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Hyperparathyroidism-Jaw Tumor Syndrome: Results of surgical management

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Abstract

Background—Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare autosomal dominant disease secondary to germline inactivating mutations of the tumor suppressor gene *HRPT2/CDC73*. The aim of the present study is to determine the optimal surgical approach to parathyroid disease in patients with HPT-JT.

Method—A retrospective analysis of clinical and genetic features, parathyroid operative outcomes, and disease outcomes in seven unrelated HPT-JT families.

Results—Seven families had five distinct germline *HRPT2/CDC73* mutations. Sixteen affected family members (median age of 30.7 years) were diagnosed with primary hyperparathyroidism. Fifteen of the 16 patients underwent preoperative tumor localization studies and uncomplicated bilateral neck exploration at initial operation - all were in biochemical remission at most recent follow up. 31% of patients had multiglandular involvement. 37.5% of patients developed parathyroid carcinoma (median overall survival 8.9 years; median follow-up 7.4 years). Long-term follow-up showed 20% of patients had recurrent primary hyperparathyroidism.

Conclusions—Given the high risk of malignancy and multiglandular involvement in our cohort, we recommend bilateral neck exploration and en-bloc resection of parathyroid tumors suspicious for cancer and life-long postoperative follow-up.

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Keywords

hyperparathyroidism-jaw tumor syndrome; parathyroidectomy; parathyroid cancer; parafibromin

Introduction

Primary hyperparathyroidism (PHPT), a common disorder, results from parathyroid adenomas (single or involving multiple glands), or carcinoma. Approximately 5% of all cases of PHPT are associated with hereditary syndromes that include multiple endocrine neoplasia types 1 and 2A (MEN1, MEN2A), familial isolated hyperparathyroidism (FIHP), and the hyperparathyroidism–jaw tumor (HPT–JT) syndrome (1, 2).

HPT-JT is a rare autosomal dominant disorder with incomplete penetrance and variable expression. The syndrome is characterized by the development of PHPT secondary to parathyroid tumors in approximately 90% of carriers. Approximately 35% of patients with HPT-JT may also develop ossifying fibromas of the mandible and/or maxilla (3). Less common manifestations of the disease include renal lesions (Wilm's tumors, polycystic disease, hamartomas and adenocarcinomas), and uterine tumors (1, 3).

The susceptibility gene for HPT-JT is *HRPT2/CDC73*, a putative tumor suppressor gene, located on chromosome 1q31.2. *HRPT2/CDC73* encodes the ubiquitously expressed nuclear protein parafibromin (4). A number of reports have linked HPT-JT to germline inactivating mutations in *HRPT2/CDC73*, with an associated loss of parafibromin expression and/or function in associated parathyroid tumors (1, 2, 5). While loss of parafibromin protein expression has been observed in sporadic parathyroid carcinomas, non-HPT-JT-related familial or sporadic benign parathyroid adenomas do not have loss of parafibromin expression (6). Parafibromin is believed to function as an inhibitor of cellular proliferation via cell cycle arrest, and as a transcriptional regulator through interactions with the RNA polymerase II-associated factor 1 (PAF1) complex. Parafibromin may also function in the Wnt signaling pathway (7).

PHPT in the context of HPT-JT has been previously characterized as a more aggressive disease relative to sporadic PHPT, with frequent multiglandular involvement, increased risk of persistent/recurrent disease, and a higher frequency of parathyroid carcinoma and metastasis (5). However, many of these studies were conducted prior to the identification of the *HRPT2/CDC73* gene, and were limited by small study cohorts and incomplete clinical data. Following the identification of *HRPT2/CDC73*, more recent studies examining larger kindreds have identified lower rates of synchronous multiglandular involvement (13.2%), biochemical recurrence (17.6–22.3%), longer disease-free intervals (mean 13.7 years), and fewer cases of parathyroid carcinoma (4.4-24.3%) (4, 8).

There is a dearth of literature examining and characterizing HPT-JT disease specific features. Furthermore, the optimal surgical approach and follow-up for patients with HPT-JT with PHPT remains controversial. A number of small studies have recommended extensive parathyroidectomy (subtotal) given the syndrome's more aggressive features and higher risk of cancer (8-10). However, Iacobone and colleagues evaluated 3 large HPT-JT families and

advocated for selective parathyroidectomy in all cases and unilateral exploration in cases with concordant preoperative imaging localizing studies showing single-gland disease. In their series of 17 patients, 82.4% of patients with pathologically confirmed parathyroid adenoma had single-gland involvement and no patients had synchronous multiglandular involvement (5). In comparison, Sarquis and colleagues in their series of 11 patients noted 45.4% of patients had single gland-involvement and 54.5% of patients had synchronous multiglandular involvement (8). Given the wide variation reported in the frequency of synchronous multiglandular involvement, the issue of whether a unilateral or bilateral approach should be used for parathyroidectomy in patients with known HPT-JT remains controversial.

The aim of the present study is to describe the clinical, pathological, demographic, and genetic features and surgical outcomes of 16 affected individuals from 7 families with HPT-JT, in order to provide recommendations for optimal management with regards to preoperative localization and surgical exploration.

