Four-Gland Exploration Versus Focused Parathyroidectomy for Hyperparathyroidism Jaw Tumor Syndrome

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Abstract

Primary hyperparathyroidism, a common endocrine disorder, is associated with familial disease in about 10% of cases. These syndromes include multiple endocrine neoplasia types 1, 2A and 4 (MEN1, MEN2A, MEN4), familial isolated hyperparathyroidism (FIHP), and the hyperparathyroidism jaw tumor (HPT-JT) syndrome. HPT-JT syndrome, an autosomal dominant disease with incomplete penetrance, results from a germline inactivating mutation in the *HRPT2* gene. HPT-JT manifests with about 20% of patients having multiple enlarged parathyroid glands and/or parathyroid carcinoma. Furthermore, 28% of patients will have a recurrence during follow-up. Since these patients have a high rate of multiple enlarged parathyroid glands, parathyroid carcinoma, and recurrence, it is controversial as to what is the optimal initial surgical approach for parathyroidectomy. Clinical evidence for the optimal initial surgical approach for HPT-JT syndrome is limited to case series and retrospective small cohort studies. Furthermore, there is scant data on the clinical utility of localization studies to select the optimal operative approach. Only one study reported the results of localization studies and showed a lack of benefit due to high rates of multigland disease that would have been missed if a focused parathyroidectomy approach was used. Given the high rates of multigland disease, parathyroid carcinoma, risk of recurrence, and the possibility of missing additional enlarged glands not seen on preoperative localizing studies, bilateral neck exploration with identification of all four glands and removal of enlarged glands would be the best surgical approach given our current knowledge.

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Keywords
Hyperparathyroidism · HRPT2 · Parathyroid carcinoma · Focused single gland parathyroidectomy · Bilateral exploration · Multiglandular disease

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disease that results from parathyroid adenoma(s) (single or multiple enlarged glands), or parathyroid carcinoma. In about 10% of cases, PHPT is associated with hereditary syndromes. These syndromes include multiple endocrine neoplasia types 1, 2A and 4 (MEN1, MEN2A, MEN4), familial isolated hyperparathyroidism (FIHP), and the hyperparathyroidism jaw tumor (HPT-JT) syndrome [1].

HPT-JT syndrome is an autosomal dominant inherited syndrome with incomplete penetrance and variable expression. In approximately 90% of carriers, PHPT will develop due to single or multiple parathyroid tumors. About 35% of patients may also develop ossifying fibromas of the mandible and/or maxilla [2]. Albeit less common, patients with HPT-JT syndrome also manifest with renal lesions (Wilm's tumors, polycystic disease, hamartomas, and adenocarcinomas) and uterine tumors [1, 2]. A recent report also indicated that there may be an association with thoracic aneurysms and HPT-JT syndrome [3].

HPT-JT syndrome is due to inactivating mutations in *HRPT2/CDC73*, a tumor suppressor gene, located on chromosome 1q31.2. The *HRPT2/CDC73* gene encodes the ubiquitously expressed nuclear protein parafibromin [4]. The function of parafibromin is believed to be inhibition of cellular proliferation through cell cycle arrest, and it is believed to act as a transcriptional regulator through interactions with the RNA polymerase II–associated factor 1 (PAF1) complex [5]. The identification of the *HRPT2/CDC73* as a susceptibility gene for HPT-JT and its presence as a somatic mutation in parathyroid carcinoma has provided additional information that should be considered when evaluating patients suspected or known to have HPT-JT. One controversial issue is what the optimal surgical approach is in patients with HPT-JT? Variable approaches have been advocated in the literature ranging from a focused parathyroidectomy approach based on preoperative localization results versus routine bilateral neck exploration with four gland identification and removal of enlarged parathyroid gland(s). The controversy exists because of the high rates of multiglandular disease, parathyroid carcinoma, and recurrence in patients with HPT-JT.

Search Strategy

A comprehensive review of the literature related to HPT-JT syndrome was performed. Literature searches were conducted in the PubMed database using the key words: hyperparathyroidism jaw-tumor syndrome, familial isolated

hyperparathyroidism, *CDC73*, and *HRPT2*. Searches were limited to the English language and human subjects. Our search returned 476 articles. Thirty-seven articles related to HPT-JT syndrome with clinical and surgical data were reviewed. When families were reported in multiple articles, either the most current article related to that family or the article reporting the largest number of kindred was included in the analysis.

