic, including perioral hyperesthesia and tingling in the extremities, as well as Chvostek and Trousseau signs. Hypocalcemia is mostly mild and temporary, but can be severe and prolonged (Witteveen et al. 2013). It is related to postoperative, often temporarily suppressed PTH secretion after the removal of a parathyroid adenoma or to hungry bone syndrome (HBS), related to high bone turnover with suppressed PTH concentrations. Risk factors for hypocalcemia are bilateral exploration, female sex, vitamin D deficiency, pregnancy, lactation, autoimmune thyroid disease, and prior gastric bypass surgery (Stack et al. 2015). The incidence of symptomatic hypocalcemia is
lower after MIP compared to BNE, in which the risk of all parathyroids to be disrupted during their visualization is higher (Bergenfelz et al. 2002).

HBS is seen in 25–90% of those with radiological findings of PHPT but only in 5% without the skeletal involvement of PHPT. It is possible that preoperative bisphosphonate treatment decreases the incidence of HBS. The postoperative biochemical findings are hypocalcemia, hypophosphatemia, and low PTH concentration together with increased serum alkaline phosphatase. Serum magnesium can be decreased. Most studies report that PTH, serum calcium and alkaline phosphatase concentrations are markedly higher preoperatively in those with subsequent HBS than in those without HBS. Depletion of vitamin D and older age seem to be risk factors for HBS (Witteveen et al. 2013).

Postoperative calcium supplementation (at a minimum 1000 mg of calcium carbonate daily) is used to minimize the risk of hypocalcemia (Udelsman et al. 2014). Hypocalcemia also often needs cholecalciferol, which enhances the intestinal absorption of calcium and liberates calcium from bones. Hypomagnesemia must also be treated as it causes PTH resistance. Acute postoperative hypocalcemia can require intravenous calcium infusions (Stack et al. 2015). A recent pilot study of 16 patients reports that short treatment with teriparatide is a safe and efficient option in treating difficult postoperative hypocalcemia (Shah et al. 2015).

### 2.9 NATURAL HISTORY, SURVEILLANCE AND MEDICAL THERAPY

In a 15-year follow-up study of 57 PHPT patients without parathyroidectomy, 37% showed disease progression fulfilling one or more criteria for parathyroidectomy. The calcium concentration of the 59 successfully operated PHPT patients stayed stable during follow-up, but their bone mineral density in the lumbar spine and femoral neck increased at 5 and 10 years from 6 to 12%, and from 7 to 10%, respectively (Rubin et al. 2008b). Other studies have reported a disease progression in 20% and 15% of unoperated PHPT patients at 7- and 5-year follow-ups, respectively (Jung et al. 2016, Yu et al. 2011).

Unoperated patients or those not fulfilling the surgical criteria need an annual follow-up with serum calcium and estimated GFR measurements (Bilezikian et al. 2014). The frequency of DXA follow-up is evaluated on an individual basis. If the patient has possible symptoms of renal stones, renal imaging (X-ray, ultrasound) and a 24-hour urine calcium and biochemical stone profile is recommended (Bilezikian et al. 2014).

All patients followed without surgery should be repleted cautiously with vitamin D to increase the serum 25(OH)D$_3$ level between 50 and 75 nmol/l (Bilezikian et al. 2016, Marcocci et al. 2014). The starting dose recommendation is 600–1000 IU of cholecalciferol daily. In an intervention study by Rolighed et al., even a daily dose (2800 IU) was safe to use. This supplementation decreases PTH levels and bone resorption without effects on serum or urinary calcium levels (Rolighed et al. 2014b). Calcium intake should follow the guidelines for healthy individuals; calcium
intake must not be limited in PHPT (Bilezikian et al. 2014). Adequate fluid intake and avoidance of dehydration is recommended for all PHPT patients (Bilezikian et al. 2016).

Some patients refuse or are unable to undergo surgery because of comorbidities. For some patients even the reoperation remains unsuccessful. Of the pharmacological options to treat PHPT, bisphosphonates improve BMD without having an effect on serum calcium, and cinacalcet reduces serum and urinary calcium but it does not affect BMD. Alendronate is the bisphosphonate that has been most studied in the medical management of PHPT. Over the course of a two-year alendronate treatment program, BMD increases 7% in the lumbar spine with no changes in serum calcium, while bone turnover markers decrease by 66% at three months (Khan et al. 2004).

Cinacalcet, a calcimimetic, improves the sensitivity of the CaSR for calcium and thus decreases serum PTH concentrations. Two prospective and randomized studies (Peacock et al. 2009, Saponaro et al. 2013) have consistent findings: During cinacalcet therapy (30 to 180 mg), serum calcium normalized in 80–90% of patients, and serum PTH decreased by 7% with no changes in BMD. Artralgia, myalgia and nausea are the most common side effects. In a study of 73 patients with mild or moderate PHPT and a mean serum calcium of 2.67 mmol/l, 73% achieved normocalcemia but three patients got hypocalcemia with the lowest dosage of cinacalcet. In 17 PHPT patients with a mean serum calcium of 3.2 mmol/l, the 140-week cinacalcet treatment (mean dosage 70 mg twice a day) improved their health-related quality of life (Marcocci et al. 2009). A quarter of patients interrupted the treatment due to side effects. Although there was no control group in the study, it suggests that cinacalcet treatment might improve the well-being and functional status of PHPT patients. The European Medicine Agency (EMA) has approved the use of cinacalcet in specific indications in patients with PHPT. This means patients in whom parathyroidectomy is indicated, but surgery is not appropriate or contraindicated. The Fourth International Workshop, held in 2014, accepted this recommendation (Marcocci et al. 2014).

Denosumab has been used for the treatment of hypercalcemia in occasional, inoperable parathyroid carcinoma patients, but no case control studies or larger reports from patients with PHPT are yet available.

2.10 CLINICAL PRESENTATION AND MANAGEMENT OF PARATHYROID CARCINOMA

2.10.1 EPIDEMIOLOGY AND MOLECULAR PATHOGENESIS

Parathyroid carcinoma (PC) causes 1–3% of PHPT. The incidence of this disease is 0.4 to 0.6 per million and it seems to be increasing, according to two studies (Brown et al. 2011, Lee et al. 2007) that report an increase of 60% since the 1980s in the United States and a fivefold increase in recent decades in Australia.
PC is most commonly a sporadic disease. It can occur in patients with CDC73 mutation as part of HPT-JT syndrome, but very rarely in MEN1 families. Neck radiation is not considered a marked risk factor for PC (Cetani, Pardi & Marcocci 2016), but, according to a Swedish population-based study, patients with previous thyroid cancer or parathyroid adenoma are at increased risk for PC (Fallah et al. 2011). The tumor suppressor gene CDC73 (described in section 3.1.1) has an important role in the molecular pathogenesis of PC. Germline mutation of CDC73 is found in up to one-third of PCs (Cetani, Pardi & Marcocci 2016), and somatic inactivating CDC73 mutations are present in 15–70% of patients with sporadic parathyroid carcinoma (Cetani et al. 2007, Haven et al. 2007, Shattuck et al. 2003). Interestingly, no CDC73 mutations were found in 70 sporadic parathyroid adenomas (Shattuck et al. 2003, Krebs, Shattuck & Arnold 2005). In contrast, an allelic loss at 11q chromosome, a common alteration in benign parathyroid adenomas, is not found in PCs (Costa-Guda, Arnold 2014). These findings indicate that PC increases de novo and parathyroid adenoma is not a pre-existing lesion for PC. As described earlier (section 4.5), parafibromin, the product of the CDC73 gene, is used in pathological assessment as a tool in the differential diagnosis between parathyroid adenoma and carcinoma.

In addition, other gene mutations in retinoblastoma, tumor protein p53 and PRAD1, for instance, have been linked to PC (Cetani, Pardi & Marcocci 2016). A recent study on whole exome sequencing in PC reports a new mutation, prune homolog 2 [Drosophila] (PRUNE2), in 18% of PCs (Yu et al. 2015).

### 2.10.2 CLINICAL PRESENTATION

The signs and symptoms of PC result from excessive PTH secretion and hypercalcemia rather than from tumor mass. The suspicion of PC should be raised when serum Ca levels exceed 3.0 mmol/l, tumor size is over 3 cm, or the patient has a family history of PHPT (Schulte et al. 2012).

Compared to benign PHPT, most, but not all, PC patients have more severe hypercalcemia and more often renal (nephrocalcinosis, renal stones, impaired renal function) or skeletal manifestations (osteitis fibrosa cystica, salt and pepper skull, osteoporosis or fragility fractures) of this disease, especially a combination of these (Talat, Schulte 2010, Wei, Harari 2012). Of note, there is no gender preference in PC, whereas there is a female predominance in benign PHPT (3 : 1). PC patients are younger than those with benign PHPT. Rare, non-functioning PCs with normocalcemia have been described. A palpable cervical mass can be a sign of PC. Laboratory tests cannot differentiate between malign and benign PHPT (Harari et al. 2011, Villar-del-Moral et al. 2014, Marcocci et al. 2008). Two small studies of eight and 10 PC patients suggest that urinary human chorionic gonadotropin (U-hCG) can be elevated in PC but remain normal in adenomas (Gupta, Mittal & Sathian 2013, Rubin et al. 2008a).

Ultrasound, scintigraphy and MRI are the most commonly used preoperative imaging modalities when PC is suspected. The use of 18F-fluorodeoxyglucose
(FDG)-PET/CT was reported in a small series and was shown to be helpful when conventional imaging modalities were negative, but it can have false-positive findings in areas of inflammation (Evangelista et al. 2011).

2.10.3 SURGICAL MANAGEMENT

Surgery is the only possible cure for PC. When PC is suspected, an *en bloc* resection, including the removal of the ipsilateral thyroid gland and/or adjacent structures and lymph nodes, is performed (Cetani, Pardi & Marcocci 2016, Schulte et al. 2012, Schulte et al. 2010). This larger resection with good margins enables better pathological evaluation of invasion that is crucial in differential diagnosis. All patients with suspected PC should be referred to an experienced surgeon: This has been noted to affect the survival (Cetani, Pardi & Marcocci 2016, Harari et al. 2011).

2.10.4 ADJUVANT TREATMENTS AND MEDICAL TREATMENT OF HYPERCALCEMIA

There are no reports suggesting that chemotherapy would be beneficial in PC (Cetani, Pardi & Marcocci 2016, Wynne et al. 1992). Cohort studies suggest (Munson et al. 2003, Busaidy et al. 2004) that external-beam radiotherapy might be used in high-risk patients, which include those with positive surgical margins, intraoperative tumor rupture, and vascular invasion. There are no randomized studies that are possible to perform related to this rare disease. The recent reviews support the assessment of radiotherapy on an individual basis (Cetani, Pardi & Marcocci 2016, Wei, Harari 2012, Schulte, Talat 2012). Doses of 40-70 Gray after surgical resection have been used.

In 2004, Betea and Bradwell et al. introduced an experimental therapy for PC, i.e. induction of anti-PTH antibodies by immunization with PTH fragments. This palliative therapy led to tumor shrinkage or stopped the tumor growth. This therapy needs further studying (Betea et al. 2004).

