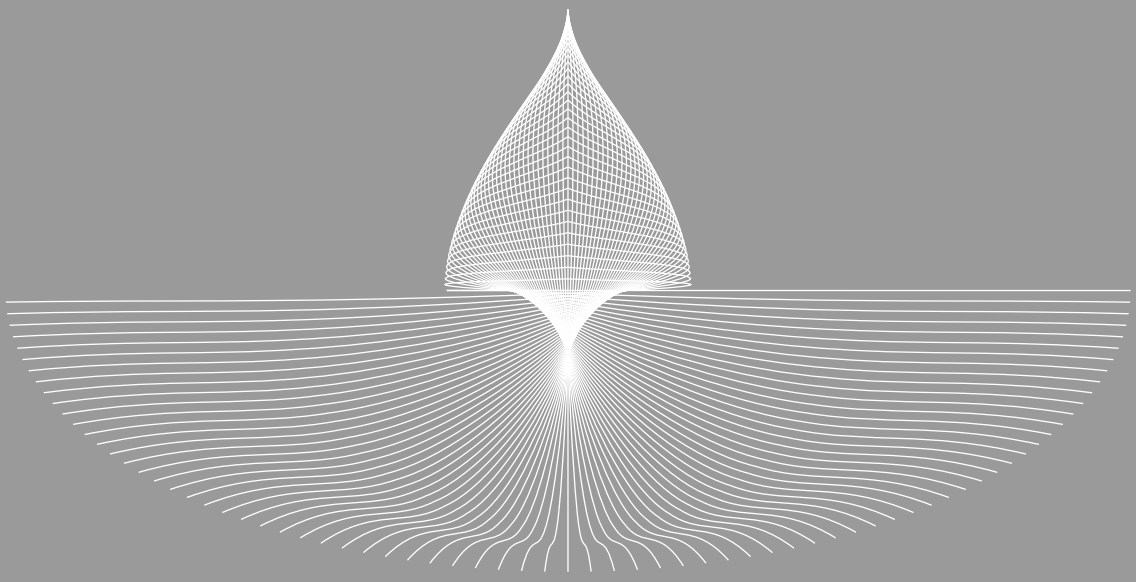
11

General Discussion



CONTENTS

I. Introduction

Primary hyperparathyroidism (PHTP) is the most common cause of hypercalcaemia in the outpatient setting. Over the past few decades, the clinical profile of PHPT has drastically changed from “bones, stones, groans and psychic moans" to an almost asymptomatic disease. Progress in pre-operative localisation studies, surgical techniques and intra-operative PTH (IOPTH) monitoring has increased cure rates following initial surgery for PHPT to 93-100% (1-3). Despite the progress in initial surgery for PHPT, management of persistent and recurrent primary hyperparathyroidism remains a challenge.

In this thesis we report the incidence of persistent PHPT after initial surgery for primary hyperparathyroidism in our hospital over a period of 24 year. We describe the demographic, clinical, biochemical, surgical and pathological characteristics of patients with persistent PHPT after initial parathyroidectomy for sporadic PHPT. In addition, we evaluate the value of pre-operative localisation studies prior to revision surgery and the skeletal and post-operative complications of chronic high circulating levels of PTH. Furthermore we discuss the management of recurrent hyperparathyroidism in parathyroid carcinoma, and the effect of molecular alterations in the *HRPT2* and *CASR* gene on prognosis in these patients.

II. Cure after parathyroidectomy for primary hyperparathyroidism

In primary hyperparathyroidism, surgical removal of all pathological parathyroid tissue is the only approach that provides a definitive and durable cure. Patients who are cured after surgery show a significant postoperative increase in bone mass (4-6), no recurrence of renal stones (4,7) and improvement in various parameters of quality of life compared to patients who had no surgery or unsuccessful surgery (8-12). Cure rate has been reported to be in the range of 94-100% for bilateral neck, as well as less invasive surgery, more than 6 months after parathyroidectomy (PTx) (13-22). Based on these findings, it has become common practice to limit the post-operative follow-up to 6 months. However, in a 5 year follow-up of 91 patients who were successfully operated for PHPT, Westerdahl *et al.* reported a rather high recurrence rate of 4%, which was largely due to previously undiagnosed germline mutations in the *MEN-1* gene and consequent multiple gland pathology (23). In ***Chapter 2*** we set out to evaluate cure rate and its maintenance in the long-term after initial parathyroidectomy in patients with sporadic PHPT who underwent surgery in our hospital in the period between 1984 and 2008. We evaluated the cure at short-term (3 and 6 months) and long-term follow-up (range 1-24 years) in 73 patients with sporadic PHPT. In the process, we also assessed the value of various factors in the prediction of cure in patients with sporadic PHPT.

At the time of first follow-up (within 3 months of surgery), 70 of the 73 patients (96%) had evidence for biochemical cure of hyperparathyroidism (HPTH). At the time of the second post-operative follow-up (6 months after PTx) and the long-term follow-up (range 1-24 years), 68 of the 73 patients (93%) had evidence for biochemical cure. There were no significant differences in gender, age at presentation, clinical presentation, biochemical and pathological findings between patients who achieved and maintained cure and patients with persistence of HPTH after initial PTx. It was of note, that all 5 patients with persistent HPTH had undergone surgery before 2001 and that with the implementation of pre-operative localisation studies and intra-operative PTH (IOPTH) monitoring in the standard care of patients with PHPT, cure rate has increased to 100% since 2001.

Our study provides evidence that 'recurrent' hyperparathyroidism does not occur in sporadic PHPT when cure is established 6 months after parathyroidectomy. This strongly suggests that long-term follow-up of these patients is not necessary. In contrast, close follow-up is advocated within the first 6 months after PTx to definitively establish cure and to enable the identification of those with residual gland pathology and thus persistent hyperparathyroidism.