Methods

Patients

Demographics, genetic tests, pathology, radiology, and operative history were reviewed in patients who were evaluated at the National Institutes of Health (NIH) Warren Magnuson Clinical Center on an Institutional Review Board approved clinical protocol (91-DK-0085, Studies of Hyperparathyroidism and Related Disorders). The study population consisted of seven families with 16 affected members (ten males, six females), followed at the NIH between July 1986 and January 2014. Previously, four of the seven families have been reported and have been included in this study (1). All patients were initially identified and referred to the NIH following biochemical evidence of hypercalcemia. While all patients in the cohort received genetic screening for the HRPT2 mutation, asymptomatic members of affected families were not screened for the HRPT2 mutation.

Clinical Investigation

HPT-JT was diagnosed when patients had biochemical evidence of PHPT as defined by hypercalcemia, inappropriately normal or increased intact parathyroid hormone (iPTH) levels, and normal or increased 24-hour urinary calcium with normal renal function, histologic evidence of an abnormal parathyroid gland, and the presence of a germ-line *HRPT2/CDC73* mutation. Definitive diagnosis also required negative screening for MEN1 or MEN2 via absence of clinical manifestations, personal or family history, and negative genetic testing (5). Genetic testing for germline *HRPT2/CDC73* mutations was performed on leukocyte DNA via direct sequencing of exons 1-17 and all intron-exon junctions of the *HRPT2/CDC73* gene and, in families with suspected HPT-JT in which no mutation was found, by deletion/duplication analysis of the *HRPT2/CDC73* gene via targeted array comparative genomic hybridization.

Imaging workup included an ultrasound of the neck, sestamibi scan, orthopantomographic X-rays and/or computed tomography (CT) of the mandible and maxilla for identification of

jaw tumors, and abdominal ultrasound and/or CT for evaluation of kidney and uterine abnormalities. Biochemical workup included testing of serum total calcium, ionized calcium, phosphate, 25OH-vitamin D levels, and iPTH levels.

Inpatient and outpatient medical records were reviewed for demographics, clinical presentation, biochemical, genetic and imaging workup, operative management (all surgical data was limited to initial operation), postoperative course, pathology, and follow-up care. All patients were contacted via telephone to assess their most recent clinical and laboratory data.

Remission was defined as postoperative normalization of serum calcium and iPTH levels for at least 6 months following parathyroidectomy; persistent disease was defined as hypercalcemia occurring within 6 months after operation; recurrent disease was defined as hypercalcemia developing after surgery with remission for at least 6 months (5). For patients with parathyroid carcinoma, overall survival (OS) was defined as time to disease-related mortality or last follow-up.

The histological diagnosis was confirmed according to the World Health Organization guidelines (11). The diagnosis of adenoma was based on the finding of a typical encapsulated lesion consisting of small uniform cells arranged with a delicate capillary network, with a rim of normal or atrophic parathyroid tissue evident outside the capsule. Parathyroid carcinoma was defined histologically by a trabecular arrangement of tumor cells, fibrous bands, mitoses, and capsular or blood vessels and/or surrounding soft tissue invasion (12). Atypical adenoma was defined as having necrosis, trabecular arrangement of tumor cells, fibrous bands and or mitoses but with no evidence of vascular or capsular invasion. Patients with parathyroid adenoma or atypical parathyroid adenoma were grouped as a benign parathyroid disease.

Immunohistochemistry

Representative formalin fixed paraffin embedded tissue sections from normocellular parathyroids and parathyroid adenomas from 9 patients with germline *HRPT2/CDC73* mutation were stained. Immunohistochemical studies were performed on a Leica BondMax automated stainer using the BondMax detection kit (Richmond, VA, USA). Antigen retrieval was performed using high pH Bond buffer H2 for 25 min. Primary antibody to Parafibromin (Santa Cruz, CA, SC-33638, mouse monoclonal 2H1) was used at a dilution of 1:400. Diaminobenzidine was used for detection, followed by a light hematoxylin counterstain.

Statistical Analyses

Statistical analysis was performed using Mann-Whitney U test and Fischer's exact test, as appropriate. A P value of <0.05 was considered statistically significant. All calculations were performed using GraphPad Software (La Jolla, CA, USA).

Results

Sixteen affected patients from 7 unrelated families with HPT-JT presented with PHPT. Genetic analysis of germline DNA identified five distinct germline mutations of the *HRPT2/CDC73* gene (Table 1). Whole gene deletion of *HRPT2/CDC73* was identified in 7 of 16 patients (from one family), duplication of two nucleotides (c.687_688dupAG) in exon 7 resulting in a frameshift mutation was identified in 5 of 16 patients (from three families), substitution of a serine for tyrosine (p.Tyr55Ser) in exon 2 was identified in 2 of 16 patients (from one family), a substitution of one nucleotide (c.664C>T) in exon 7 resulting in protein truncation (p.Arg222X) was identified in a single patient, and a substitution of one nucleotide (c.226C>T) in exon 2 resulting in protein truncation (p.Arg76X) was identified in a single patient.