If parathyroid carcinoma is inoperable or there are metastases and hypercalcemia proceeds, medical therapy is warranted. Debulking of metastasis, if possible, can reduce serum calcium levels. Rehydration and furosemide can be used in mild hypercalcemia. Zoledronic acid and cinacalcet are used in more severe hypercalcemia (Cetani, Pardi & Marcocci 2016, Silverberg et al. 2007). Cinacalcet is used to reduce serum calcium in PC. Denosumab, a monoclonal antibody against RANK ligand, has been shown to lower serum calcium levels in PC (Vellanki et al. 2014, Nadarasa et al. 2014). However, these situations have required higher dosages than in conventional use, and the safety of this treatment is uncertain (Tong, Hussein 2016).
2.10.5 PROGNOSIS AND SURVIVAL

The recurrence rate in PC is between 40 and 60% according to most reports (Harari et al. 2011, Talat, Schulte 2010, Sadler et al. 2014), but only 23% according to a recent Spanish cohort (Villar-del-Moral et al. 2014). Most recurrences occur within 2–3 years, and are local (Cetani, Pardi & Marcocci 2016). Lymph node metastasis can occur. The lungs and bone are the most common sites for distant metastasis. PC patients experience recurrences and 60% of them suffer complications due to reoperations to the neck (Harari et al. 2011).

Reported data suggests that there is an overall survival rate at 10 years in the range of 49–77% (Harari et al. 2011, Lee et al. 2007, Busaidy et al. 2004, Hundahl et al. 1999, Sandelin et al. 1992), but 19% at a 55-month follow-up in the Spanish cohort (Villar-del-Moral et al. 2014).
3 AIMS OF THE STUDY

The specific aims of this present study were:

1) To assess the accuracies and surgical benefits of $^{123}\text{I}$/$^{99m}\text{Tc}$-MIBI dual-phase scintigraphy compared to dual-phase $^{99m}\text{Tc}$-MIBI scintigraphy before primary operation of PHPT.

2) To compare the planar dual-phase $^{123}\text{I}$/$^{99m}\text{Tc}$-MIBI scintigraphy, $^{99m}\text{Tc}$-MIBI-SPECT/CT, selective venous sampling (SVS) and $^{11}\text{C}$-methionine PET/CT in localizing parathyroid tumors before reoperation of PHPT.

3) To compare health-related quality of life in PHPT patients to that of an age- and gender-adjusted sample from the general population, and to evaluate the possible effect of surgery on HRQoL in PHPT.

4) To investigate whether the incidence of parathyroid carcinoma in Finland changed between 1955 and 2013.

5) To collect data on all the parathyroid carcinoma patients diagnosed in Finland between 2000 and 2011, and to improve the understanding of the disease by comparing clinical and histological characteristics of parathyroid carcinoma, atypical parathyroid adenoma, and parathyroid adenoma.
4 PATIENTS AND METHODS

4.1 PATIENTS AND DATA COLLECTION

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Table 1. Summary of the thesis study patients.

Study I. Patient data was retrospectively collected from 543 consecutive patients referred for parathyroid scintigraphy between November 2006 and November 2009 at Helsinki University Hospital Medical Imaging Center, in the Department of Clinical Physiology and Nuclear Medicine. The final study cohort consisted of 269 PHPT patients who underwent the primary operation for PHPT in the hospitals of the Hospital District of Helsinki and Uusimaa (HUS). Clinical, laboratory and imaging data was collected retrospectively from medical records.

Study II included 21 patients with persistent PHPT referred to Helsinki University Hospital for reoperation. The patients were prospectively investigated with $^{123}$I/ $^{99m}$Tc-MIBI scintigraphy, $^{99m}$Tc SPECT/CT (n = 19), $^{11}$C-methionine-PET/CT, and SVS (n = 18) before surgery, and were reoperated on between November 2009 and February 2012. None of the patients had been diagnosed for a familial form of PHPT. Seven patients had no pathological glands removed in the previous operation(s). Fourteen of the 21 study patients had a persistent PHPT and at least one pathological parathyroid gland previously removed, so they had a multiglandular PHPT. These previous operation(s) revealed 1–2 hyperplastic gland(s) in eight patients, an adenoma in five patients and an atypical adenoma in one patient.
Study III comprised 124 PHPT patients operated on for the disease at the Department of Surgery at Helsinki University Hospital between October 2010 and May 2013. All patients who completed the 15D questionnaire preoperatively were included. Demographic, biochemical, and clinical data as well as surgery results were collected from the patient register of the hospital. The HRQoL of the study patients, as assessed by the 15D instrument, were compared to that of an age- and gender-standardized sample of the Finnish general population from the Finnish Health 2011 survey (n = 4924) (201). Fifty-one of the 124 patients (41.4%) suffered from possible PHPT-related symptoms such as fatigue, depression, loss of memory, abdominal pain or nausea, muscle weakness, or joint pain. The surgical criteria for PHPT according to the Third International Workshop on the Management of Asymptomatic PHPT in 2008 (Udelsman et al. 2009b) were met by 80.6% of patients: 48.3% had osteoporosis, 13.7% had impaired kidney function, 29.0% had serum ionized calcium over 1.50 mmol/l, 9.7% were under 50 years of age, and 7.3% had kidney stones.

Study IV included 39 patients diagnosed with parathyroid carcinoma in Finland between 2000 and 2011. The PC patients were identified from the Finnish Cancer Registry, from the database of the Department of Pathology (Huslab and University of Helsinki, Finland), from the hospital databases of the Finnish university hospitals, and from eight Finnish central hospitals using the International Classification of Diseases 10 (ICD-10) code (C75.0). The PCs confirmed to have unequivocal invasion or metastasis according to the 2004 WHO classification (Grimelius et al. 2004). In three patients, PC could not be confirmed and were excluded from the study. Four other patients’ PCs were reclassified as APAs. The final PC group consisted of 32 patients. All the 28 APA patients retrieved from the Helsinki pathology database and that were diagnosed between 2000 and 2011 were included. The 72 parathyroid adenoma patients (A) also retrieved from the Helsinki pathology database were matched for age and gender with regard to the PC group.

Clinical, biochemical, and surgical data as well as data were monitored until death or until the end of follow-up (August 30th, 2015). The survival data and cause of death of the study patients were obtained from Statistics Finland. The nationwide number of PC cases from 1955 to 2013 was retrieved from the Finnish Cancer Registry.

4.2 LABORATORY MEASUREMENTS

Data on available laboratory measurements from medical records was collected from the time of diagnosis until the end of follow-up. All laboratory tests were performed at Huslab (and in Study IV at the central laboratories of each hospital taking part in the study) using in-house methods and standard accredited assays.
4.3 IMAGING TECHNIQUES AND EVALUATION OF THE LOCALIZATION STUDIES

All imaging studies except the PET/CT of Study II and those of Study IV evaluated outside the Hospital District of Helsinki and Uusimaa were performed at Helsinki University Hospital Medical Imaging Center, in the Department of Clinical Physiology and Nuclear Medicine. The imaging studies of patients treated in other hospital districts were performed in those hospitals. All PET/CTs were performed at Turku PET center.

4.3.1 IMAGING TECHNIQUES

The planar and SPECT/CT scintigraphies were performed according to the 2009 guidelines of the European Association of Nuclear Medicine (Studies I, II, IV) (Hindie et al. 2009). A $^{123}$I-capsule of 13-15 MBq was administered three hours before imaging. Immediately after the planar $^{123}$I-imaging, 790-940 MBq of $^{99m}$Tc-MIBI was injected intravenously and an early planar acquisition started after five minutes. An all-purpose collimator was used for planar imaging. $^{123}$I-images were subtracted from $^{99m}$Tc-MIBI images. Dual-phase $^{99m}$Tc-MIBI planar scintigraphy (Studies I and IV) comprises early and late planar $^{99m}$Tc-MIBI images. The $^{99m}$Tc-MIBI images from Study I were obtained from $^{123}$I-$^{99m}$TcMIBI images.

In the $^{11}$C-methionine PET/CT (Study II), patients fasted for six hours before the study. Twenty minutes after intravenous injection of $^{11}$C-methionine (440 MBq), static PET/CT imaging in 3-dimensional mode covering the head and neck and mediastinum was started. A low-dose CT protocol was performed for attenuation correction.

SVS (Study II) was performed at Helsinki University Central Hospital by an experienced intervention radiologist. Nineteen samples were taken from each patient through the femoral vein in different veins (Jones et al. 2002), and analyzed for PTH.

Ultrasounds (Study IV) were performed by radiologists as a routine hospital procedure.

4.3.2 THE IMAGING RESULT EVALUATION

Studies I and II: The side of the abnormal gland was reported. The scintigraphy was considered accurate if the lesion(s) detected by the localization technique was removed from the same side in the operation, patients reached normocalcemia, thus no pathological glands remained in the patient, and the removed gland(s) was/were pathological (hyperplastic, adenoma, or carcinoma).

To confirm the reproducibility of results in Study I, two experienced nuclear medicine physicians re-evaluated the data blindly. The original and re-evaluation reports differed in 4.8% of cases. In Study II, all scintigraphy studies were reviewed by five investigators.
Study II: SVS: A twofold increase in PTH in one sample, with an elevated but
decreasing concentration in a second adjacent samples in the direction of venous
blood flow, was considered to be a positive result. The positive SVS findings were
categorized into six groups, corresponding to different locations.

4.4 SURGERY

Studies I–III: All operations were performed by an experienced parathyroid surgeon
at Helsinki University Hospital except one patient in Study II (no. 17) who was
operated on at Satakunta Central Hospital.

Study I: The type of surgery depended on the preoperative localization review,
but any condition indicating of the possibility of hyperplasia favored bilateral neck
exploration (BNE). In unilateral neck exploration (UNE), only the side of the
expected pathological gland was dissected. In focused parathyroidectomy or minimal
invasive parathyroidectomy (MIP), only the suspected gland was dissected.

Study II: Based on the preoperative imaging results, one patient underwent a
sternotomy in addition to neck surgery, and a thoracic surgeon participated in this
operation.

Study IV: The types of operation were classified into two groups: Local
resections (removal of the tumor following the peritumoral capsule), or en
bloc/radical resections (with at least a parathyroidectomy with the removal of the
ipsilateral thyroid lobe, adjacent structures or lymph nodes).

The criteria for surgery in the studies were those of the Third International
Workshop in use between 2008 and 2014 (see section 6.3). Normal serum ionized
calcium and a 50% decrease in serum PTH concentrations on the first postoperative
day were considered as a remission criteria for PHPT. In severe hypercalcemia, a
slower decrease to normocalcemia within one month was accepted. Recurrent PHPT
cases were confirmed as having hypercalcemia and an elevated serum PTH level. In
Study IV, recurrent PCs were confirmed as also having a pathological parathyroid
gland at reoperation.