III. Localisation studies in persistent primary hyperparathyroidism

In ***Chapter 2*** we demonstrated that the use of pre-operative localisation studies increased the cure rate in patients with sporadic PHPT who underwent initial PTx. Before initial bilateral neck surgery preoperative localisation studies are not deemed necessary, because experienced surgeons have, on average, a 98% chance of excising all pathological tissue (22,24). However, localisation studies become mandatory when the surgeon opts for a more focused unilateral or minimally invasive approach and before reoperative parathyroidectomy for persistent hyperparathyroidism, as a second (or more) neck exploration is technically more challenging than initial surgery and may be associated with as much as a threefold increase in morbidity (22,25-27). Limited data suggest that the localizing value of Tc99m-MIBI-SPECT is much lower for the preoperative localisation of residual active parathyroid glands before reoperative parathyroidectomy (28-30).

In ***Chapter 3*** we evaluated the predictive value of Tc99m-MIBI-SPECT in patients with persistent PHPT prior to revision surgery and compared this to the predictive value of this localisation study in patients with sporadic PHPT prior to initial surgery.

Tc99m-MIBI-SPECT was able to detect and accurately localize 61% of the pathological glands removed at initial surgery in patients with sporadic PHPT and 33% of the pathological glands removed at reoperative parathyroidectomy in patients with persistent PHPT. Compared to patients with sporadic PHPT cured after initial surgery, patients with persistent PHPT had a higher proportion of

hyperplastic glands (55% vs. 26%), more ectopically located glands (44% vs. 22%), and smaller pathological gland size (1.21 cm vs. 2.03 cm). We demonstrate that the ability of Tc99m-MIBI-SPECT to detect and accurately localize pathological parathyroid glands was decreased in the case of hyperplasia and a gland diameter <1.5 cm, explaining the decreased diagnostic value of Tc99m-MIBI-SPECT observed in patients with persistent PHPT.

The combined effect of disturbance in the local vascular supply by previous surgery, as well as differences in gland pathology and size ultimately affecting radiopharmaceutical uptake, are likely to lead to the limited ability of the widely used Tc99m-MIBI-SPECT to detect and accurately localize pathological parathyroid glands in patients with persistent hyperparathyroidism before reoperative parathyroidectomy.

Because of the limited diagnostic value of Tc99m-MIBI-SPECT prior to revision surgery for persistent PHPT, we assessed in ***Chapter 4*** whether selective venous sampling (SVS) of parathyroid hormone (PTH) could contribute to a more accurate preoperative localisation of residual hyperactive parathyroid tissue in patients with persistent hyperparathyroidism. The diagnostic value of SVS is based on the assumption that regional drainage of each one of the four parathyroid glands is into the adjacent superior, middle and inferior thyroid veins, respectively (31). Despite potential anatomical variations, SVS is successful in predicting the side of a pathological parathyroid gland in 39-93% of patients with PHPT (31-41) and, more importantly, in 66-75% of patients with negative noninvasive studies (36,37,42). However, the major limitation of SVS is that it pinpoints the area of venous drainage of a hyperactive gland rather than its exact anatomical location.

We evaluated the results of Tc99m-MIBI-SPECT and SVS performed prior to 20 revision surgeries in 18 patients with persistent or recurrent PHPT or with autonomous tertiary hyperparathyroidism (THPT) due to end-stage renal failure. Tc99m-MIBI-SPECT was found to have a sensitivity of 30% compared to a sensitivity of 75% with SVS. SVS was found to accurately localize 10 of the 14 pathological glands (71%) which had been inaccurately localized or completely

missed by Tc99m-MIBI-SPECT, while Tc99m-MIBI-SPECT was only able to localise 1 of the 6 pathological glands (17%) inaccurately localised by SVS. Localising sensitivity was 100% when concordance was achieved between SVS and Tc99m-MIBI-SPECT. In keeping with Tc99m-MIBI-SPECT, the diagnostic value of SVS was also decreased, although to a lesser extent, in the case of hyperplastic parathyroid glands and glands with a diameter of less than 1.5 cm. In contrast to Tc99m-MIBI-SPECT, SVS had a sensitivity of 83% for ectopic parathyroid glands, which are a frequent cause of persistent PHPT. This study also demonstrates that the ability of selective venous sampling for PTH to accurately localize residual hyperactive parathyroid glands in patients with persistent PHPT is significantly higher than that of the non-invasive Tc99m-MIBI-SPECT imaging technique.

These data hold implications for the management of patients with persistent PHPT. From a practical point of view, and in keeping with recent guidelines of the European Association of Nuclear Medicine (43), our data suggest that it is always worth to perform a Tc99m-MIBI-SPECT scan as a first preoperative localisation study in patients with persistent hyperparathyroidism, followed by the invasive, but more reliable, selective venous sampling for PTH technique. Concordance of both techniques leads to a reassuring sensitivity of 100%. Our data clearly suggest that SVS for PTH should be reinstated as a valuable tool in the armamentarium of localisation studies in the pre-operative work-up of patients with persistent hyperparathyroidism.

IV. Complications of the surgical management of primary hyperparathyroidism

High circulating levels of PTH are associated with increased bone turnover in favour of bone resorption leading to mineral depletion and decreased bone mass (44). This effect is achieved by the binding of PTH to its specific receptor (PTHR1) on stromal/osteoblastic cells of the bone marrow, which stimulates the production of RANK ligand and decreases that of its decoy receptor osteoprotegerin (OPG) (45-59). Following successful surgery, the rapid decrease in serum PTH levels and

the pre-operative high bone turnover state, lead to a transient hypocalcaemia, due to increased influx of calcium, phosphate and magnesium into bone. Post-operative, severe and persistent hypocalcaemia is usually due to a "hungry bone syndrome", a syndrome seldom seen in patients with sporadic PHPT. The syndrome is predominantly observed in patients with severe hyperparathyroidism-associated increase in bone turnover, particularly in patients with parathyroid carcinoma. In ***Chapter 5***, we performed a systemic review of the literature on hungry bone syndrome, summarizing its main features and suggestions for its prevention and management.