Clinical and demographic information is summarized in Table 1 and Figure 1. All 16 patients had symptomatic PHPT on presentation. The average total calcium was 12.2 mg/dl (median 12.0 mg/dl, ref. range 8.5 – 10.2 mg/dl) and the average iPTH was 236.6 pg/ml (median 190.4 pg/ml, ref. range 10 – 55 pg/ml). Neck ultrasound and/or sestamibi scan were performed in 14 of the 16 patients. Imaging correctly identified 11 patients with single-gland disease and two patients with multigland disease, as confirmed by pathology. One patient had preoperative imaging which suggested single-gland disease, and was found to have multigland disease intraoperatively. The patient was in biochemical remission postoperatively and the intraoperative findings were confirmed on pathology. Sestamibi scan was completely correct for preoperative lateralization in 46.2% of patients.

Fifteen of the 16 patients underwent uncomplicated bilateral neck exploration at initial operation and all were in biochemical remission postoperatively. Ten patients had intraoperative PTH monitoring. Nine of the ten patients had a decrease of ≥75% from their baseline PTH on IOPTH monitoring and all had evidence of biochemical remission (Figure 2). Three of the 16 patients had recurrent PHPT and were all ultimately diagnosed with parathyroid carcinoma either at initial operation or subsequent operation. One patient who did not have intraoperative PTH monitoring on initial operation was found to have persistent PHPT, with final pathology revealing parathyroid carcinoma. Five patients had multiglandular disease, and six patients underwent subtotal parathyroidectomy (3.5 glands). There were no cases of recurrent laryngeal nerve injury, and/or neck hematoma following the initial operation. However, one patient had a case of permanent recurrent laryngeal nerve injury during a reoperation for recurrent PHPT. Ten of the 16 patients had postoperative transient hypoparathyroidism following initial operation, requiring calcium supplementation. Two patients had permanent hypoparathyroidism with both patients having undergone a subtotal parathyroidectomy.

On final pathology, 37.5% percent of patients were found to have parathyroid carcinoma of which two-thirds subsequently developed bone, lung, and /or liver metastases. At initial surgery, only one of the six patients with parathyroid carcinoma had a palpable neck mass. Intraoperatively, patients with parathyroid carcinoma demonstrated features of malignancy, including enlarged gland size, firm texture, grey/white-color and/or gross adherence/ invasion of adjacent tissue. Median OS following initial operation for these patients was 8.9

years (median follow up of 7.4 years), with 3 of the 6 patients dying secondary to complications from parathyroid carcinoma. Total calcium levels, iPTH levels and parathyroid gland size were compared between patients with benign parathyroid disease and parathyroid carcinoma. Average total calcium levels for patients with benign parathyroid disease was 11.7 mg/dl compared to 13.1 mg/dl (Figure 3A, p=0.056). Intact PTH levels for patients with benign parathyroid disease was 212.6 pg/dl compared to 356.5 pg/dl for patients with parathyroid carcinoma (p=0.12). Average parathyroid gland size was 19.3 mm for patients with benign parathyroid disease compared to 26.3 mm for patients with parathyroid carcinoma (Figure 3B, p=0.23). The average age of diagnosis for parathyroid carcinomas was 35.4 years, compared to 30.5 years for benign parathyroid disease (p=0.38).

Parafibromin staining was performed on 9 parathyroid adenomas from HRPT2 patients and was matched to normocellular parathyroids from the same patients, which were stained as control tissue. All normocellular parathyroids showed nuclear positivity throughout the gland (Figure 4A). In 7 cases there was diffuse loss of nuclear parafibromin staining in the adenomatous component with preservation of staining in adjacent normal parathyroid (where present) and within fibrovascular septa (Figure 4B). Interestingly, in two adenoma cases (both with a substitution of a serine for tyrosine (p.Tyr55Ser)) preservation of nuclear parafibromin was present (Figure 4C).

Discussion

HPT-JT syndrome is a rare autosomal dominant disease characterized by PHPT, fibroosseous jaw tumors, uterine tumors, and renal lesions. Genetic mutation analysis, preoperative localization studies, operative data, and postoperative findings showed that there is a high frequency of multiglandular disease and parathyroid carcinoma.

Given the familial history and genetic predisposition to parathyroid adenomas, nearly all of the patients underwent bilateral neck exploration at their initial operation regardless of preoperative localization studies. HPT-JT, classically described as a disease with frequent multiglandular involvement, has a 21.3% prevalence of multiglandular disease from previous published cases in the literature (Table 2). Sarquis and colleagues reported that 54.5% of patients had synchronous multiglandular involvement (8) compared to no synchronous multiglandular involvement in a cohort reported by Iacobone and colleagues. Iacobone and colleagues recommended unilateral exploration in patients with concordant preoperative localizing studies suggesting single-gland disease (5). In this series of patients, the data show 31.3% of patients with synchronous multiglandular involvement. In a familial syndrome such as HPT-JT with a high rate of multiglandular disease, and a predisposition to parathyroid carcinoma, a high failure rate may result with limited neck exploration. Many of these patients undergo multiple operations due to recurrences and parathyroid carcinoma, which exposes them to an increased risk for complications like recurrent laryngeal nerve injury and hypoparathyroidism. Thus, the initial operation should be performed to not only provide the best chance for definitive treatment, but to avoid the need for reoperation and associated morbidity. However, normal parathyroid glands should not be removed as 2 of the 16 patients had permanent hypoparathyroidism when an initial subtotal parathyroidectomy was performed.