4.5 CDC73 GENE MUTATION ANALYSIS,
HISTOLOGICAL, AND IMMUNOHISTOCHEMICAL
STUDIES

Study I: All the removed glands were analyzed by pathologists, and classified as
normal, hyperplastic, adenoma, carcinoma, or hyperplasia/adenoma tissue (if a
differential diagnosis was not possible). The diagnosis of a multiglandular disease
(MGD) was set when two or more pathological parathyroid glands were removed, or
when removal of one hyperplastic or adenoma gland did not lead to normocalcemia
and the disease continued.

Study II: All tissue and glands removed both in the previous neck operations and
in the reoperation were re-evaluated by an experienced pathologist.
PATIENTS AND METHODS

Study IV: Formalin-fixed and paraffin-embedded tissue samples of the primary operations were retrieved for all patients and re-examined. Immunohistochemical studies were performed using the Tissue Micro Array (TMA) technique. For construction of the TMA blocks, between three and six cores were sampled from representative areas of each tumor specimen and inserted into a recipient paraffin block. TMA blocks were cut into 4-µm sections and prepared for further staining. MIB-1 and parafibromin antibodies as well as PTH were incubated in appropriate solution concentrations with a distinct incubation time for each marker.

The Ki67 proliferation index by MIB-1 staining was assessed by the Immunoratio program as described by Tuominen et al. (Tuominen et al. 2010). The parafibromin staining was considered positive (2) if >95% of the nuclei of the neoplastic cells in the TMA spot were positive, and negative (0) if >99% of all these nuclei were negative (Kim et al. 2012). Counts between these cut-offs were considered as weak positives (1). PTH stains were considered negative or positive.

The CDC73 gene mutation analysis was performed for 18 PC and 16 APA, 27 of them were collected and analysis during the study, and others were analyzed at diagnosis. Genomic DNA was extracted from blood samples and next generation targeted sequencing was performed for the 17 exons of CDC73 gene. Multiplex ligation-dependent probe amplification (MPLA) analysis was performed to detect deletions and duplications of the CDC73 gene.

4.6 MEASURING HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life was assessed by the 15D. The 15D is a generic, standardized, well-validated, and self-administered questionnaire to measure HRQoL. It can be used as a profile or a single score to describe HRQoL (Sintonen 2001). Each dimension (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity) has five levels. The results of HRQoL are also reported as a distribution of the clinically important changes of 15D on the Global Assessment Scale to improve the understanding of the results (Alanne et al. 2015).

In Study III, a 15D questionnaire (Appendices 1–2) and an explanatory letter were mailed to the patients along with the surgical invitation letter. An additional questionnaire assessing education level (Appendix 3) was sent along with the first 15D. It is not possible to count the total number of questionnaires sent from three surgical units over three years. Those one hundred and twenty-four patients who returned this preoperative questionnaire received two 15D questionnaires six and 12 months after the operation.
4.7 STATISTICS

The statistical analyses were carried out using a SAS software (S+ version 8.1 for Study II, version 9.2 for study I + IV; SAS Institute Inc.). A $P$-value less than 0.05 was considered statistically significant.

Study I: McNemar and Fisher’s test exact tests were used to compare operative and imaging findings and the accuracy between $^{123}\text{I}/^{99m}\text{Tc}$-MIBI and $^{99m}\text{Tc}$-MIBI scintigraphies. The duration of the operative procedures was log-transformed before comparison according to the type of surgery with one-way analysis of variance. Tukey’s method was used for pairwise comparisons between the different types of surgery. All tests were used as two-sided tests.

Study II: Differences in laboratory measurements were assessed with the Wilcoxon signed-rank test and Student’s $t$-test. McNemar’s test was used to compare SVS, SPECT/CT, and PET/CT to $^{99m}\text{Tc}/^{123}\text{I}$ planar scintigraphy, which was used the reference method. Cohen’s $\kappa$-coefficient was calculated to quantify agreement of accuracies between the techniques.

In Study III, Student’s $t$-test was used to test the statistical significance of the differences in the continuous variables. The association between the baseline 15D score and some independent variables was evaluated with linear regression. Binary logistic regression was used to evaluate the association of those variables and improvement of 15D scores.

Study IV: Statistical significance between the three subgroups was evaluated with Fisher’s exact test for categorical variables and with the Kruskal-Wallis test for continuous variables. Correlation between immunohistochemical results of the original samples and of TMA was assessed with Pearson’s correlation coefficient, and survival analysis with the Kaplan-Meier method, respectively. The number of new PC cases were compared to the respective average Finnish adult population over the specific time periods (1955–2013) with a chi square-test. Incidence rates are reported as average annual incidences per 10,000,000 population.

4.8 ETHICS

All studies were conducted according to the guidelines of the Declaration of Helsinki and their protocols were approved by the Ethical Committee of the Helsinki University Central Hospital (Turku University Central Hospital for Study II). In Study III, all patients gave their signed informed consent to participate in the study. The Study IV protocol was also approved by the ethics committees of four other university hospitals in Finland, by the National Supervisory Authority for Welfare and Health in Finland (Valvira), and by the National Institute for Health and Welfare in Finland (THL).
RESULTS

5 RESULTS

5.1 COMPARISON OF DUAL-PHASE $^{123}$I/$^{99m}$Tc-MIBI AND $^{99m}$Tc-MIBI SCINTIGRAPHIES BEFORE PRIMARY OPERATION FOR PHPT (STUDY I)

5.1.1 CHARACTERISTICS AND IMAGING FINDINGS OF THE STUDY COHORT.

All the 269 study patients had PHPT and were referred for the first parathyroidectomy. Patients with familial forms of PHPT were excluded. Patients underwent a primary operation for PHPT had a mean age of 61 (16–91) years and 74% of them were female (Table 2). $^{123}$I/$^{99m}$Tc-MIBI scintigraphy revealed one (n=193) or two (n=13) findings in 206 (76.6%) patients. $^{99m}$Tc-MIBI scintigraphy had one finding in 102, and two findings in nine patients; a total of 111 patients (41.3%; P < 0.001). Surgery was successful in 245 (92.5%) of the 269 study patients. Sixteen of the 19 failures (84.2%) were related to the multiglandular disease (MGD).

<table>
<thead>
<tr>
<th></th>
<th>All study patients (n=269)</th>
<th>Single adenomas detected in $^{123}$I/$^{99m}$Tc-MIBI scan (n=159)</th>
<th>Single adenomas not detected in $^{123}$I/$^{99m}$Tc-MIBI scan (n=47)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ionized calcium (mmol/l)</td>
<td>1.49 (1.30–2.42)</td>
<td>1.46 (1.3–2.24)</td>
<td>1.43 (1.3–1.74)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Serum PTH (µg/l)</td>
<td>159 (53–3765)</td>
<td>168 (71–1887)</td>
<td>133 (82–388)</td>
<td>0.0055*</td>
</tr>
<tr>
<td>Serum 25-OHD (nmol/l)</td>
<td>42.5 (13–99)</td>
<td>44 (14–98)</td>
<td>48 (22–67)</td>
<td>0.68</td>
</tr>
<tr>
<td>Serum creatinine (mmol/l)</td>
<td>68 (42–330)</td>
<td>69 (45–225)</td>
<td>66 (46–137)</td>
<td>0.43</td>
</tr>
<tr>
<td>Urinary calcium (mmol/24h)</td>
<td>8.76 (0.23–29.38)</td>
<td>9.02 (0.49–29.38)</td>
<td>8.00 (0.69–18.56)</td>
<td>0.37</td>
</tr>
<tr>
<td>Weight of adenoma (g)</td>
<td>0.65 (0.037–22)</td>
<td>0.78 (0.08–8.49)</td>
<td>0.35 (0.13–1.30)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

All data presented as median and range. *P-value < 0.05 was considered significant (for a comparison of single adenomas detected and not detected by $^{123}$I/$^{99m}$Tc-MIBI scan).

Table 2: Characteristics of the study patients and of those with single adenoma detected or not detected by dual-tracer scintigraphy.
5.1.2 COMPARISON OF $^{123}$I/$^{99m}$Tc-MIBI AND $^{99m}$Tc-MIBI SCINTIGRAPHIES

$^{123}$I/$^{99m}$Tc-MIBI and $^{99m}$Tc-MIBI scintigraphies were positive in 77% and 41% of patients, respectively (P < 0.001) (Table 3). Table 2 show the accuracies of the two scintigraphy techniques in single gland and multiglandular disease (MGD). The $^{123}$I/$^{99m}$Tc-MIBI scan demonstrated one finding in 193 patients. In 164 (85%) of these, the scan result was accurate and those patients were cured. In 17 patients the operation was extended to a BNE and the pathological gland or an additional pathological gland was found on the contralateral side. Twelve patients were not cured; ten of these had MGD. Thirteen (4.8%) of 269 patients had a bilateral finding on $^{123}$I/$^{99m}$Tc-MIBI scintigraphy, and only 77% of these were cured. The accuracy was 46%, but rose to 69% when the reoperation findings were also evaluated. $^{123}$I/$^{99m}$Tc-MIBI scintigraphy demonstrated no uptake in 63 (23%) patients, and 54 (86%) of them were proved to have a single gland disease, seven had a MGD and two had no pathological glands identified.

5.1.3 COMPARISON OF SCINTIGRAPHIC AND HISTOPATHOLOGICAL FINDINGS

Histopathology confirmed a single adenoma in 218 (81%) of the study patients. $^{123}$I/$^{99m}$Tc-MIBI and $^{99m}$Tc-MIBI scintigraphies were accurate in 76% and 42% of patients (P < 0.001). For the 47 patients with other histological diagnoses (hyperplasia, a combination of hyperplasia and adenoma, carcinoma) or multiglandular disease, 37 out of 76 (49%) pathological glands were accurately found in $^{123}$I/$^{99m}$Tc-MIBI scintigraphy. All parathyroid carcinomas were found by the $^{123}$I/$^{99m}$Tc-MIBI scan.

<table>
<thead>
<tr>
<th>Scintigraphy</th>
<th>No findings</th>
<th>One finding</th>
<th>Two findings</th>
<th>Accuracy for one findinga</th>
<th>Accuracy in MGDa</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc-MIBI</td>
<td>58.7%</td>
<td>37.9%</td>
<td>3.3%</td>
<td>34.2%*</td>
<td>9.7%*</td>
</tr>
<tr>
<td>$^{123}$I/$^{99m}$Tc MIBI</td>
<td>23.4%</td>
<td>71.7%</td>
<td>4.8%</td>
<td>60.9%*</td>
<td>14.6%*</td>
</tr>
</tbody>
</table>

* P-value < 0.001 for comparison of accuracies between $^{123}$I/$^{99m}$Tc-MIBI and $^{99m}$Tc-MIBI scintigraphies. Data presented in percentages and 95% confidence intervals. a in the whole cohort

Table 3: Outcome of $^{123}$I/$^{99m}$Tc-MIBI and $^{99m}$Tc-MIBI scintigraphies and accuracies compared to surgical findings.
5.1.4 MULTIGLANDULAR DISEASE (MGD)

The rate of MGD in this cohort was 15.7%. The accuracies of $^{123}$I/$^{99m}$Tc-MIBI and $^{99m}$Tc-MIBI scans are shown in Table 2. The cure rate in MGD was 61.0%.