Although exact numbers are missing, the number of patients who develop hungry bone syndrome is presumed to have largely decreased due to a considerable decrease in the number of patients with clinically evident bone disease, such as osteitis fibrosa cystica, due to the earlier detection of mostly asymptomatic PHPT by routine calcium screening (60,61). An older age at diagnosis, radiological evidence of PHPT-related bone disease, and greater weight/volume of the resected parathyroid glands have been reported to be risk factors associated with the development of a post-operative hungry bone syndrome. There are scarce data on the best means to treat, minimize or prevent this severe complication of parathyroidectomy. Treatment of the hungry bone syndrome is aimed in the short term primarily at replenishing the circulating calcium deficit caused by the increased calcium utilisation to refill the multiple resorption cavities. In the longer term, treatment is aimed at restoring calcium homeostasis by substituting the temporarily missing stimulatory effect of PTH on the 1α-hydroxylase enzyme by providing the active form of vitamin D to ensure adequate intestinal absorption of calcium (61-66). Pre-operative normalisation of bone turnover with the use of bisphosphonates and pre-operative $1,25(OH)_2D$ supplementation are useful options to prevent the hungry bone syndrome, but there are no available prospective data to confirm this premise (60,67-72).

V. Aspects of osteocyte function in primary hyperparathyroidism

The PTH/PTHrP receptor (PTHR1) is also present on osteocytes (73). Recent *in vitro* and animal studies suggest that binding of PTH to the PTHR1 on osteocytes leads to inhibition of the expression of the *SOST* gene (74-77). This gene encodes sclerostin, a protein exclusively expressed in osteocytes in the skeleton (78), which decreases bone formation by binding to LRP5/6, resulting in inhibition of the Wnt signaling pathway in osteoblasts (79,80). To evaluate whether chronic PTH excess has similar effects on sclerostin secretion in humans as in animal models, we tested the hypothesis that chronic hypersecretion of PTH, as seen in PHPT, may decrease sclerostin secretion, and that PTH may thus represent a potential regulator of sclerostin production in humans in ***Chapter 6***.

To this effect, we measured sclerostin in serum of 34 patients with untreated, persistent, or recurrent PHPT and in 54 patients cured after successful parathyroidectomy for PHPT (EuPTH). Mean serum sclerostin level of patients with PHPT (30.5 pg/ml, 95% CI: 26.0-35.1) was significantly lower than that of patients with EuPTH (45.4 pg/ml, 95% CI: 40.5-50.2; $P<0.001$). There was a negative correlation between serum sclerostin and PTH concentrations when all patients were pooled together ($r= -0.44$, $P<0.001$).

Data from our study demonstrate that in humans, chronic PTH excess, as observed in patients with PHPT, is associated with a significant decrease in circulating sclerostin levels and that there is a significant negative correlation between PTH and serum sclerostin levels. Taken together, these results suggest that, similar to the case in animal models (74-77), PTH has a regulatory role on sclerostin production also in humans. The functional significance of circulating sclerostin is as yet to be established.

Recent *in vitro* studies have also shown that binding of PTH to the PTHR1 on osteocytes upregulates Fibroblast Growth Factor 23 (FGF23) mRNA expression (81,82). FGF23 is believed to be the major player in the bone-kidney axis controlling phosphate homeostasis. FGF23 acts as a phosphaturic factor by the

same mechanism of action as PTH, by down regulating the cotransporters NaPi2a and NaPi2c in the proximal tubules of the kidney after binding to its receptor, FGFR-1, in the presence of Klotho (83,84). FGF23 also decreases $1,25(OH)_2D$ synthesis in the proximal tubules by direct inhibition of the 1α-hydroxylase enzyme (83-85). In patients with PHPT, data on the relationship between PTH and FGF23 are scarce and not always concordant. Compared to healthy controls, circulating FGF23 levels have been found to be elevated in patients with PHPT before parathyroidectomy (86,87) and to decrease immediately post-operatively (87), supporting the notion that PTH stimulates FGF23 secretion. The aim of the study described in ***Chapter 7*** was to address the relationship between PTH and FGF23 in patients with PHPT and in patients cured after successful parathyroidectomy for PHPT.

We measured serum intact FGF23 in 22 patients with untreated, persistent, or recurrent PHPT and in 24 patients cured after successful parathyroidectomy for PHPT (EuPTH). Mean serum FGF23 concentration was significantly higher in patients with PHPT than in EuPTH patients (50.4 ± 27.2 pg/ml vs. 33.1 ± 12.5 pg/ml, P=0.01). There was a positive correlation between PTH and FGF23 levels (r=0.362, P=0.01), and this relationship was sustained and more pronounced after correction for $1,25(OH)_2D$ levels (r=0.422, P=0.01). In patients with PHPT, there was a significant negative correlation between FGF23 and $1,25(OH)_2D$ (r= −0.780, P<0.01). This relationship remained significant albeit less marked in EuPTH patients (r= −0.519, P=0.02).

In conclusion, we demonstrate that FGF23 production is increased in the presence of high circulating PTH levels and that this increase is reversible after the euparathyroid state is achieved following successful PTx. We further demonstrate a significant negative relationship between FGF23 and $1,25(OH)_2D$ levels, which is more pronounced in patients with PHPT. Based on the more pronounced negative relationship between FGF23 and $1,25(OH)_2D$ in PHPT patients, we propose that the PTH-induced increase in FGF23 levels may be an adaptive mechanism to maintain serum phosphate levels within normal limits by counteracting the potentially deleterious $1,25(OH)_2D$-induced phosphate retention.

The findings that PTH inhibits sclerostin production and stimulates FGF23 production demonstrate that the actions of PTH on bone are more complex than previously suggested, involving a variety of signaling pathways within bone itself, but also in the parathyroid-bone-kidney axis. Despite the significant progress in our understanding of the actions of PTH on bone, it should be appreciated that the cellular and molecular actions of PTH have only been partially unraveled and studies are needed to further elucidate these actions.

VI. Clinical and molecular aspects of parathyroid carcinoma

Surgical and medical advances have secured longer survival in patients with parathyroid carcinoma. To illustrate this point, we report in ***Chapter 8*** the case of a patient with metastatic parathyroid carcinoma with a follow up spanning 17 years. We also review all original case reports and case series on patients with parathyroid carcinoma, who fulfill the WHO criteria for this malignancy who had been followed-up for at least 6 months after initial parathyroidectomy, which were published in the English literature since the last large review on this topic in 2001 (88).