Iacobone and colleagues recommended unilateral exploration with concordant preoperative imaging studies showing single-gland disease (5). This approach assumes that preoperative localization studies are accurate and have a low false-positive rate. However, in this cohort, the preoperative studies in patients with multiglandular disease were not as reliable. Preoperative localization studies were available for three out of the five patients with synchronous multiglandular involvement. The studies were accurate in two out of the three patients. The patient with inaccurate preoperative localization had an ultrasound and a Sestamibi scan showing only single gland disease, and upon exploration was found to have synchronous multiglandular disease. Given the high rate of multiglandular disease in these patients, their genetic predisposition, and the risk of reoperation, initial surgical management should include a bilateral neck exploration.

Although parathyroid carcinoma is a rare tumor causing less than one percent of cases of PHPT in the Western world, parathyroid carcinoma has been reported to be relatively common in patients with HPT-JT syndrome (13). Iacobone and colleagues reported that 11.8% of their cohort was diagnosed with parathyroid carcinoma and an extensive review of the literature by that study revealed that the prevalence of parathyroid carcinoma was 18.7% (5). In comparison, 37.5% of the patients in this cohort developed parathyroid carcinoma either at initial operation and/or during follow-up. Evidence from literature shows total calcium levels and the size of gland as potential markers of parathyroid carcinoma (14). No significant difference in gland size between benign parathyroid tumors and parathyroid carcinoma was found in this cohort. Total calcium levels were higher in patients with parathyroid carcinoma, but the findings were not statistically significant. Previous studies have reported high levels of total calcium in patients with parathyroid carcinoma associated with increased renal (56% nephrolithiasis and 84% renal insufficiency) and skeletal (greater than 40%) involvement compared to patients with benign primary hyperparathyroidism (less than 20% renal and less than 5% bone involvement)(15). In this series, patients with parathyroid carcinoma had less renal involvement (16.7%) and increased bone involvement (66.7%). Furthermore, one of the patients on initial operation had a 30 mm right inferior parathyroid adenoma and an unremarkable right superior parathyroid gland. Subsequently, the patient developed recurrent PHPT within two years and on reoperation was found to have a right superior parathyroid carcinoma. The high incidence of parathyroid carcinoma in this cohort indicates the need for surgical intervention in cases of even mild PHPT. For parathyroid glands suspicious for malignancy based on intraoperative findings such as large gland size, firm texture, grey/whitecolor and/or gross adherence to adjacent tissue, we recommend *en-bloc* resection of the tumor with a hemithyroidectomy.

Given their high susceptibility to parathyroid cancer, there is also clearly a need for longterm follow-up in patients with HPT-JT syndrome and frequent monitoring to detect the potential development of parathyroid carcinoma. Family members of affected patients should be offered genetic counseling and testing if a *CDC73* germline mutation is identified. The youngest reported case of PHPT in a family diagnosed with HPT-JT syndrome is in a 7 year old child. Therefore, we recommend genetic screening within affected families at 5 years of age (16). For those found to be asymptomatic carriers, current recommendations include lifelong serum testing for biochemical evidence of PHPT every 6 to 12 months, with

panoramic dental imaging and renal ultrasound at least every 5 years after identification of germline mutation. Asymptomatic female carriers should also have close gynecologic follow-up to address the risk of benign and malignant uterine tumors (17). Iacobone and colleagues advocate the use of parafibromin immunostaining as a first –line screening tool in cases of suspected familial non-MEN HPT, suggesting that it serves as a distinguishing feature of HPT-JT (5). However, in this series, immunostaining in two of nine adenoma cases (both with a substitution of a serine for tyrosine (p.Tyr55Ser)) showed preservation of nuclear parafibromin. Consequently, while parafibromin immunostaining may prove a cost-effective strategy for initial screening, physicians and researchers should be mindful of the significant risk for false-negative results. Given the high rate of recurrence and parathyroid carcinoma in HPT-JT patients, we advocate physicians proceed to genetic testing for *HRPT2/CDC73* mutations despite parafibromin staining if clinical suspicion is high.

Previous studies have reported a high rate of PHPT recurrence in patients with the *HRPT2/CDC73* germline mutation. A recent study by Silveira and colleagues showed a high rate of recurrence (4/9) and/or persistent (2/9) PHPT. The authors speculated that aggressive treatment may be warranted and genotype-phenotype data may be able to direct the surgeon (18). The recurrence rate of PHPT in this cohort was 25.0%. Of the four patients who had recurrent disease, all four patients were ultimately diagnosed with parathyroid carcinoma and had either whole gene deletion of *CDC73* or duplication of two nucleotides (c. 687_688dupAG) in exon 7 resulting in a frameshift mutation. Unfortunately, the small sample size did not allow sufficient power to correlate between the type of genetic mutation and phenotypic expression of parathyroid carcinoma. Furthermore, a literature review showed that the rate of recurrence of PHPT was 14.2%. Although the low rate of recurrence may lead the clinician to offer a less aggressive initial operation, given the risk of recurrence and parathyroid carcinoma, patients would likely benefit from a more complete exploration and parathyroidectomy in the initial setting of any abnormal glands.