5.1.5 DETERMINANTS OF TRUE POSITIVE $^{123}$I/$^{99m}$Tc-MIBI SCINTIGRAPHY FINDINGS

Comparison of single adenomas detected and not detected on scintigraphy showed that patients with an accurate $^{123}$I/$^{99m}$Tc-MIBI scintigraphy result had higher tumor weight, preoperative serum ionized calcium and PTH levels than those with a negative scintigraphy (Table 2) ($P < 0.05$).

5.1.6 EFFECT OF LOCALIZATION FINDINGS TO OPERATIVE TECHNIQUE AND TIME

In the study cohort, bilateral neck exploration (BNE) was performed in 103 patients (38.2%): 88.9% of those with a negative $^{123}$I/$^{99m}$Tc-MIBI scintigraphy and 22.8% of those with a positive $^{123}$I/$^{99m}$Tc-MIBI scan underwent BNE ($P < 0.001$). A unilateral operation was performed in 166 patients: 54 of these were unilateral neck explorations (UNE) to two quadrants of the neck, and 102 were targeted to one quadrant (97 focused parathyroidectomies and 15 minimal invasive parathyroidectomies). The cure rate between patients with negative or positive scan did not differ (93.7% vs 92.7%, $P = NS$).

The duration of the operative procedure was assessed in the 219 cured patients without simultaneous thyroid surgery. The median operation lengths (range) in BNE, in UNE to two quadrants and to one quadrant were 67.9 (33.0–181.2), 52.4 (33.0–160.0) and 46.2 (22.0–135.0) minutes ($P < 0.001$ for all comparisons).

5.2 COMPARISON OF PREOPERATIVE $^{123}$I/$^{99m}$Tc-MIBI PLANAR SCINTIGRAPHY, $^{99m}$Tc-MIBI SPECT/CT, $^{11}$C-METHIONINE PET/CT, AND SVS BEFORE REOPERATION IN PHPT

5.2.1 PATIENT CHARACTERISTICS

All the 23 study patients had a PHPT with a persistent hypercalcemia after the first one or two operations. The mean age of the patients was 55 years (range 31–78) and 23.8% were men. Postoperatively, the mean (SD) serum ionized calcium and PTH
levels decreased significantly from preoperative levels (1.46 ± 0.09 vs. 1.25 ± 0.10 mmol/l and 169 ± 95 vs. 48 ± 64 ng/l, respectively, P <0.001 for both). The cure rate for the reoperations was 86% (18/21). Nineteen pathological glands were removed from 17 patients, one biochemically cured patient had no abnormal glands removed. Two patients had the pathologic parathyroid gland located within the thyroid gland, and two patients in the mediastinum.

5.2.2 COMPARISON OF $^{123}$I/$^{99m}$Tc-MIBI SCINTIGRAPHY, $^{99m}$Tc-MIBI SPECT/CT, $^{11}$C-METHIONINE-PET/CT, AND SVS

<table>
<thead>
<tr>
<th></th>
<th>$^{123}$I/$^{99m}$Tc-MIBI scintigraphy (n=21)</th>
<th>$^{99m}$Tc-MIBI SPECT/CT (n=19)</th>
<th>$^{11}$C-methionine-PET/CT (n=21)</th>
<th>SVS (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (focuses)</td>
<td>14</td>
<td>5</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>N (false predictive)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Accuracy (correct side of neck)</td>
<td>59% (36–79)</td>
<td>19%* (5–42)</td>
<td>65% (43–84)</td>
<td>40% (19–64)</td>
</tr>
<tr>
<td>Accuracy (correct quadrant)</td>
<td>48% (27–69)</td>
<td>14%# (3–36)</td>
<td>61% (39–80)</td>
<td>25% (9–49)</td>
</tr>
</tbody>
</table>

Data presented as percentages with a 95% confidence interval. * P-value < 0.01 and # P-value < 0.02 vs $^{123}$I/$^{99m}$Tc-MIBI scintigraphy

Table 4. Summary of the findings and the accuracies of the four different localization techniques.

Results of the comparison of the four localization techniques are presented in Table 4. In one patient only, all four imaging techniques correctly localized the pathological parathyroid gland. In the three patients with persistent disease after reoperation, no pathological parathyroid tissue was removed. In all these three patients, $^{123}$I/$^{99m}$Tc-MIBI scintigraphy and SPECT/CT were negative while SVS was false predictive. $^{11}$C-methionine-PET/CT was false predictive in one of these three patients. There were four patients cured by the reoperation, in whom $^{11}$C-methionine-PET/CT correctly identified the four pathological glands while the three other imaging techniques remained negative.
5.3 HEALTH-RELATED QUALITY OF LIFE (HRQOL) BEFORE AND AFTER PARATHYROIDECTOMY IN PRIMARY HYPERPARATHYROIDISM

5.3.1 PATIENT CHARACTERISTICS

The study comprised 124 PHPT patients who were referred for surgery and had completed the 15D questionnaire preoperatively. The mean age of the patients was 65 ± 10 years and 81.5% of them were women. The biochemical and clinical features of the study cohort are presented in Table 5. Parathyroidectomy resulted in normocalcemia in 112 of 125 (89.6%) patients. The sample of the general population (n=4295) was adjusted for age and gender. Of those 124 respondents to the first 15D questionnaire, 94.4% replied to the questionnaire at six months and 93.5% at 12 months.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD (or n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>N (women/men)</td>
<td>101/23</td>
</tr>
<tr>
<td>Number on regular medication</td>
<td>3.9 ± 2.9</td>
</tr>
<tr>
<td>Educational level</td>
<td>56/66/3</td>
</tr>
<tr>
<td>Preoperative serum ionized calcium (mmol/l)</td>
<td>1.47 ± 0.12</td>
</tr>
<tr>
<td>Postoperative serum ionized calcium (mmol/l)</td>
<td>1.25 ± 0.08</td>
</tr>
<tr>
<td>Preoperative serum PTH (ng/l)</td>
<td>176.3 ± 155.6</td>
</tr>
<tr>
<td>Postoperative serum PTH (ng/l)</td>
<td>35.8 ± 33.4</td>
</tr>
<tr>
<td>Serum 25-OH D (nmol/l)</td>
<td>57.2 ± 17.8</td>
</tr>
</tbody>
</table>

Table 5. Characteristics of 124 study patients before surgery

5.3.2 HRQOL IN PHPT COMPARED TO AGE- AND GENDER-ADJUSTED CONTROLS

The mean total preoperative 15D score of PHPT patients was significantly lower compared to that of the controls (P < 0.001). All five dimensions measuring cognitive and psychiatric well-being were severely impaired compared to controls as well as excretion, usual activities, and sexual activity (all P < 0.001).
5.3.3 IMPACT OF PARATHYROIDECTOMY ON HRQOL IN PHPT

Figure 6 presents a significant difference both in total 15D score and in 13 of 15 dimensions when comparing the preoperative 15D of PHPT patients with age- and gender-adjusted patients. Figure 6 also shows an increase in the 15D score in PHPT patients from a baseline at six months after surgery ($P < 0.001$). After surgery, 77.4% of patients experienced at least a minimum clinically important improvement and 13.7% a minimum clinically important deterioration in HRQoL. The change of 15D was significant in 10 of the 15 dimensions. There was no significant difference in the postoperative change of 15D between the patients meeting (80.6%) and those not meeting (19.4%) the Third International Workshop Criteria for surgery in PHPT (see section 6.3). Nearly half (42%) of the 125 patients had reported possible PHPT-related symptoms (fatigue, depression, loss of memory, abdominal pain or nausea, muscle weakness, or joint pains).

![Figure 6. Health-related quality of life in patients with primary hyperparathyroidism before and after surgery](image)

5.3.4 PREDICTORS OF PREOPERATIVE HRQOL AND OF CHANGE IN HRQOL IN PHPT

Of several possible factors evaluated, only the number of medications ($\beta = -0.012$, $P < 0.001$) and whether one experienced subjective symptoms ($\beta = -0.040$, $P < 0.029$) had an impact on HRQoL before surgery. The serum 25 OH D level had borderline
RESULTS

significance ($\beta = 0.001$, $P = 0.051$) in predicting impaired HRQoL. Only higher educational level predicted improved HRQoL in PHPT of the different variables assessed, and a low preoperative 15D score was of borderline significance ($P = 0.057$).

5.4 INCREASING INCIDENCE OF PARATHYROID CARCINOMA – A NATIONWIDE STUDY INCLUDING CLINICAL AND HISTOLOGICAL COMPARISON TO ATYPICAL AND BENIGN PARATHYROID ADENOMAS

5.4.1 INCIDENCE OF PARATHYROID CARCINOMA BETWEEN 1955 AND 2013

Figure 7 shows the change in incidence of PC. Between 1955 and 2000, the mean incidence of PC was 1.4 cases/10,000,000 persons per year (range 0.5–2.1), but this rose to 3.4 cases/10,000,000 persons per year (2000–2004) and up to 10.4 cases/10,000,000 persons per year (2010–2013), $P < 0.001$ (Figure 7).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1955-1959</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1960-1969</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>1970-1979</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>11</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>1980-1989</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>1990-1999</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>2000-2009</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>2010-2013</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Male(%)</td>
<td>66.7</td>
<td>33.3</td>
<td>20.0</td>
<td>50.0</td>
<td>42.9</td>
<td>50.0</td>
<td>50.0</td>
<td>46.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>24</td>
<td>18</td>
<td>64</td>
</tr>
</tbody>
</table>

Figure 7. Incidence of parathyroid carcinoma between 1955 and 2013 in Finland.

5.4.2 CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE STUDY PATIENTS

Of the 32 patients with PC, 18 (56%) were female and 14 (44%) male. The median age at diagnosis was 61 (17–83), 59 (31–84) and 62 (15–83) years for the PC, APA, and PA subgroups, respectively (Table 6). In the PC group, the median age of women and men was 68 (48–84) and 54 (17–76) years, respectively, and the median follow-up time (FU) was 6.7 (range 2.0–13.9) years. The characteristics of patients
in the PC, APA, and PA groups are presented in Table 5. Of the PC patients, 44% had a hypercalcemic crisis or a hospital-treated hypercalcemia. A third (35%) had a benign parathyroid tumor previously or at follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Parathyroid carcinoma (n=32)</th>
<th>Atypical adenoma (n=28)</th>
<th>Adenoma (n=72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca-ion (mmol/l)</td>
<td>1.76 (1.61–1.97)</td>
<td>1.56 (1.50–1.70)</td>
<td>1.44 (1.38–1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTH (ng/l)</td>
<td>989 (461–1518)</td>
<td>355 (149–959)</td>
<td>160 (122–251)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal manifestation</td>
<td>16 (50%)</td>
<td>13 (48%)</td>
<td>16 (22%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Bone manifestation</td>
<td>15 (47%)</td>
<td>4 (15%)</td>
<td>27 (38%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Both renal and bone manifestations</td>
<td>9 (28%)</td>
<td>2 (7%)</td>
<td>4 (6%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

All continuous variables are presented as medians and interquartile range (IQR). Normal ranges: Ca-ion 1.15–1.30 mmol/l, PTH 15–65 ng/l.