Data from our case are in keeping with those obtained from our review of the literature on this topic, showing that radical initial surgery is of paramount importance to prevent local seeding of tumor tissue, thereby not only increasing disease-free survival and survival, but also decreasing the chance of having to undergo re-operative surgery. Invasive growth of tumor tissue in adjacent structures, such as the recurrent laryngeal nerve or esophagus, increases the morbidity associated with re-operative surgery in patients with parathyroid carcinoma. The increasing morbidity associated with repeated surgical interventions has led to the search for other treatment options for this malignancy, such as radiotherapy, chemotherapy, radiofrequency (RF) ablation, embolization, use of the calcimimetic Cinacalcet and that of PTH immunisation. Parathyroid tumors are relatively resistant to chemotherapy and radiotherapy (88-93) and the use of both therapies has significantly decreased over the last 10 years. Successful embolization

has only been described in combination with RF ablation (94) and was unsuccessful in our patient, while RF ablation has been shown to be successful in 3 cases (95-97) as well as in our patient. The eventual inability to control hypercalcaemia is associated with increased bone turnover with an increased risk of fractures and with fatal renal and cardiovascular complications (89,90,98,99). When attempts at reducing tumor load are not successful, intensive rehydration, use of medications such as bisphosphonates and calcimimetics and use of dialysis are used with variable results. A potential non-invasive option is PTH immunisation, although experience with this approach is still limited (100-102).

In conclusion, the long-term management of patients with metastatic parathyroid carcinoma remains indeed a daunting task, despite all recent imaging, surgical and medical advances.

Several genes have been discovered to play a role in the etiology of PHPT among which are the *MEN-1*, *HRPT2/CDC73* and *CASR* genes. Mutations in the *HRPT2/CDC73* gene, which encodes for the protein parafibromin (103), are associated with the hyperparathyroidism-jaw tumor syndrome (HPT-JT; OMIM 607393). Patients with a HPT-JT syndrome have a 15-24% chance of developing parathyroid carcinoma (88,104-106). In patients with the HPT-JT syndrome, as well as patients with sporadic carcinoma, downregulation of the calcium sensing receptor (CASR) was also discovered (107). Moreover, downregulation of CASR expression, mutations in the *HRPT2/CDC73* gene and loss of its protein, parafibromin, have been shown to be valuable markers to assist in establishing a diagnosis of parathyroid carcinoma. There are, however, no available data on the prognostic value of these markers in parathyroid carcinoma. In ***Chapter 9*** we evaluated the prognostic value of downregulation of CASR expression, loss of parafibromin staining and the presence of mutations in the *HRPT2/CDC73* gene in patients with a WHO criteria based diagnosis of parathyroid carcinoma.

We determined the disease-free survival and overall survival in 23 patients who had initial surgery for parathyroid carcinoma in various hospitals in the Netherlands in the period 1985-2000. Resected primary parathyroid carcinomas of all 23 patients

had previously undergone *HRPT2/CDC73* and *MEN-1* gene mutations analysis (108) and parafibromin and CASR staining analysis (104,109).

The 5-year disease-free survival and the 5-year overall survival were lower in patients with downregulation of CASR expression compared to patients with normal CASR expression (81% vs. 0% and 94% vs. 29%, respectively). Both the 5-year disease-free survival (73% vs. zero) and the 5-year overall survival (79% vs. 50%) were lower in patients with a *HRPT2/CDC73* mutation compared to patients without this mutation. Both the 5-year disease-free survival (89% vs. 41%) and the 5-year overall survival (100% vs. 57%*)* were lower in patients with global parafibromin loss compared to patients with focal parafibromin loss. The risk of developing a local or distant metastasis was 16-fold increased in the case of downregulation of CASR expression, 7-fold increased in the case of *HRPT2/CDC73* mutations and also 7-fold increased in the case of global parafibromin loss. The 5-year disease-free survival and the 5-year overall survival were lower in patients with somatic *MEN-1* mutations compared to patients without this mutation (respectively 64% vs. 33% and 80% vs. 33%), but somatic *MEN-1* mutations were not associated with a significant increased risk of developing a local recurrence and/or distant metastasis.

Findings from this study hold several clinical implications. Firstly, downregulation of CASR, *HRPT2/CDC73* mutations and global loss of parafibromin are strong negative determinants of the malignant potential of parathyroid carcinomas. Secondly, the finding of somatic *MEN-1* mutations in patients with parathyroid carcinoma, suggests that these mutations could play a role in parathyroid carcinogenesis, although they do not influence the prognosis of parathyroid carcinoma. Thirdly, evaluation of CASR expression may also serve to determine whether calcimimetics may play a role in the therapeutic management of patients with parathyroid carcinoma.

On the basis of the findings described in ***Chapter 9***, we advocate the use of the assessment of downregulation of CASR, *HRPT2/CDC73* mutations and global loss of parafibromin not only as diagnostic tools but also as prognostic tools in the management of patients with parathyroid carcinoma.

VII. Management of patients with persistent primary hyperparathyroidism

The management of patients with persistent sporadic PHPT represents a significant clinical challenge, which requires a multidisciplinary approach. In ***Chapter 10*** we report in a case serie, the demographic, clinical, biochemical, surgical and pathological characteristics of patients with persistent PHPT after initial parathyroidectomy for sporadic PHPT.

Our data suggest that the most common causes of persistent hyperparathyroidism are a missed ectopic gland at initial surgery (33%) and missed multiglandular disease (15%). We documented parathyromatosis in 9% of patients. Pre-operative localisation studies had poor sensitivity: ultrasound 18%, Tc99m-MIBI-SPECT 25%, CT 30%, MRI 20%. In contrast, selective venous sampling for PTH had a sensitivity of 50% and a specificity of 89%. The decrease in intraoperative PTH was significantly less marked in patients in whom hyperparathyroidism persisted compared to those who achieved cure (63 ± 26 vs. 89 ± 11%, P=0.003). The risk of complications increased with each subsequent surgery: 20% after first, 50% after 2nd and 67% after 3rd surgery.

Our findings from this case series indicate that the management of patients with persistent PHPT is complex and challenging. When initial surgery fails to achieve cure, each reoperation jeopardizes the ability of localisation studies to accurately localise residual hyperactive parathyroid glands and increases the risk of complications in its own right because of distortion and scarring of surgical planes as a result of previous interventions. In these patients, re-operation should be carefully planned and attempts at surgery strongly discouraged if a clear localisation of hyperactive tissue is not secured pre-operatively.