The type of operation did not influence whether the patient had a longer disease-free interval. Immunohistochemistry from a single patient undergoing a subtotal parathyroidectomy comparing a normal parathyroid gland and an abnormal parathyroid adenoma showed discordant results. The abnormal parathyroid gland showed absence of nuclear staining, while positive parafibromin nuclear staining was identified in the unaffected gland. Postoperatively, this patient subsequently developed permanent hypoparathyroidism. Given these findings, routine subtotal or total parathyroidectomy confers no benefit and likely leads to increased risk of permanent hypoparathyroidism. Furthermore, total parathyroidectomy with autotransplantation may also allow the seeding and dissemination of parathyroid cancer cells via the autotransplantation.

HPT-JT syndrome is a rare genetic disorder resulting in PHPT, a high likelihood of multiglandular disease, and a high risk for parathyroid carcinoma. Given the genetic predisposition and high cancer risk, bilateral neck exploration to assess all four parathyroid glands with *en-bloc* resection of enlarged glands suspicious for cancer would serve these patients best.

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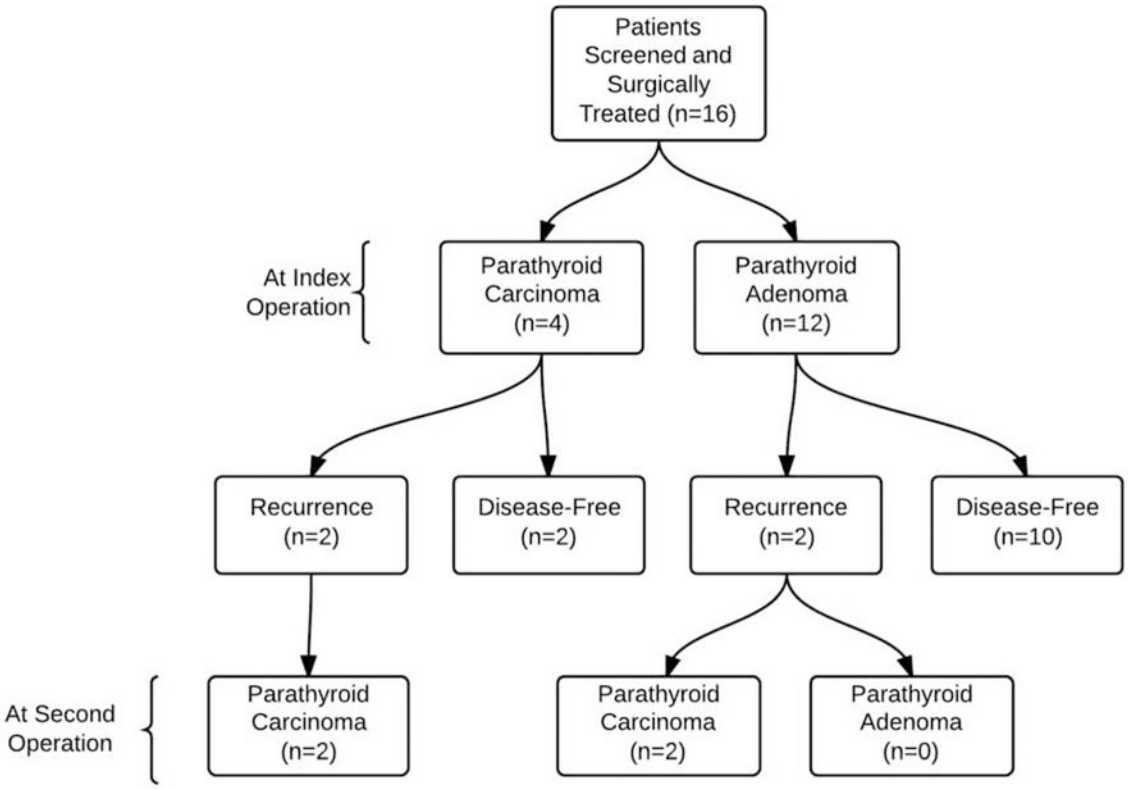

Figure 1.
Pathologic and operative findings and patient outcome.