Table 5. Clinical and biochemical characteristics of PC, APA, and PA groups.

### 5.4.3 PREOPERATIVE LOCALIZATION STUDIES AND SURGERY

Planar isotope imaging with $^{99m}$Tc-Technetium-sestamibi alone or combined with $^{123}$Iodine did not differ in the PC compared to the APA or PA groups ($P = 0.62$), but the subgroups differed in ultrasound imaging (accurate finding in 77%, 43% and 39% of PC (n= 26), APA (n= 23), and PA (n=64) groups, respectively, $P < 0.001$).

The proportions of successful primary operation in the PC, APA, and PA subgroups were 91%, 93% and 91%; and the postoperative status of one APA patient remains unknown. *En bloc* or radical resection was performed on 47%, 18% and 8%, respectively ($P < 0.001$). The PC tumors were significantly larger compared to APA and PA tumors (2.95 (2.0–3.0) cm, 2.0 (1.4–3.0) cm, and 1.6 (1.2–2.0) cm, respectively, $P < 0.001$)

### 5.4.4 HISTOLOGY

Histological findings are shown in Table 7. Capsular, vascular, and perineural invasions were present in 72%, 72%, and 9% of the PC specimens, and were, by definition, absent in APA and PA tumors. In PC tumors, chief cell type and diffuse growth pattern dominated. Differences in mitotic activity, nuclear atypia necrosis, hemosiderin deposits, and fibrous septae were observed between subgroups.
RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Parathyroid carcinoma (n=32)</th>
<th>Atypical adenoma (n=28)</th>
<th>Adenoma (n=72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotic activity:</td>
<td>8 (25%)</td>
<td>3 (9%)</td>
<td>1 (1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Strong mitotic activity (&gt;1/10 cells)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>14 (44%)</td>
<td>5 (18%)</td>
<td>8 (11%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dominant cell type</td>
<td>Chief 100%</td>
<td>22 (69%)</td>
<td>19 (68%)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>≥ 50% 28 (88%)</td>
<td>23 (82%)</td>
<td>30 (41%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Diffuse ≥50%</td>
<td>24 (75%)</td>
<td>17 (61%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>100% 20 (63%)</td>
<td>11 (39%)</td>
<td>25 (34%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 (17%)</td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>3 (9%)</td>
<td>0</td>
<td>0</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Table 7. Histological findings in the different subgroups

5.4.5 IMMUNOCHEMISTRY AND CDC73 MUTATION ANALYSIS

Of PC tumors, 13% had a negative and 22% a positive parafibromin stain (Table 8). None of the adenoma tumors had a negative and 76% had a positive stain. Ki-67 indices analyzed by Immunoratio (TMA) were significantly higher compared to APA and PA groups ($P < 0.001$).

CDC73 gene mutation was analyzed in 56% and 57% of the PC and APA patients, respectively. The mutation was detected in one 18-year-old man with negative parafibromin staining in his PC sample, and in one 31-year-old man with a weak positive parafibromin staining in his APA tumor.

<table>
<thead>
<tr>
<th></th>
<th>Parathyroid carcinoma (n=32)</th>
<th>Atypical adenoma (n=27)</th>
<th>Adenoma (n=71)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative parafibromin</td>
<td>13%</td>
<td>4%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Ki-67indices* (TMA)</td>
<td>2.7% (0.4–15.6)</td>
<td>2.0% (0.3–7.5)</td>
<td>0.9% (0.2–4.7)</td>
<td></td>
</tr>
<tr>
<td>CDC73 gene mutation</td>
<td>6% (n=18)</td>
<td>6% (n=16)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*median and range, **for comparison of three subgroups, for PC vs PA, and for APA vs PA
*for comparison of PC vs APA

Table 8. Immunohistochemical results obtained from the Tissue Micro Array and CDC73 mutation analysis in the different subgroups.
5.4.6 FOLLOW-UP

5.4.6.1 Recurrences and mortality
In PC, three patients had a persistent disease (Table 9). Five of the six patients with recurrence (at a median of 24 months from primary operation, range 4–60) developed distant metastasis during FU. Four of them (12.5% of all PCs) died of disease a median of 43.9 (range 23.4–61.3) months after diagnosis. Overall 5- and 10-year survivals in PC did not differ from APA and PA (91% vs 84% vs 92%, and 72% vs 73% vs 83%, respectively, P= NS for both comparisons). In APA, all deaths occurred in cured patients and were unrelated to PHPT.

5.4.6.2 Treatments
The number of operations and other treatments given are shown in in Table 8. The prevalence of both transient or persistent hypocalcemia and laryngeal nerve palsy were significantly increased in the PC group compared to APA and PA (56% vs. 11% vs. 4% and 34% vs 11% vs 3%, respectively P < 0.001 for both). In PC patients, preoperatively increased creatinine did not improve after surgery. Preoperative and 1-year after operation, serum creatinines were 106 (76–147) and 100 (80–145) µmol/l, respectively (P = 0.39). Of PC patients, 22% received radiotherapy and 13% chemotherapy.

<table>
<thead>
<tr>
<th>Persistent disease</th>
<th>Parathyroid carcinoma (n=32)</th>
<th>Atypical adenoma (n=28)</th>
<th>Adenoma (n=72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>6 (21%)</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total number of operations for PHPT (mean and range)</td>
<td>2 (1–5)</td>
<td>1 (1–4)</td>
<td>1 (1–3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 2 neck operations</td>
<td>47%</td>
<td>22%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Metastasis during follow-up time</td>
<td>5 (cervical lymph nodes, lungs, bone)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Recurrences and treatments in the different subgroups

5.4.7 FACTORS ASSOCIATED WITH CANCER DEATHS

Recurrent PCs and non-recurrent PCs differed in the presentation of lymph node metastases (in 33% vs. 0%, P = 0.03), in parafibromin expression (mean level of PF stain 0.5 vs 1 on a scale of 0–2, P= 0.01) and slightly in PI (Ki-67 indices 8.2 vs 3.1%, P = 0.11).
RESULTS

Of preoperative and biochemical factors, serum ionized calcium and PTH concentrations differed slightly in recurrent and non-recurrent PCs (1.86 (1.61–2.42) vs 1.72 (1.55–1.97) mmol/l, ($P = 0.20$); and 1030 (358–2120) vs 904 (68–2220) ng/l, $P = 0.41$).

Of all histological aspects assessed, vascular invasion was found in all recurrent PCs (and in 72% of non-recurrent PCs), and all tumors characterized with necrosis recurred. Significantly higher mitotic activity, the number of pathological mitoses, and more marked nuclear atypia ($P < 0.05$, $P < 0.03$ and $P < 0.03$, respectively), were found in recurrent tumors.
6 DISCUSSION

6.1 RADIONUCLIDE IMAGING BEFORE SURGICAL MANAGEMENT IN PHPT

The first part of our study compares the accuracies of preoperative imaging techniques in primary and reoperation settings.

6.1.1 IMAGING BEFORE PRIMARY SURGERY

Surgery is the only definitive treatment for PHPT. Until the last few decades, a bilateral exploration under general anesthesia was the standard operation. The objectives of a parathyroidectomy are to achieve a long-lasting normocalcemia, and to provoke minimal complications with the shortest possible operation time. The development of preoperative imaging techniques and intraoperative tools has made focused parathyroidectomies possible. Despite the large number of studies regarding preoperative imaging in PHPT, there are still two schools of thought regarding the extent of preoperative imaging and parathyroidectomy techniques (Norman, Lopez & Politz 2012, Hindie et al. 2015, Minisola et al. 2016). However, a consensus exists that imaging studies are needed before parathyroidectomies (Bergenfelz et al. 2009, Hindie et al. 2009, Udelsman et al. 2014).

In our study on scintigraphy methods before primary operation, the accuracy of $^{123}$Iodine/$^{99m}$Tc-MIBI was clearly superior to that of $^{99m}$Tc-MIBI: 63% vs. 34%, ($P < 0.001$). Many previous studies (Tunninen et al. 2013, Caveny et al. 2012, Chen et al. 1997, Hindie et al. 1998, Leslie et al. 2002, Philippon et al. 2014), but not all (Jorna et al. 2007) report similar findings. The European Association of Nuclear Medicine (EANM) guidelines and a recent review (Hindie et al. 2009, Hindie et al. 2015) recommend the use of a double-tracer method in scintigraphies. A recent study from the Mayo Clinic (Lee et al. 2016) reported a higher accuracy for planar $^{123}$Iodine/$^{99m}$Tc-MIBI scintigraphy with a pinhole collimator compared to $^{99m}$Tc-MIBI SPECT or SPECT/CT. The use of a pinhole collimator, which improves the resolution and thus detects glands of unequal size, is also recommended by others (Hindie et al. 2015, Klingensmith et al. 2013).

According to our study, the scintigraphy result had a crucial effect on the operation type. A quarter (23%) of patients with a localized tumor had a BNE, whereas 89% of those with negative scintigraphy had a BNE. We did not observe any significant difference in the outcome of surgery between the patients with positive and negative scintigraphies (92.7% vs 93.7%, respectively, $P =$NS). In contrast to our results, previous studies report a lower cure rate for patients with negative imaging studies (Allendorf et al. 2003, Bergenfelz et al. 2011). In nearly all operations not leading to normocalcemia, at least one pathological gland was removed and calcium decreased to near-normal levels.
One finding in $^{123}$Iodine/$^{99m}$Tc-MIBI was present in 193 (72%) of study patients. In 85% of these 193 patients, the imaging result was accurate, but 12 patients (6%) were not cured. The cure rate was lowest among those with bilateral $^{123}$Iodine/$^{99m}$Tc-MIBI findings, with only 76.9% cured. Thus, a bilateral finding can be considered to be an operation failure risk. The factors contributing to positive imaging finding were concordant with other reports (Berber et al. 2008): higher serum calcium and PTH and gland weight were associated with a positive scintigraphy finding.

Sixteen of the nineteen unsuccessful operations (84%) in the study were related to MGD. Of note, hereditary forms of PHPT were excluded from the study. According to the earlier literature, the vast majority (77%) of operation failures were due to undetected solitary adenomas (Udelsman 2011, Jaskowiak et al. 1996). The results of another recent study were in line with our results: 22% of the reoperations in the tertiary unit and 56% of patients operated elsewhere were related to an undetected single adenoma (Karakas et al. 2013). The overall proportion of MGD in our study, 15.7%, was similar to other studies (Lee et al. 2016, Minisola et al. 2016). Unfortunately, the cure rate for MGD was only 61%.

In our study, the accuracies for a detection of a single adenoma and for MGD differed dramatically: 76% vs 15% for $^{123}$Iodine/$^{99m}$Tc-MIBI, and 42% vs 10% for $^{99m}$Tc-MIBI. In the meta-analysis, the sensitivities of $^{99m}$Tc-MIBI for detecting a single adenoma and MGD, 88% and 45%, also differed markedly (Ruda, Hollenbeak & Stack 2005). Hyperplastic glands are smaller than adenomas and therefore more difficult to localize (Berber et al. 2008). Intraoperative localizing methods, IoPTH and a gamma probe are also at risk of missing hyperplastic glands (Hindie et al. 2015, Siperstein et al. 2008). MGD continues to be a big challenge, and thus some have even returned to perform BNE on all patients (Norman, Lopez & Politz 2012).