VIII. Summary

- In patients with sporadic PHPT, the rate of persistence after initial PTx is 7% and that of recurrence none.

- In the case of persistent PHPT, the sensitivity of the widely used, non-invasive Tc99m-MIBI-SPECT imaging technique is decreased and is significantly lower than that of the invasive technique of selective venous sampling for PTH.
- Chronic excess of PTH has a catabolic effect on bone, leading to mineral depletion of bone. Patients with pre-operative radiological signs of severe PTH-associated bone disease are at risk of developing hungry bone syndrome after surgery, which may be prevented by pre-operative treatment with bisphosphonates and 1,25(OH)2D.
- PTH inhibits sclerostin production and stimulates FGF23 production, presumably to counterbalance its own actions on bone and on 1,25(OH)2D, resulting in novel feedback loops.
- In contrast to sporadic PHPT, recurrent PHPT does occur in patients with parathyroid carcinoma. In these patients, downregulation of CASR, *HRPT2/CDC73* mutations and global loss of parafibromin are strong negative determinants of the disease-free survival and overall survival.
- Recent progresses in surgical and medical treatment of patients with parathyroid carcinoma have made it possible to secure longer survival, even in patients with tumors demonstrating 2 of the 3 identified molecular negative prognostic factors.

REFERENCES

1. Calva-Cerqueira D, Smith BJ, Hostetler ML, Lal G, Menda Y, O'Dorisio TM, Howe JR. Minimally invasive parathyroidectomy and preoperative MIBI scans: correlation of gland weight and preoperative PTH. J Am Coll Surg 2007;205(4 Suppl):S38-S44.
2. Palmer RM, Lokey JS. Is minimally invasive parathyroidectomy reasonable in the nonuniversity setting? Am J Surg 2006;192(6):865-868.
3. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. Ann Surg 2002;236(5):543-551.
4. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, Udesky J et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab 2008;93(9):3462-3470.
5. Hagstrom E, Lundgren E, Mallmin H, Rastad J, Hellman P. Positive effect of parathyroidectomy on bone mineral density in mild asymptomatic primary hyperparathyroidism. J Intern Med 2006;259(2):191-198.
6. Nomura R, Sugimoto T, Tsukamoto T, Yamauchi M, Sowa H, Chen Q, Yamaguchi T et al. Marked and sustained increase in bone mineral density after parathyroidectomy in patients with primary hyperparathyroidism; a six-year longitudinal study with or without parathyroidectomy in a Japanese population. Clin Endocrinol (Oxf) 2004;60(3):335-342.
7. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med 1999;341(17):1249-1255.
8. Talpos GB, Bone HG, III, Kleerekoper M, Phillips ER, Alam M, Honasoge M, Divine GW et al. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. Surgery 2000;128(6):1013-1020.
9. Mihai R, Sadler GP. Pasieka's parathyroid symptoms scores correlate with SF-36 scores in patients undergoing surgery for primary hyperparathyroidism. World J Surg 2008;32(5):807-814.
10. Coker LH, Rorie K, Cantley L, Kirkland K, Stump D, Burbank N, Tembreull T et al. Primary hyperparathyroidism, cognition, and health-related quality of life. Ann Surg 2005;242(5):642-650.
11. Pasieka JL, Parsons LL. Prospective surgical outcome study of relief of symptoms following surgery in patients with primary hyperparathyroidism. World J Surg 1998;22(6):513-518.
12. Adler JT, Sippel RS, Schaefer S, Chen H. Preserving function and quality of life after thyroid and parathyroid surgery. Lancet Oncol 2008;9(11):1069-1075.
13. Chiu B, Sturgeon C, Angelos P. What is the link between nonlocalizing sestamibi scans, multigland disease, and persistent hypercalcemia? A study of 401 consecutive patients undergoing parathyroidectomy. Surgery 2006;140(3):418-422.
14. Calva-Cerqueira D, Smith BJ, Hostetler ML, Lal G, Menda Y, O'Dorisio TM, Howe JR. Minimally invasive parathyroidectomy and preoperative MIBI scans: correlation of gland weight and preoperative PTH. J Am Coll Surg 2007;205(4 Suppl):S38-S44.
15. Jones JM, Russell CF, Ferguson WR, Laird JD. Pre-operative sestamibi-technetium subtraction scintigraphy in primary hyperparathyroidism: experience with 156 consecutive patients. Clin Radiol 2001;56(7):556-559.
16. Palmer RM, Lokey JS. Is minimally invasive parathyroidectomy reasonable in the nonuniversity setting? Am J Surg 2006;192(6):865-868.
17. Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. Ann Surg 2002;236(5):543-551.
18. Westerdahl J, Bergenfelz A. Sestamibi scan-directed parathyroid surgery: potentially high failure rate without measurement of intraoperative parathyroid hormone. World J Surg 2004;28(11):1132-1138.