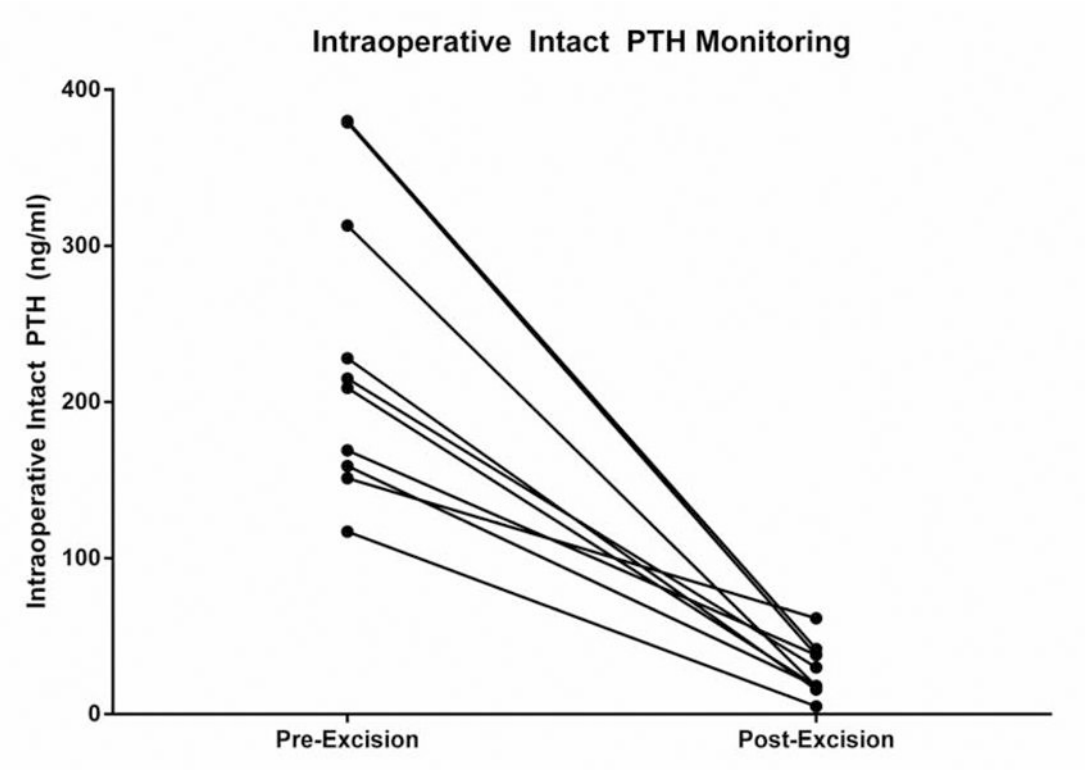

Figure 2.
Pair wise comparison of pre-excision and post-excision intact PTH levels in patients undergoing parathyroidectomy.

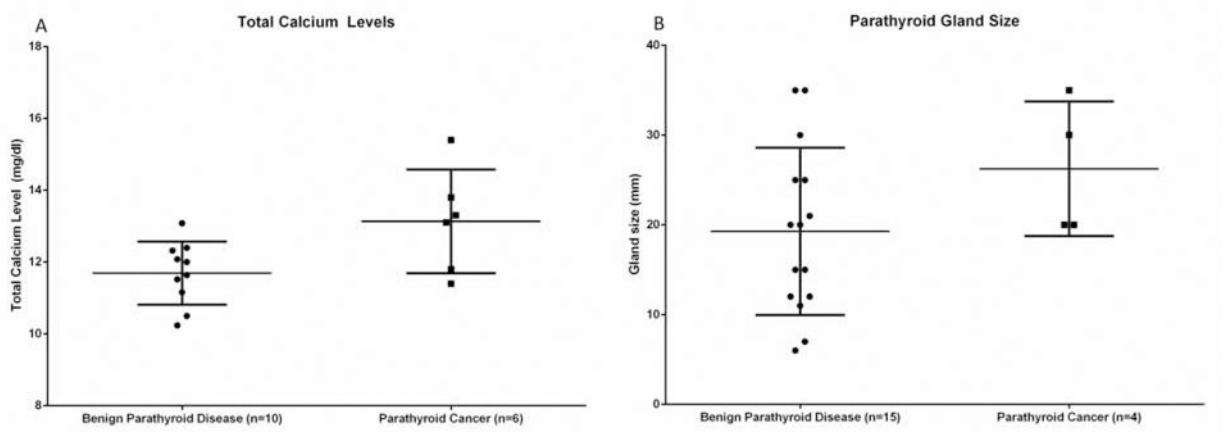

Figure 3.

Comparison of patients with parathyroid adenoma and parathyroid carcinoma with respect to (a) total calcium level (p=0.056), and (b) parathyroid gland size (p=0.230).