The duration of unilateral operations to one and two quadrants and of BNE were 46, 52, and 68 minutes, respectively. Another study reported operation lengths of 78 min for MIP and 144 min for BNE, and concluded that BNE was more expensive compared to focused parathyroidectomies with preoperative imaging (Lubitz et al. 2012). Differences in pre- and intraoperative localizing methods and in the constitution of operation costs elsewhere and in our country make the cost-effectiveness assessment difficult.

Preoperative imaging studies provide valuable information to surgeons, but they must not be used as a diagnostic tool. However, these should be performed before every parathyroidectomy. As recommended by ESES, after two concordant imaging studies with sestamibi scintigraphy and ultrasound, a focused parathyroidectomy can be performed (Bergenfelz et al. 2009). A discordant finding should lead to either BNE or unilateral exploration with the use of IoPTH. Scintographies are able to reveal an ectopic gland, whereas ultrasound also provides information about the thyroid gland. Each institution must assess what is the most suitable algorithm to be used regarding localization and surgery strategies. The availability, the accuracies and the costs of different pre- and intraoperative localizing methods, the radiation exposure to the patient, as well as the local expertise regarding surgery, radiology, and nuclear medicine needs to be assessed (Hindie et al. 2015, Kunstman et al. 2013, Minisola et al. 2016). The Mayo Clinic chose to improve and continue to use planar
Iodine/\textsuperscript{99m}Tc-MIBI scintigraphy and reserves SPECT or SPECT/CT for reoperations. In this clinic, ioPTH is used in all parathyroidectomies (Lee et al. 2016). In our institution, enlarged PHPT glands are localized by planar dual-phase Iodine/\textsuperscript{99m}Tc-MIBI scintigraphy and ultrasound.

\section*{6.1.2 PREOPERATIVE IMAGING BEFORE REOPERATION}

The majority of reoperations are related to persistent PHPT after primary operations. Recurrent PHPT, in which normal calcium and PTH concentrations are maintained for at least six months after surgery, is far less common than persistent disease and occurs mostly in familial PHPT. In addition, patients with previous non-parathyroid-related neck surgery should be included in this challenging reoperation group (Udelsman 2011).

Our study presents the preoperative imaging results of 21 patients in the reoperation setting. All underwent a planar Iodine/\textsuperscript{99m}Tc-MIBI scintigraphy and \textsuperscript{11}C-methionine-PET/CT. SVS was performed on 18 and \textsuperscript{99m}Tc-MIBI SPECT/CT on 19 patients. The cure rate was 86\%, in line with other studies (Ogilvie et al. 2006, Karakas et al. 2013). Two patients had the abnormal gland in mediastinum, and two others had an intrathyroidal parathyroid tumor. The accuracy of the Iodine/\textsuperscript{99m}Tc-MIBI scan was 59\%, slightly lower than in the primary operation setting but higher than that of \textsuperscript{99m}Tc-MIBI SPECT/CT, which was only 19\%. This is in line with other studies comparing these two imaging modalities (Lee et al. 2016, Tunninen et al. 2013).

SVS, an invasive localization method, has been a gold standard and used if other available noninvasive methods are negative. The sensitivity of SVS varies between 71–90\% (Kunstman et al. 2013), but the rate of false positives has been one of its disadvantages (Jones et al. 2002). The low accuracy of SVS in our study compared to \textsuperscript{11}C-methionine-PET/CT led to a marked decrease in using this method in our institution and the routine use of PET/CT as a second-line method in the reoperation setting.

In our study, \textsuperscript{11}C-methionine-PET/CT had the highest accuracy, 65\%. According to a meta-analysis of 14 studies on PET tracers in parathyroid localizing, the sensitivity of \textsuperscript{11}C-methionine-PET/CT was on average 77\% and a PPV of 98\% for detecting the pathological parathyroid in the correct quadrant (Kluijfhout et al. 2016a). A recent study on 15 patients with previous neck operations and negative \textsuperscript{99m}Tc-MIBI SPECT/CT reported \textsuperscript{11}C-methionine-PET/CT to be positive in only six out of 15 (40\%) patients. In five of them, operation findings correlated to the PET/CT findings (Traub-Weidinger et al. 2014). A series of 23 patients who were scheduled for a reoperation showed that the sensitivity of \textsuperscript{11}C-methionine-PET/CT in MGD was similar (30\%) to \textsuperscript{99m}Tc-MIBI SPECT/CT (Kluijfhout et al. 2016a, Hayakawa et al. 2015). In MGD, \textsuperscript{11}C-methionine PET/CT did not have an additional value (Hayakawa et al. 2015). Because of the reduced availability and the costs, PET/CT is suitable as a complimentary imaging modality (Hindie et al. 2015). In conclusion, \textsuperscript{11}C-methionine-PET/CT is a reliable second-line imaging modality with
The latest studies suggest that radiolabeled choline PET/CT might be a new tracer for localizing abnormal parathyroid glands. In a study of 24 PHPT patients, $^{18}$F-fluorocholine PET/CT (FCH-PET/CT) had a PPV of 100%, a higher sensitivity (92% vs 64%), and a better performance in MGD compared to $^{99m}$Tc-pertechnetate subtraction scintigraphy (Lezaic et al. 2014), in line with others (Kluijfhout et al. 2015, Michaud et al. 2015). Disadvantages of this method are higher costs as well as possible false positives from thyroid nodules and inflammatory lymph nodes in the absence of a thyroid-specific tracer. Larger studies are needed, especially before reoperation or when conventional imaging remains negative or discordant (Hindie et al. 2015).

Four-dimensional CT, available only in some centers, has been recommended even before primary operation when two imaging studies are discordant (Minisola et al. 2016), before reoperation, or in cases with mediastinal glands (Hindie et al. 2015, Udelsman 2011). 4D CTs should be used with caution in young patients as the radiation exposure (in average 10.4 mSv) to the thyroid area is high (Minisola et al. 2016). Studied in 68 patients before reoperation, a regular MRI performed at 1.5 T in most patients, had a sensitivity of 82%, and a PPV of 85%. The sensitivity and PPV of 23 patients before primary operation were lower, only 64% and 67%, respectively (Grayev et al. 2012, Kluijfhout et al. 2016b). In some cases, MRI can provide additional information if other imaging methods remain negative (Kluijfhout et al. 2016b).

Of the latest modalities, $^{18}$F-fluorocholine-PET/CT seems an interesting option for patients with discordant imaging. Thus far it has only been studied in a primary operation setting, but the sensitivity and specificity are better than those of planar $^{123}$Iodine/$^{99m}$Tc-MIBI or $^{99m}$Tc-MIBI SPECT/CT (Lezaic et al. 2014). There is preliminary data on $^{18}$F-fluorocholine-PET combined with MRI and this seems to be useful in patients with negative or discordant imaging studies (Kluijfhout et al. 2016a).

Intraoperative PTH, recommended in all reoperations (Bergenfelz et al. 2009, Udelsman 2011), was not available in these operations. The 21 patients in our study did not have any postoperative complications, which suggests slightly better results compared to other studies reporting 9% for permanent recurrent laryngeal nerve palsy (Karakas et al. 2013). In addition to good expertise in preoperative imaging, successful reoperations require an experienced surgeon.

According to ESES guidelines and recent reviews, two concordant imaging studies (a sestamibi scintigraphy, preferably with SPECT or double-tracer, and ultrasound) are performed before reoperation. If these are discordant or negative, the second-line options include 4-dimensional CT, ultrasound-guided thin-needle biopsy, MRI, and PET/CT, depending on the availability (Bergenfelz et al. 2009, Hindie et al. 2015, Kunstman et al. 2013). SVS is used if results are inconclusive. If a positive or suggestive result is obtained, surgery is possible. IoPTH is recommended for all reoperations. For appropriate patients with negative imaging,
surgery can be performed in a primary operation setting. Others are offered the best possible medical therapy (Kunstman et al. 2013).

### 6.2 HEALTH-RELATED QUALITY OF LIFE IN PHPT

The third part of the present study compared the preoperative HRQoL of PHPT patients referred to surgery to the Finnish control population standardized for gender and age (n=4295). The HRQoL questionnaire is a tool to assess those symptoms otherwise difficult-to-measure but necessary-to-evaluate in PHPT. Twenty percent of patients did not fulfill the criteria for surgery. Nearly 41% of the study patients complained of possibly PHPT-related symptoms. We followed these patients’ HRQoL postoperatively for 12 months and compared it to preoperative HRQoL results and to the control group.

15D. We used the Finnish, well-validated and generic 15D instrument (Saarni et al. 2006, Kontodimopoulos et al. 2012) instead of disease-specific questionnaires to be able to compare the results with those of the large Finnish age- and gender-standardized control group from the national Health 2011 project (Saarni, Luoma & Koskinen 2012). 15D gives a single score and a profile of 15 dimension to describe HRQoL. The SF-36 questionnaire, used in the three prospective, randomized studies on mild PHPT (Ambrogi et al. 2007, Bollerslev et al. 2007, Rao et al. 2004), evaluates HRQoL with two values and a profile. Therefore, SF-36 can not assess or compare the overall effect of the changes to HRQoL (Sintonen 2013).

**Preoperative HRQoL.** In this study, the preoperative HRQoL was markedly lower than in the general population and a significant difference was present in 13 of 15 dimensions. The five dimensions (mental function, discomfort and symptoms, depression, distress, and vitality) measuring cognitive and psychiatric well-being differed the most from the general population. Deterioration in moving, speech and breathing can be explained by altered muscle function. That seen in excretion may be related to polyuria. A decrease in sexual activity might reflect dissatisfaction in overall well-being. The lower score in seeing remains unexplained. Only hearing and eating did not differ from the sample of the general population.

The preoperative HRQoL was lower in those with a higher amount of regular medications, was also previously reported to decrease HRQoL (Andersson, Marcusson & Wressle 2014), and in those who preoperatively complained of possibly PHPT-related symptoms. In this study, the number of regular medications describes the burden of possible comorbidities.

**Postoperative HRQoL.** During the first six postoperative months, HRQoL improved in 10 of 15 dimensions, and in one more dimension during the next six months near to the normal level of the controls. The recent data from our PHPT cohort after a mean follow-up time of 3.3 years after surgery confirms that the improvement in HRQoL is postoperationally sustained (Storvall et al., unpublished data). Of the 13 preoperatively impaired dimensions, only those of seeing and breathing remained unchanged. When converted to the GAS scale, which estimates the minimal important change of HRQoL (Alanne et al. 2015), 77% of the cohort
showed a clinically important improvement. The change in HRQoL was similar between those fulfilling and not fulfilling the surgery criteria and between those with and without possible symptoms. Only a higher educational level and a lower preoperative 15D score, both known to affect the improvement of HRQoL after interventions (Torvinen et al. 2013), increased the improvement in HRQoL.