19. Moka D, Voth E, Dietlein M, Larena-Avellaneda A, Schicha H. Technetium 99m-MIBI-SPECT: A highly sensitive diagnostic tool for localization of parathyroid adenomas. Surgery 2000;128(1):29-35.
20. Goldstein RE, Billheimer D, Martin WH, Richards K. Sestamibi scanning and minimally invasive radioguided parathyroidectomy without intraoperative parathyroid hormone measurement. Ann Surg 2003;237(5):722-730.
21. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 2002;235(5):665-670.
22. Ruda JM, Hollenbeak CS, Stack BC, Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg 2005;132(3):359-372.
23. Westerdahl J, Bergenfelz A. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: five-year follow-up of a randomized controlled trial. Ann Surg 2007;246(6):976-980.
24. Simental A, Ferris RL. Reoperative parathyroidectomy. Otolaryngol Clin North Am 2008;41(6):1269-74, xii.
25. Shen W, Duren M, Morita E, Higgins C, Duh QY, Siperstein AE, Clark OH. Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg 1996;131(8):861-867.
26. Hasse C, Sitter H, Brune M, Wollenteit I, Nies C, Rothmund M. Quality of life and patient satisfaction after reoperation for primary hyperparathyroidism: analysis of long-term results. World J Surg 2002;26(8):1029-1036.
27. Gough I. Reoperative parathyroid surgery: the importance of ectopic location and multigland disease. ANZ J Surg 2006;76(12):1048-1050.
28. Rotstein L, Irish J, Gullane P, Keller MA, Sniderman K. Reoperative parathyroidectomy in the era of localization technology. Head Neck 1998;20(6):535-539.
29. Chen CC, Skarulis MC, Fraker DL, Alexander R, Marx SJ, Spiegel AM. Technetium-99m-sestamibi imaging before reoperation for primary hyperparathyroidism. J Nucl Med 1995;36(12):2186-2191.
30. Fayet P, Hoeffel C, Fulla Y, Legmann P, Hazebroucq V, Luton JP, Chapuis Y et al. Technetium-99m sestamibi scintigraphy, magnetic resonance imaging and venous blood sampling in persistent and recurrent hyperparathyroidism. Br J Radiol 1997;70(833):459-464.
31. Dunlop DA, Papapoulos SE, Lodge RW, Fulton AJ, Kendall BE, O'Riordan JL. Parathyroid venous sampling: anatomic considerations and results in 95 patients with primary hyperparathyroidism. Br J Radiol 1980;53(627):183-191.
32. Reidel MA, Schilling T, Graf S, Hinz U, Nawroth P, Buchler MW, Weber T. Localization of hyperfunctioning parathyroid glands by selective venous sampling in reoperation for primary or secondary hyperparathyroidism. Surgery 2006;140(6):907-913.
33. Mariette C, Pellissier L, Combemale F, Quievreux JL, Carnaille B, Proye C. Reoperation for persistent or recurrent primary hyperparathyroidism. Langenbecks Arch Surg 1998;383(2):174-179.
34. Nilsson BE, Tisell LE, Jansson S, Zackrisson BF, Lindstedt G, Lundberg PA. Parathyroid localization by catheterization of large cervical and mediastinal veins to determine serum concentrations of intact parathyroid hormone. World J Surg 1994;18(4):605-610.
35. Jaskowiak N, Norton JA, Alexander HR, Doppman JL, Shawker T, Skarulis M, Marx S et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. Ann Surg 1996;224(3):308-320.
36. Jones JJ, Brunaud L, Dowd CF, Duh QY, Morita E, Clark OH. Accuracy of selective venous sampling for intact parathyroid hormone in difficult patients with recurrent or persistent hyperparathyroidism. Surgery 2002;132(6):944-950.
37. Sugg SL, Fraker DL, Alexander R, Doppman JL, Miller DL, Chang R, Skarulis MC et al. Prospective evaluation of selective venous sampling for parathyroid hormone concentration in patients undergoing reoperations for primary hyperparathyroidism. Surgery 1993;114(6):1004-1009.
38. Yen TW, Wang TS, Doffek KM, Krzywda EA, Wilson SD. Reoperative parathyroidectomy: an algorithm for imaging and monitoring of intraoperative parathyroid hormone levels that results in a successful focused approach. Surgery 2008;144(4):611-619.

39. Estella E, Leong MS, Bennett I, Hartley L, Wetzig N, Archibald CA, Harper JS et al. Parathyroid hormone venous sampling prior to reoperation for primary hyperparathyroidism. ANZ J Surg 2003;73(10):800-805.
40. Satava RM, Jr., Beahrs OH, Scholz DA. Success rate of cervical exploration for hyperparathyroidism. Arch Surg 1975;110(5):625-628.
41. Hessman O, Stalberg P, Sundin A, Garske U, Rudberg C, Eriksson LG, Hellman P et al. High success rate of parathyroid reoperation may be achieved with improved localization diagnosis. World J Surg 2008;32(5):774-781.
42. Clark OH, Okerlund MD, Moss AA, Stark D, Norman D, Newton TH, Duh QY et al. Localization studies in patients with persistent or recurrent hyperparathyroidism. Surgery 1985;98(6):1083-1094.
43. Hindie E, Ugur O, Fuster D, O'Doherty M, Grassetto G, Urena P, Kettle A et al. 2009 EANM parathyroid guidelines. Eur J Nucl Med Mol Imaging 2009;36(7):1201-1216.
44. Mosekilde L. Primary hyperparathyroidism and the skeleton. Clin Endocrinol (Oxf) 2008;69(1):1-19.
45. Huang JC, Sakata T, Pfleger LL, Bencsik M, Halloran BP, Bikle DD, Nissenson RA. PTH differentially regulates expression of RANKL and OPG. J Bone Miner Res 2004;19(2):235-244.
46. Lee SK, Lorenzo JA. Parathyroid hormone stimulates TRANCE and inhibits osteoprotegerin messenger ribonucleic acid expression in murine bone marrow cultures: correlation with osteoclast-like cell formation. Endocrinology 1999;140(8):3552-3561.
47. Locklin RM, Khosla S, Turner RT, Riggs BL. Mediators of the biphasic responses of bone to intermittent and continuously administered parathyroid hormone. J Cell Biochem 2003;89(1):180-190.
48. Ma YL, Cain RL, Halladay DL, Yang X, Zeng Q, Miles RR, Chandrasekhar S et al. Catabolic effects of continuous human PTH (1--38) in vivo is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation. Endocrinology 2001;142(9):4047-4054.
49. Hamdy NA. Denosumab: RANKL inhibition in the management of bone loss. Drugs Today (Barc) 2008;44(1):7-21.
50. Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 2004;292(4):490-495.
51. Udagawa N, Takahashi N, Yasuda H, Mizuno A, Itoh K, Ueno Y, Shinki T et al. Osteoprotegerin produced by osteoblasts is an important regulator in osteoclast development and function. Endocrinology 2000;141(9):3478-3484.
52. Fu Q, Jilka RL, Manolagas SC, O'Brien CA. Parathyroid hormone stimulates receptor activator of NFkappa B ligand and inhibits osteoprotegerin expression via protein kinase A activation of cAMP-response element-binding protein. J Biol Chem 2002;277(50):48868-48875.
53. Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, Elliott R et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93(2):165-176.
54. Jimi E, Akiyama S, Tsurukai T, Okahashi N, Kobayashi K, Udagawa N, Nishihara T et al. Osteoclast differentiation factor acts as a multifunctional regulator in murine osteoclast differentiation and function. J Immunol 1999;163(1):434-442.
55. Stilgren LS, Rettmer E, Eriksen EF, Hegedus L, Beck-Nielsen H, Abrahamsen B. Skeletal changes in osteoprotegerin and receptor activator of nuclear factor-kappab ligand mRNA levels in primary hyperparathyroidism: effect of parathyroidectomy and association with bone metabolism. Bone 2004;35(1):256-265.
56. Kudlacek S, Schneider B, Woloszczuk W, Pietschmann P, Willvonseder R. Serum levels of osteoprotegerin increase with age in a healthy adult population. Bone 2003;32(6):681-686.
57. Nakagawa N, Kinosaki M, Yamaguchi K, Shima N, Yasuda H, Yano K, Morinaga T et al. RANK is the essential signaling receptor for osteoclast differentiation factor in osteoclastogenesis. Biochem Biophys Res Commun 1998;253(2):395-400.
58. Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S, Tomoyasu A et al. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci U S A 1998;95(7):3597-3602.