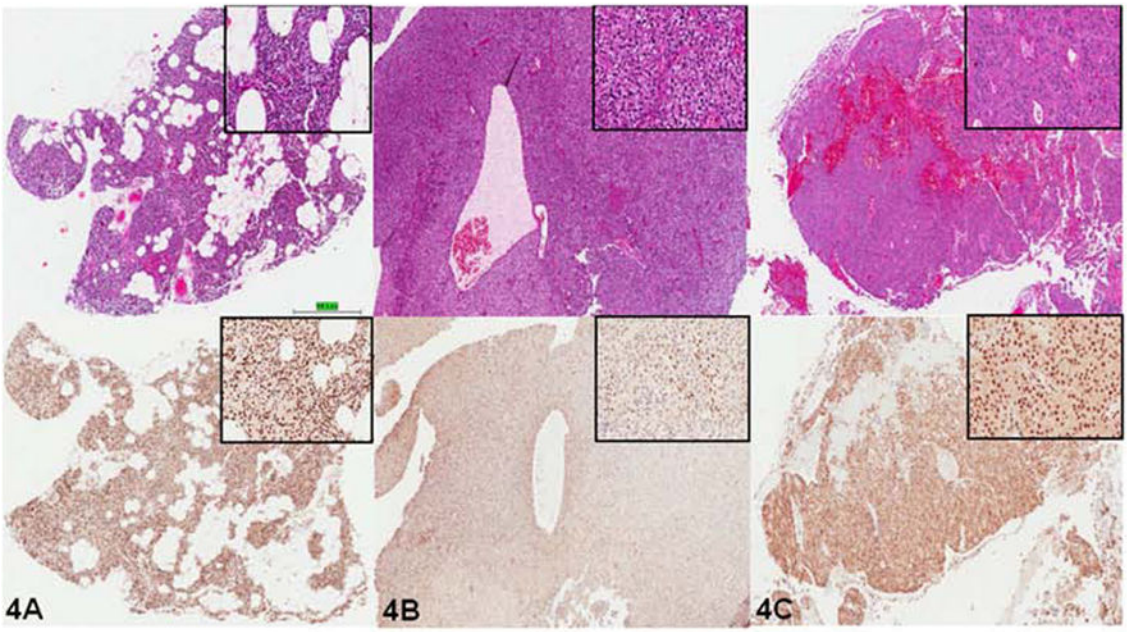

Figure 4.

Immunohistochemical analysis of parafibromin expression in patients with HPT-JT syndrome. The upper panels were stained with Hematoxylin and Eosin, and the lower panels were stained for parafibromin. (a) Normocellular parathyroid tissue showing strong diffuse nuclear immunostaining. (b) Benign parathyroid adenoma showing loss of positivity in the same HPT-JT patient. (c) Benign parathyroid adenoma from patient with substitution of a serine for tyrosine (p.Tyr55Ser) showing retained positive nuclear immunostaining. Note magnified (40x) inserts of tissue samples on top right.

Table 1
Clinical, biochemical and genetic data for cohort

	Benign Parathyroid Disease	Parathyroid Carcinoma	Entire Cohort
Gender			
Male/Female	7/3	3/3	10/6
Age at Diagnosis (years)			
Median	26.4	29.9	30.7
Range	18-38	31-49	18-49
Signs/Symptoms at Presentation			
Psychiatric/Neurologic *	4/10 (40.0%)	3/6 (50%)	7/16 (43.8%)
Fatigue	5/10 (50.0%)	1/6 (16.7%)	6/16 (37.5%)
GastrointestinaI symptoms **	2/10 (20.0%)	3/6 (50%)	5/16 (31.3%)
Renal ***	2/10 (20.0%)	1/6 (16.7%)	3/16 (18.8%)
Bony pain	3/10 (30.0%)	4/6 (66.7%)	3/16 (18.8%)
Fractures	1/10 (10.0%)	1/6 (16.7%)	2/16 (12.5%)
Neck mass	0/10 (0%)	1/6 (16.7%)	1/16 (6.3%)
Laboratory Findings			
Average total calcium §	11.7 mg/dl	13.1 mg/dl	12.2 mg/dl
Intact PTH (benign parathyroid disease)?	212.6 pg/ml	356.5 pg/ml	236.6 pg/ml
Associated Pathology			
Uterine tumor	0/3 (0%)	2/3 (66.7%)	2/6 (33.3%)
Renal lesions	0/10 (0%)	3/6 (50.0%)	3/16 (18.8%)
Jaw tumor	0/10 (0%)	2/6 (12.5%)	2/16 (12.5%)
Genetics/Mutation Type			
CDC73 (whole gene deletion)	3/10 (30.0%)	4/6 (66.7%)	7/16 (43.8%)
c.687_688dupAG (exon 7)	3/10 (30.0%)	2/6 (33.3%)	5/16 (31.3%)
Y552 (exon 2)	2/10 (20.0%)	0/6 (0%)	2/16 (12.5%)
R222X (exon 7)	1/10 (10.0%)	0/6 (0%)	1/16 (6.3%)
R76X (exon 2)	1/10 (10.0%)	0/6 (0%)	1/16 (6.3%)
Post-operative Complications			
Hypoparathyroidism (permanent)	1/10 (10.0%)	1/6 (16.7%)	2/16 (12.5%)
Permanent recurrent laryngeal nerve injury ¶#	0/10 (0%)	0/10 (0%)	0/16 (0%)
Hematoma	0/10 (0%)	0/10 (0%)	0/16 (0%)
Follow-Up (years)			
Median	2.3	7.4	3.7
Range	0.05-13.4	0.04-11.4	0.05-13.4

* Headaches, memory loss/changes, difficulty concentrating

** Abdominal pain, constipation, Gastroesophageal Reflux Disease (GERD)

*** Polyuria, nephrolithiasis

[§] Total calcium reference range (8.5 – 10.2 mg/dl)

[?] Intact PTH reference range (10 – 55 pg/ml)

[¶] At initial operation.