There is consensus based on several studies that HRQoL is decreased in PHPT, and even in mild PHPT (Weber et al. 2013, Pasieka et al. 2002, Burney et al. 1999, Caillard et al. 2007, Dulfer et al. 2016). According to Weber et al. (Weber et al. 2013), 22% of PHPT patients reported having suicidal ideation, twice as much as in the control group. This proportion decreased to 10% one year after surgery. The studies show that PHPT is associated with cognitive disturbances and psychological symptoms (Babinska et al. 2012, Walker et al. 2009, Roman et al. 2011b). The three prospective, randomized studies on PHPT patients who did not fulfill the current surgical criteria randomized patients into observation and surgery subgroups and used the SF-36 questionnaire in the follow-up. Two of these (Ambrogini et al. 2007, Rao et al. 2004) showed improvement in HRQoL. The largest of these, on 191 PHPT patients not fulfilling the surgery criteria, showed impaired HRQoL preoperatively without any postoperative change in the surgery group. However, a meta-analysis combined these three studies and concluded an overall improvement in mild PHPT (Cheng et al. 2015). Smaller patient groups in other studies (Blanchard et al. 2014, Caillard et al. 2007) have shown a postoperatively improved impairment of HRQoL in PHPT patients, which did not meet the surgery criteria. Unfortunately, both of these lacked a control group. In addition, neurocognitive symptoms, depression, and anxiety improve postoperatively (Babinska et al. 2012, Walker et al. 2009, Roman et al. 2011a).

We did not find any correlation between calcium concentration or PTH concentration and preoperative levels or improvement in HRQoL. The correlation between calcium and the improvement of HRQoL has been found in some (Weber et al. 2013, Blanchard et al. 2014, Sheldon et al. 2002), but not all cohorts (Burney et al. 1999, Gopinath, Sadler & Mihai 2010).

The limitation of our study was the lack of non-operated controls with PHPT. It was not possible to count the number of patients to whom the information letter and first 15D questionnaire was sent. Nearly all those (94%) who replied to the first questionnaire also responded to the two subsequent questionnaires.

Most existing data suggests that HRQoL is decreased in PHPT (Silverberg et al. 2014). HRQoL should be evaluated, especially in PHPT patients without obvious surgery criteria, as it may give additional information in decision-making. This study now shows that the 15D questionnaire detects the changes in the state of health related to PHPT. The distinct 15D profile shown in PHPT patients demonstrates deterioration, especially in dimensions of mental well-being. SF-36 includes questions related to pain (often absent in PHPT), anxiety, and depression, whereas 15D asks about discomfort and symptoms which also include nausea or other types of discomfort. The question of mental function in 15D asks about fatigue and memory loss, both typical for PHPT. Vitality and usual activities are both clearly reduced in PHPT. The use of the 15D questionnaire requires specific software and
briefing of staff. However, the age- and gender-matched general population provides reference levels for HRQoL in 15D. An easy-to-use disease-specific tool of 16 questions, Primary Hyperparathyroidism Quality of Life (PHPQoL), was recently introduced. PHPQoL correlated with the SF-36 in a prospective, case control study in PHPT. PHPQoL showed both lower HRQoL for patients fulfilling the international surgery criteria compared to those for whom surveillance was planned, and an improvement in HRQoL at a one-year follow-up after surgery (Webb et al. 2016). However, HRQoL is affected by the person’s gender and age, and PHPQoL lacks the comparison to general population.

The effect of parathyroidectomy on HRQoL is a subject of debate. However, the majority of studies have observed a change in HRQoL after operation (Ambrogini et al. 2007, Weber et al. 2013, Caillard et al. 2007, Dulfer et al. 2016). Serum calcium concentration is considered a criterion for surgery. As serum calcium seems not to correlate with HRQoL or symptoms, some patients with only mild hypercalcemia may suffer from PHPT-related symptoms. It is often impossible to be certain whether a patient’s symptoms are related to PHPT and whether the extent of discomfort and the decrease in HRQoL allows a surgical intervention to be performed. However, the improvement in the 15D score after parathyroidectomy in PHPT is among the largest described by 15D after interventions, and is at least similar to that after primary hip replacement or obesity surgery (Helmio et al. 2011, Rasanen et al. 2007). Cinacalcet treatment decreases serum calcium concentrations (Marcocci et al. 2009). It can be used temporarily to normalize serum calcium in order to relieve possible symptoms. More medical intervention studies on this topic are needed (Grant, Velusamy 2014).

6.3 PARATHYROID CARCINOMA IN FINLAND

**Incidence.** Our study presents a nationwide cohort of PC from 2000 to 2011, with 32 new cases of PC. We also demonstrate a highly significant increase in the incidence of PC during the last 20 years in Finland. Similar increases in the same time period have been reported in the United States and Australia (Brown et al. 2011, Lee et al. 2007). The incidence of PHPT has increased through the wider use of serum calcium measurements, and pathologic diagnostics have improved (Bilezikian et al. 2016). However, it is unlikely that these aspects explain all the change.

**The clinical presentation.** PC patients more often experienced a renal or bone involvement in PHPT and especially both of these (28%). Nearly half (44%) of our PC patients had a hypercalcemic crisis before diagnosis. As seen in other PC cohorts (Cetani, Pardi & Marcocci 2016, Harari et al. 2011, Villar-del-Moral et al. 2014, Marcocci et al. 2008), a third of patients also had a parathyroid adenoma diagnosed either before the PC or at follow-up. In APA patients, the clinical presentation was milder regarding renal and bone manifestations and hypercalcemic crises. Only 4% had a parathyroid adenoma at the end of FU. The calcium concentration in PC, APA, and PA were 1.76, 1.56 and 1.44 mmol/l, respectively. Serum PTH and creatinine
DISCUSSION

levels showed similar tendencies in subgroups. This is concordant with other comparisons of APA and PC (Quinn et al. 2015).

**Histology.** All our PC patients had a confirmed invasion, capsular in 72%, vascular in 72%, and perineural in 9% of patients. Signs of proliferation (the mitotic activity, nuclear atypia) were documented more often in the PC than the APA group. In PCs, chief cells and diffuse growth type dominated in 88% and 75%, respectively. Necrosis was present in 9% of PCs but absent in APAs. Fibrous septae and hemosiderin deposits were a common finding in both the APA and the PC group. The WHO criteria for PC include capsular invasion (Bondeson et al. 2004). It should be distinguished from “pseudocapsular” invasion, where tumor cells are trapped within the capsule (Cetani, Pardi & Marcocci 2016). We confirmed the diagnosis of PC and consequently some PCs were transferred to the APA group if the tumor invasion was not unequivocal. The difficulty of the evaluation of the invasion is shown in the recent study comparing PCs and APAs (Quinn et al. 2015). In the subgroups of APA, based on the original diagnosis, the re-evaluation showed invasion of surrounding tissues, and capsular and vascular invasion in 21%, 56%, and 9% of cases, respectively.

We performed parafibromin and Ki-67 stainings for all tissue samples using the TMA technique. We used a scale of negative, intermediate, and completely positive for parafibromin. Overall, parafibromin stain was weaker in PCs but negative in only 13% of PCs compared to 4% in APAs and 0% in adenomas. According to previous studies, parafibromin is negative in 32–46% of PCs (Fernandez-Ranvier et al. 2007, Truran et al. 2014). None of the parafibromin positive APAs or PCs recurred similarly to others (Kruijff et al. 2014). The TMA technique, which was used to assess only a few spots of the tissue specimen, resulted with lower PIs than originally, when the whole sample was assessed. However, these values correlated, and the median Ki-67 for PCs in the original evaluation was 5%. Ki-67 is over 5% in 21–60% of PC samples (Fernandez-Ranvier et al. 2007, Truran et al. 2014). Ki-67 was significantly lower in the APA than in PC group, but the values overlapped.

Because the parathyroids are surrounded by a thin capsule and vital organs, the enlarged glands are enucleated without any tumor margins. The challenging differential diagnosis between APA and PC would benefit, if possible, from larger tumor margins. The distinction between PC and APA is of critical importance in evaluating the risk of recurrence and determining the appropriate extent of surgery and the length of follow-up.

The cell division cycle’s (CDC73) germline gene status was available in 56% of PC and 57% of APA study patients. According to the literature, the prevalence of this gene mutation in PC varies between 15% and 70% of cases (Cetani, Pardi & Marcocci 2016). In our study, only 6% and 6% of PCs and APAs, respectively, had a mutation in this gene. The PC patient with the CDC73 mutation was an 18-year old male who had a strong family history of PHPT associated with PC, caused by a deletion of the CDC73 gene demonstrated in several affected family members (Korpi-Hyövälti et al. 2014). Our nationwide PC cohort seems to also include CDC73-mutation negative PCs that are possibly related to better survival and less
Treatments and prognosis Half (47%) of PCs underwent an en bloc resection compared to 18% in the APA group, and a local parathyroidectomy was performed on others. The PC tumors were larger than the APA tumors, in line with that previously reported (Quinn et al. 2015). En bloc resection including at least a tumor resection with a sufficient margin, and the removal of the ipsilateral thyroid lobe, recommended when there is a suspicion of PC (Cetani, Pardi & Marcocci 2016, Talat, Schulte 2010, Schulte et al. 2014), is important to ensure sufficient tumor margins in PCs and to improve the assessment of local/capsular invasion. Schulte et al. even suggest (Schulte et al. 2010) the dissection of the centrocervical lymph node compartment in all patients.

The PC patients in our study underwent an average of two neck operations. Recurrences were observed in six (21%) patients, five of whom developed metastasis. The only recurrence of APA was in a man with a CDC73-mutation. The very low recurrence rate during FU suggests an accurate diagnosis of APA in our cohort. In some PC patients, the reoperation for recurrent hypercalcemia revealed a benign adenoma, not the PC. Cumulative amounts of persistent hypocalcemia and laryngeal nerve palsy were 22% and 22% less, respectively, than in another report (Harari et al. 2011). Every fifth patient received radiotherapy and 13% received chemotherapy. Interestingly, the impaired renal function seen only in the PC group did not improve during the FU. The 5- and 10-year survival rates were 91% and 72% in our study. This is in line with one study (Villar-del-Moral et al. 2014) but is much better than others reported (Harari et al. 2011). Of 32 PCs, four died of the disease at nearly four years in the FU. The patients in our study and that of Villar-del-Moral were diagnosed and treated rather recently, and the lower recurrence rate and mortality may reflect an improvement in prognosis.