59. Hamdy NA. Targeting the RANK/RANKL/OPG signaling pathway: a novel approach in the management of osteoporosis. Curr Opin Investig Drugs 2007;8(4):299-303.
60. Graal MB, Wolffenbuttel BH. Consequences of long-term hyperparathyroidism. Neth J Med 1998;53(1):37-42.
61. Natsui K, Tanaka K, Suda M, Yasoda A, Shigeno C, Konishi J, Nakao K. Oxyphil parathyroid adenoma associated with primary hyperparathyroidism and marked post-operative hungry bone syndrome. Intern Med 1996;35(7):545-549.
62. Zamboni WA, Folse R. Adenoma weight: a predictor of transient hypocalcemia after parathyroidectomy. Am J Surg 1986;152(6):611-615.
63. Falko JM, Bush CA, Tzagournis M, Thomas FB. Case report. Congestive heart failure complicating the hungry bone syndrome. Am J Med Sci 1976;271(1):85-89.
64. Jones CT, Sellwood RA, Evanson JM. Symptomatic hypomagnesaemia after parathyroidectomy. Br Med J 1973;3(5876):391-392.
65. Ahuja MM, Chopra IJ. Coexistent hyperthyroidism and hyperparathyroidism. Metabolism 1968;17(10):854-866.
66. Davies DR, Friedman M. Complications after parathyroidectomy. Fractures from low calcium and magnesium convulsions. J Bone Joint Surg Br 1966;48(1):117-126.
67. Brasier AR, Nussbaum SR. Hungry bone syndrome: clinical and biochemical predictors of its occurrence after parathyroid surgery. Am J Med 1988;84(4):654-660.
68. Brossard JH, Garon J, Lepage R, Gascon-Barre M, D'Amour P. Inhibition of 1,25(OH)2D production by hypercalcemia in osteitis fibrosa cystica: influence on parathyroid hormone secretion and hungry bone disease. Bone Miner 1993;23(1):15-26.
69. Boyle IT, Fogelman I, Boyce B, Thomson JE, Beastall GH, McIntosh WB, McLennan I. 1alpha-hydroxyvitamin D3 in primary hyperparathyroidism. Clin Endocrinol (Oxf) 1977;7 Suppl:215s-222s.:215s-222s.
70. Kumar A, Ralston SH. Bisphosphonates prevent the hungry bone syndrome. Nephron 1996;74(4):729.
71. Malabu UH, Founda MA. Primary hyperparathyroidism in Saudi Arabia: a review of 46 cases. Med J Malaysia 2007;62(5):394-397.
72. Lee IT, Sheu WH, Tu ST, Kuo SW, Pei D. Bisphosphonate pretreatment attenuates hungry bone syndrome postoperatively in subjects with primary hyperparathyroidism. J Bone Miner Metab 2006;24(3):255-258.
73. Galitzer H, Ben-Dov I, Lavi-Moshayoff V, Naveh-Many T, Silver J. Fibroblast growth factor 23 acts on the parathyroid to decrease parathyroid hormone secretion. Current Opinion in Nephrology and Hypertension 2008;17(4):363-367.
74. Bellido T, Ali AA, Gubrij I, Plotkin LI, Fu Q, O'Brien CA, Manolagas SC et al. Chronic elevation of parathyroid hormone in mice reduces expression of sclerostin by osteocytes: a novel mechanism for hormonal control of osteoblastogenesis. Endocrinology 2005;146(11):4577-4583.
75. Keller H, Kneissel M. SOST is a target gene for PTH in bone. Bone 2005;37(2):148-158.
76. O'Brien CA, Plotkin LI, Galli C, Goellner JJ, Gortazar AR, Allen MR, Robling AG et al. Control of bone mass and remodeling by PTH receptor signaling in osteocytes. PLoS One 2008;3(8):e2942.
77. Silvestrini G, Ballanti P, Leopizzi M, Sebastiani M, Berni S, Di VM, Bonucci E. Effects of intermittent parathyroid hormone (PTH) administration on SOST mRNA and protein in rat bone. J Mol Histol 2007;38(4):261-269.
78. van Bezooijen RL, Roelen BA, Visser A, van dW-P, de WE, Karperien M, Hamersma H et al. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. J Exp Med 2004;199(6):805-814.
79. Li X, Zhang Y, Kang H, Liu W, Liu P, Zhang J, Harris SE et al. Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem 2005;280(20):19883-19887.
80. Ellies DL, Viviano B, McCarthy J, Rey JP, Itasaki N, Saunders S, Krumlauf R. Bone density ligand, Sclerostin, directly interacts with LRP5 but not LRP5G171V to modulate Wnt activity. J Bone Miner Res 2006;21(11):1738-1749.
81. Rhee Y, Farrow E, Lee R, Bivi N, Lazcano V, Plotkin L, White K et al. FGF23 expression is upregulated by PTH receptor activation in osteocytes in vitro and in vivo: a parathyroid-bone link influencing the endocrine function of osteocytes. J Bone Miner Res 2009;24(S1).