[#] 1 patient had RLN injury during the 2nd operation.

Table 2

Review of the literature focusing on HRPT2-related HPT (period 2002-2013)

Reference	Family (n)	Affected patients (n)	Patients with PHPT (n)	Single-gland involvement (n)	Synchronous multiglandular involvement (n)	Recurrences (n)	Jaw-Tumor (n)	Parathyro id Carcinom a (n)	Renal lesions (n)	Uterine lesions (n)
Carpten (1)	14	66	66/66	NA	NA	NA	30/66	11/66	18/66	NA
Shattuck (19)	3	3	3/3	NA	NA	NA	NA	3/3	NA	NA
Howell (20)	3	7	7/7	NA	NA	0/7	0/7	3/7	0/7	NA
Simonds (21)	1	4	4/4	4/4	0/4	0/4	0/4	1/4	0/4	NA
Cetani (22)	2	4	4/4	3/4	1/4	NA	0/4	0/4	0/4	NA
Villablanca (23)	2	9	9/9	7/9	2/9	3/9	0/9	0/9	0/9	NA
Cavaco (24)	6	11	9/11	5/9*	1/9*	0/9	2/11	0/11	2/11	NA
Howell (25)	1	2	2/2	2/2	0/2	0/2	1/2	0/2	NA	NA
Gimm (26)	1	3	3	NA	NA	1/3	NA	1/3	NA	NA
Bradley (3)	2	11	9	NA	NA	NA	0/11	2/11	0/11	6/7
Moon (27)	1	2	2	2/2	0/2	NA	1/2	2/2	NA	NA
Mizusawa (28)	3	7	7/7	6/7**	NA**	1/7	1/7	1/7	0/7	0/3
Aldred (29)	1	3	3/3	3/3	0/3	0/3	2/3	0/3	NA	NA
Bradley (30)	5	5	5/5	4/5	1/5	NA	2/5	0/5	0/5	1/4
Juhlin (31)	1	1	1/1	1/1	0/1	NA	NA	0/1	NA	NA
Guarnieri (32)	1	5	4/5	4/4	0/4	1/4	NA	1/5	0/4	2/3
Kelly (33)	1	2	2/2	1/2	1/2	2/2	NA	2/2	NA	NA
Yamashita (34)	1	1	1/1	1/1	0/1	0/1	1/1	0/1	NA	NA
Cetani (35)	1	1	1/1	1/1	0/1	1/1	0/1	0/1	0/1	NA
Cetani (36)	2	3	3/3	NA	NA	NA	NA	3/3	NA	NA
Raue (37)	1	2	2/2	1/2	1/2	NA	1/2	1/2	NA	NA
Cetani (38)	1	1	1/1	1/1	0/1	NA	0/1	1/1	NA	NA
Sarquis (8)	3	11	11/11	5/11	6/11	8/11	1/11	1/11	4/11	5/6
Guarnieri (39)	4	9	6/9	6/6	0/6	3/6	0/9	3/9	3/9	NA
Howell (40)	1	1	1/1	1/1	0/1	0/1	NA	NA	NA	NA
Silveira (18)	1	9	9/9	3/9	6/9	6/9	0/9	1/9	4/9	5/9
Iacobone (5)	3	17	16/17	15/16***	0/16***	3/16	1/17	1/17	1/17	8/13
Rekik (41)	1	1	1/1	1/1	0/1	0/1	1/1	0/1	0/1	1/1
Panicker (42)	1	6	5/6	NA	NA	0/5	1/6	0/6	0/6	1/2
Cavaco (43)	2	2	2/2	2/2	0/2	1/2	0/2	2/2	0/2	0/2

Reference	Family (n)	Affected patients (n)	Patients with PHPT (n)	Single-gland involvement (n)	Synchronous multiglandular involvement (n)	Recurrences (n)	Jaw-Tumor (n)	Parathyro id Carcinom a (n)	Renal lesions (n)	Uterine lesions (n)
Pichardo-Lowden (16)	1	1	1/1	1/1	0/1	1/1	0/1	0/1	1/1	NA
Domingues (44)	1	1	1/1	1/1	0/1	0/1	0/1	0/1	0/1	NA
Bricaire (45)	15	13	12/13	NA	NA	NA	3/15	2/15	2/15	2/6
Total	**87**	**224**	**213/224**	**78.7%**	**21.3**	**29.5%**	**23.5%**	**18.7%**	**17.4%**	**50%**
Present series	**7**	**16**	**16/16**	**11/16 (68.8%)**	**5/16 (31.3%)**	**4/16 (25.0%)**	**2/16 (12.5%)**	**6/16 (37.5%)**	**3/16 (18.8%)**	**2/6 (33.3%)**

*Three patients with known PHPT were not operated on; pathology (gland no., histology) unknown.

**Information concerning gland involvement not available for the patient with PHPT and parathyroid carcinoma.

***One patient with known PHPT was not operated on; pathology (gland no., histology) unknown