Factors associated with recurrent PC. Tumors with lymph node metastasis or invasion to surrounding organs (trachea and muscle) at diagnosis recurred. The three tumors with necrosis at histological evaluation also recurred. All recurrent tumors had vascular invasion at diagnosis, which is considered an important factor for recurrence (Talat, Schulte 2010, Schulte et al. 2012). In line with most previous studies (Talat, Schulte 2010, Villar-del-Moral et al. 2014, Sadler et al. 2014), but not all (Asare et al. 2015), tumor size was not associated with recurrence. Histological features of proliferations were significantly more common in recurrent tumors. Schulte et al. have introduced two staging systems: Schulte A divides PCs into stages I to IV, whereas Schulte B consists of low-risk and high-risk groups. The latter consists of PCs with vascular invasion, invasion to vital organs (not soft tissue), lymph node or distant metastasis. The pilot cohort of Schulte et al. (Schulte et al. 2012) and three others (Talat, Schulte 2010, Villar-del-Moral et al. 2014, Sadler et al. 2014) used these stagings for their PC cohorts. The higher Schulte risk groups had more recurrences and higher risk of death. All recurrent PCs in our study would belong to the high-risk group in Schulte B. In Schulte A, three would be Stage II (vascular invasion) and three Stage III (positive lymph nodes and invasion to
Of the non-recurrent PCs, 74% had vascular invasion and those would also belong to the Schulte A high-risk group.

Our study suggests that PC should be suspected in patients with serum ionized calcium over 1.70mmol/l and especially both renal and bone manifestations of PHPT. Intraoperative decision-making by an experienced endocrine surgeon plays a major role in performing an appropriate procedure decreasing recurrence rates. Tumor invasion to surrounding vital organs or lymph node metastasis seems to represent an increased recurrence risk in a similar way to signs of proliferation or necrosis, negative parafibromin staining and Ki67 over 5%. Immunohistochemical markers, or a combination of clinical and histological features, may provide a tool for the differential diagnosis of parathyroid tumors.
7 CONCLUSION AND FUTURE PROSPECTS

The first part of this study shows that the dual-phase double-tracer scintigraphy with $^{123}$Iodine and $^{99m}$Tc-MIBI is superior to dual-phase $^{99m}$Tc-MIBI scintigraphy. According to the related literature, this $^{123}$Iodine/$^{99m}$Tc-MIBI scan is also the scintigraphy of choice before primary operation. In primary operations, 84% of operation failures were due to MGD being present in 15.6% of patients. The use of dual-tracer scintigraphy has improved the imaging of parathyroids. However, additional tools, such as the use of intraoperative PTH measurement, might be of further benefit.

Patients with persistent or recurrent PHPT and those with previous non-thyroid-related neck operations need two concordant imaging results before reoperation. If ultrasound and scintigraphy are discordant or negative, we suggest the use of $^{11}$C-methionine-PET/CT instead of SVS as a second-line technique. A future technique may be choline PET for challenging cases combined with CT or MRI. IoPTH or a gamma probe can also help to locate the enlarged gland intraoperatively.

The HRQoL in PHPT is decreased and improves after surgery at a rate close to control population level at one-year follow-up. The dimension profile of 15D is able to describe the symptoms of mild PHPT. As serum calcium did not correlate to the HRQoL in PHPT, PHPT-related symptoms are possible in mild PHPT. The non-specific symptoms of PHPT and HRQoL require close questioning and warrant being objectively measured in an out-patient clinic. Prospective case control studies on the benefits of cinacalcet in improving the PHPT-related symptoms might offer further information on the use of this medication in inoperable PHPT.

The incidence of parathyroid carcinoma has markedly increased in Finland. The clinical and histological presentation of our cohort of 32 PC patients diagnosed in Finland between 2000 and 2011 is similar to previous reports. However, the recurrence rate and mortality were lower than in most earlier reports, suggesting that the prognosis of PC might be improving. Atypical adenomas represent a borderline type of parathyroid tumor, sharing properties with both benign adenomas and PCs, but signs of invasion are lacking. Of 28 APAs, the only recurrence was in a patient with CDC73-mutation. This mutation may be assessed in the most aggressive cases of both PCs and APAs. Recurrence risk seems higher in patients with vital organ or lymph node invasion at diagnosis, negative parafibromin stain, or tumor necrosis. All recurrent cases also presented with vascular invasion. According to our study, PC should be suspected in patients with serum ionized calcium over 1.70 mmol/l.

Further studies on the use of immunohistochemical markers in differential diagnosis or in the recurrence risk assessment are needed. Assessment of the risk for PC by combining some clinical and histological risk factors could help in treating PHPT patients.
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Helsinki, November 15th, 2016

Eeva Ryhänen
APPENDIX 1

QUALITY OF LIFE QUESTIONNAIRE (15D©)
Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes your present health status. Continue through all 15 questions in this manner, giving only one answer to each.

QUESTION 1. MOBILITY
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION
1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING
1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING
1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING
1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING
1( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH
1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, halting, stammering or stammered.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. ELIMINATION
1 ( ) My bladder and bowels work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES
1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION
1 ( ) I am able to think clearly and logically, and my memory functions well.
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.
QUESTION 11. DISCOMFORT AND SYMPTOMS
1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.

QUESTION 12. DEPRESSION
1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS
1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY
1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY
1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

Appendix 2

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)/Harri Sintonen
(in Finnish)


KYSYMYS 1. Liikuntakyky
1) Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2) Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja tai portaissa on pieniä vaikeuksia.
3) Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4() Pystyn kävelemään sisälläkin vain toisen avustamana.
5() Olen täysin liikutetypyttöm ja vuoteenoma.

KYSYMYS 2. Näkö
1 ( ) Näen normaalisti eli näen lukea ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ( ) Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ( ) Näen lukea lehteä ja/tai TV:n tekstejä huomattavasti vaikeuksin (silmälaseilla tai ilman).
4 ( ) En näe lukea lehteä enkä TV:n tekstejä ilman silmalaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ( ) En näen lukea oppaatta eli olen lähes tai täysin sokea.

KYSYMYS 3. Kuulo
1 ( ) Kuulen normaalisti eli kuulen hyvin normaaliala puheääntä (kuulokojeella tai ilman).
2 ( ) Kuulen normaaliala puheääntä pienin vaikeuksin.
3 ( ) Minun on melko vaikea kuulla normaaliala puheääntä, keskusteluissa on käytettävä normaaliala kovempaa puheääntä.
4 ( ) Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ( ) Olen täysin kuuro.

KYSYMYS 4. Hengitys
1 ( ) Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ( ) Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievääsä ylämääessä.
3 ( ) Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäisien.
4 ( ) Minulla on hengenahdistusta pienin kirsi laiskuusen jälkeen, esim. peseytyessä tai pukeutuessa.
5 ( ) Minulla on hengenahdistusta lähes koko ajan, myös levossa.

KYSYMYS 5. Nukkuminen
1 ( ) Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
2 ( ) Minulla on lieviä uniongelmia, esim. nukahdistusvaikeuksia tai satunnaisesti yöherääillyä.
3 ( ) Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai un on aikaan riittävästi.
4 ( ) Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkkeitä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
5 ( ) Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

KYSYMYS 6. Syöminen
1 ( ) Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
2 ( ) Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, törmeltösti, vavisten tai erityisapuneuvoin).
3 ( ) Tarvitsen hieman toisen apua syömisessä.
4 ( ) En pysty syömään itse lainkaan, vaan minulla on mitään syötää käyttämänä.
5 ( ) En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa avulla tai suonensäisesti.

KYSYMYS 7. Puhuminen
1 ( ) Pystyn puhumana normaalisti eli selvästi, kuuluvasti ja sjuuvasti.
2 ( ) Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
3 ( ) Pystyn puhumaan ymmärrettävästi, mutta katkonaisteesti, ääni vavisten, sammaltaen tai äntyttäen.
4 ( ) Muilla on vaikeuksia ymmärtää puhettani.
5 ( ) Pystyn ilmaisemaan itseäni vain elein.

KYSYMYS 8. Eriyttäminen
1 ( ) Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmita.
2 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa
3 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.
4 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.
5 ( ) En hallitse lainkaan virtsaamista ja/tai ulostamista.

KYSYMYS 9. Tavanomaiset toiminnot
1 ( ) Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).
2 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.
3 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.
4 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.
5 ( ) En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

KYSYMYS 10. Henkinen toiminta
1 ( ) Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
2 ( ) Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti.
3 ( ) Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistin menetystä.
4 ( ) Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistin menetystä.
5 ( ) Olen koko ajan sekaisin ja vailla ajan tai paikan taju

KYSYMYS 11. Vaivat ja oireet
1 ( ) Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
2 ( ) Minulla on lieviä vaivoja tai oireita, esim. lievä kipua, särkyä, pahoinvointia, kutinaa jne.
3 ( ) Minulla on melkoisia vaivoja tai oireita, esim. melkoist kipua, särkyä, pahoinvointia, kutinaa jne.
4 ( ) Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
5 ( ) Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

KYSYMYS 12. Masentuneisuus
1 ( ) En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
2 ( ) Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
3 ( ) Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
4 ( ) Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
5 ( ) Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

KYSYMYS 13. Ahdistuneisuus
1 ( ) En tunne itséäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
2 ( ) Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
3 ( ) Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
4 ( ) Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
5 ( ) Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

KYSYMYS 14. Energisyys
1 ( ) Tunnen itseni terveeksi ja elinvoimaiseksi.
2 ( ) Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
3 ( ) Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
4 ( ) Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes ”loppuun palaneeksi”.
5 ( ) Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin ”loppuun palaneeksi”.

KYSYMYS 15. Sukupuolielämää
1 ( ) Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.
2 ( ) Terveydentilani vaikeuttaa hieman sukupuolielämääni.
3 ( ) Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.
4 ( ) Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.
5 ( ) Terveydentilani tekee sukupuolielämäni mahdottomaksi.

Appendix 3

PRIMAARI HYPERPARATYREOOSI JA ELÄMÄNLAATU – TUTKIMUS

Kysymme tämän ensimmäisen elämänlaatukyselyn yhteydessä joitakin tarkentavia tietoja.
Pyydämme Teitä valitsemaan sopivimmat vaihtoehdot:

Henkilötunnus: __________________________

1) Mikä on siviilisäätynne?
   naimaton _____
   avoliitossa _____
   naimisissa _____
   eronnut tai asumuserossa _____
   leski _____

2) Mikä on koulutuksenne (korkein loppuun suoritettu koulutus) ?
   peruskoulu tai vähemmän _____
   ammattikoulu _____
   lukio _____
   opistotasoinen koulutus _____
   ammattikorkeakoulu _____
   yliopisto/korkeakoulu _____

3) Mitä seuraavista oireista Teillä on esiintynyt?
   vatsakivut _____
   nivel- tai luustokivut _____
väsymys _____
masentuneisuus _____
muistihäiriö _____
lihasheikkous _____

4) Kuinka usein nämä oireet häiritsevät Teitä?
viikottain _____ kuukausittain _____ muutaman kuukauden välein _____

5) Jos olette työssä, kuinka paljon oireet vaikuttavat työntekoonne?
en ole työssä _____
merkittävästi _____ jonkin verran _____ eivät lainkaan _____

6) Kuinka paljon oireet häiritsevät vapaa-ajan toimintaanne tai aktiviteettejanne?
merkittävästi _____ jonkin verran _____ eivät lainkaan _____
References


References

anti-parathyroid hormone immunotherapy in a patient with metastatic parathyroid carcinoma”,


"Prospective evaluation of quality of life (SF-36v2) and nonspecific symptoms before and after cure of primary hyperparathyroidism (1-year follow-up)". Surgery, vol. 141, no. 2, pp. 153-9; discussion 159-60.


References


References


References


Thakker, R.V. 2016, "Genetics of parathyroid tumours", *Journal of internal medicine*.