82. Lavi-Moshayoff V, Wasserman G, Meir T, Silver J, Naveh-Many T. PTH increases FGF23 gene expression and mediates the high FGF23 levels of experimental kidney failure: a bone parathyroid feedback loop. American Journal of Physiology Renal Physiology 2010.
83. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. The Journal of Clinical Investigation 2008;118(12):3820-3828.
84. Liu S, Gupta A, Quarles LD. Emerging role of fibroblast growth factor 23 in a bone-kidney axis regulating systemic phosphate homeostasis and extracellular matrix mineralization. Current Opinion in Nephrology and Hypertension 2007;16(4):329-335.
85. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 2004;19(3):429-435.
86. Yamashita H, Yamashita T, Miyamoto M, Shigematsu T, Kazama JJ, Shimada T, Yamazaki Y et al. Fibroblast growth factor (FGF)-23 in patients with primary hyperparathyroidism. European Journal of Endocrinology 2004;151(1):55-60.
87. Kobayashi K, Imanishi Y, Miyauchi A, Onoda N, Kawata T, Tahara H, Goto H et al. Regulation of plasma fibroblast growth factor 23 by calcium in primary hyperparathyroidism. European Journal of Endocrinology 2006;154(1):93-99.
88. Shane E. Clinical review 122: Parathyroid carcinoma. J Clin Endocrinol Metab 2001;86(2):485-493.
89. Shane E, Bilezikian JP. Parathyroid carcinoma: a review of 62 patients. Endocr Rev 1982;3(2):218-226.
90. Wynne AG, van HJ, Carney JA, Fitzpatrick LA. Parathyroid carcinoma: clinical and pathologic features in 43 patients. Medicine (Baltimore) 1992;71(4):197-205.
91. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. Cancer 1973;31(3):600-605.
92. August DA, Flynn SD, Jones MA, Bagwell CB, Kinder BK. Parathyroid carcinoma: the relationship of nuclear DNA content to clinical outcome. Surgery 1993;113(3):290-296.
93. Chow E, Tsang RW, Brierley JD, Filice S. Parathyroid carcinoma--the Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys 1998;41(3):569-572.
94. Artinyan A, Guzman E, Maghami E, Al-Sayed M, D'Apuzzo M, Wagman L, Kim J. Metastatic parathyroid carcinoma to the liver treated with radiofrequency ablation and transcatheter arterial embolization. J Clin Oncol 2008;26(24):4039-4041.
95. Iguchi T, Yasui K, Hiraki T, Gobara H, Mimura H, Sato S, Fujiwara H et al. Radiofrequency ablation of functioning lung metastases from parathyroid carcinoma. J Vasc Interv Radiol 2008;19(3):462-464.
96. Tochio M, Takaki H, Yamakado K, Uraki J, Kashima M, Nakatsuka A, Takao M et al. A case report of 20 lung radiofrequency ablation sessions for 50 lung metastases from parathyroid carcinoma causing hyperparathyroidism. Cardiovasc Intervent Radiol 2010;33(3):657-659.
97. Hiraki T, Sakurai J, Tsuda T, Gobara H, Sano Y, Mukai T, Hase S et al. Risk factors for local progression after percutaneous radiofrequency ablation of lung tumors: evaluation based on a preliminary review of 342 tumors. Cancer 2006;107(12):2873-2880.
98. Kebebew E. Parathyroid carcinoma. Curr Treat Options Oncol 2001;2(4):347-354.
99. Kebebew E, Arici C, Duh QY, Clark OH. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. Arch Surg 2001;136(8):878-885.
100. Betea D, Bradwell AR, Harvey TC, Mead GP, Schmidt-Gayk H, Ghaye B, Daly AF et al. Hormonal and biochemical normalization and tumor shrinkage induced by anti-parathyroid hormone immunotherapy in a patient with metastatic parathyroid carcinoma. J Clin Endocrinol Metab 2004;89(7):3413-3420.
101. Bradwell AR, Harvey TC. Control of hypercalcaemia of parathyroid carcinoma by immunisation. Lancet 1999;353(9150):370-373.
102. Horie I, Ando T, Inokuchi N, Mihara Y, Miura S, Imaizumi M, Usa T et al. First Japanese Patient Treated with Parathyroid Hormone Peptide Immunization for Refractory Hypercalcemia Caused by Metastatic Parathyroid Carcinoma. Endocr J 2010.
103. Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, Simonds WF et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet 2002;32(4):676-680.

104. Tan MH, Morrison C, Wang P, Yang X, Haven CJ, Zhang C, Zhao P et al. Loss of parafibromin immunoreactivity is a distinguishing feature of parathyroid carcinoma. Clin Cancer Res 2004;10(19):6629-6637.
105. Iacobone M, Masi G, Barzon L, Porzionato A, Macchi V, Ciarleglio FA, Palu G et al. Hyperparathyroidism-jaw tumor syndrome: a report of three large kindred. Langenbecks Arch Surg 2009;394(5):817-825.
106. Marx SJ, Simonds WF, Agarwal SK, Burns AL, Weinstein LS, Cochran C, Skarulis MC et al. Hyperparathyroidism in hereditary syndromes: special expressions and special managements. J Bone Miner Res 2002;17 Suppl 2:N37-N43.
107. Haven CJ, Howell VM, Eilers PH, Dunne R, Takahashi M, van PM, Furge K et al. Gene expression of parathyroid tumors: molecular subclassification and identification of the potential malignant phenotype. Cancer Res 2004;64(20):7405-7411.
108. Haven CJ, van PM, Tan MH, Teh BT, Fleuren GJ, van WT, Morreau H. Identification of MEN1 and HRPT2 somatic mutations in paraffin-embedded (sporadic) parathyroid carcinomas. Clin Endocrinol (Oxf) 2007;67(3):370-376.
109. Haven CJ, van PM, Karperien M, Fleuren GJ, Morreau H. Differential expression of the calcium sensing receptor and combined loss of chromosomes 1q and 11q in parathyroid carcinoma. J Pathol 2004;202(1):86-94.