Intervention

Approximately 90% of individuals with germline *HRPT2/CDC73* inactivating mutations will develop biochemical evidence of PHPT [2]. Given the genetic predisposition, these patients pose a clinical question as to what is the optimal surgical approach. The standard surgical approach for these patients has been bilateral neck exploration with four gland identification. A recent study by Iacobone et al. questioned whether a focused parathyroidectomy may be a superior approach compared to a bilateral neck exploration in order to reduce morbidity. Iacobone et al. reported retrospective results of parathyroidectomy in 17 affected members in three large families. In this study, 23 out of 44 patients who underwent clinical examination were found to be carriers. Of the 23 patients, one patient was excluded due to death from metastatic renal cell carcinoma and lack of clinical data regarding parathyroid pathology. Six patients were asymptomatic, and in the remaining 16 patients, the authors reported biochemical evidence of PHPT. All 16 patients underwent bilateral neck exploration with identification of all four parathyroid glands. At the time of surgery, all patients had only a single parathyroid adenoma. Final pathology showed parathyroid adenoma for fifteen patients, and one patient had an atypical parathyroid adenoma (classified as parathyroid carcinoma by the authors).

Based on these results and a review of the literature, the authors proposed a focused parathyroidectomy should be considered in patients with HPT-JT syndrome who have localizing studies suggesting single gland disease. In their analysis of the literature, they found that there was single gland involvement in 89.0% of patients and synchronous multiglandular involvement in only 13.2% of patients [1, 2, 6–28]. In addition, the authors reported that the rate of parathyroid carcinoma in their series was only 11.8%, compared to data in the literature showing 24.3% of patients with HPT-JT syndrome have parathyroid carcinoma. The theoretical advantage of such an approach would be to avoid tissue trauma, leading to less scar tissue in reoperative cases, and possibly lower rate of recurrent laryngeal nerve injury and hypoparathyroidism as only one side of the neck would be explored. However, a major weakness in this study was that preoperative localization data was not reported. A recommendation of using a focused approach for parathyroidectomy in patients with HPT-JT syndrome should be based on data on the clinical utility of localizing studies similar to what has been done in patients with sporadic PHPT. Thus, the data presented by the authors can only speculate as to whether this approach would have been possible [29].

Comparator

As in other familial PHPT syndromes, bilateral neck exploration and the identification of four glands has been the gold standard surgical approach given the high rate of multigland disease in patients with germline mutations of *HRPT2/CDC73*. A comprehensive review of the literature showed a nearly one in five chance of having multigland disease at the initial neck exploration (Table 20.1). The rate of multiglandular disease in these patients is higher as compared to sporadic PHPT. Sarquis et al. reported their findings in three families [26]. The largest family had nine members affected, and six out of the nine patients who had neck exploration and parathyroidectomy had multigland disease. Preoperative localization data was not reported [26]. The evidence in this case series provides a strong case for bilateral neck exploration and four gland identification due to the rate of synchronous multigland involvement.

In another large cohort of patients, Mehta et al. examined the rate of multigland disease and parathyroid carcinoma. In that cohort, there were 16 affected family members, and the rate of synchronous multigland disease was 31.3%, or five out of 16 patients. Most strikingly, however, was the rate of parathyroid carcinoma, which was 37.5%. Given the rate of synchronous multigland disease and the risk of parathyroid carcinoma, the authors recommended a bilateral neck exploration and four-gland identification in all patients. Furthermore, in a thorough analysis of the literature, this study was the only study to report preoperative localization data with surgical approach and pathology with long term follow up. The authors found that preoperative localization was not always accurate for patients with synchronous multigland involvement with only two out of three patients being correctly identified with synchronous multigland involvement with preoperative localization studies [30].

The high risk of multigland disease and parathyroid carcinoma is also underscored by an affected patient reported by Korpi-Hyovalti et al.. In their series of patients, there were seven patients with HTP-JT and one patient had synchronous multigland disease. The patient underwent bilateral neck exploration and was found to have a 1.5 cm enlarged upper right parathyroid gland and a 1.4 cm enlarged upper left parathyroid gland. On final pathology, the authors reported that the right gland was parathyroid carcinoma based on histology showing vascular invasion and a Ki-67 proliferation index of 5%. The left parathyroid gland was reported as an atypical adenoma. Preoperative localization studies were, unfortunately, not reported in this study [3].

Outcome

In the literature, nearly all studies have defined cure as postoperative normalization of serum calcium and intact PTH levels for at least 6 months. Persistent disease has been defined as biochemical evidence of PHPT recurring within 6 months. Recurrent disease has been defined as biochemical evidence of PHPT occurring 6 months after

Table 20.1 Review of the literature focusing on HRPT2-related HPT (period 2002–2015)

Reference	Family (n)	Affected patients (n)	Patients with PHPT (n)	Single-gland involvement (n)	Synchronous multiglandular involvement (n)	Recurrences (n)	Follow-up (average years)	Jaw-tumor (n)	Parathyroid carcinoma (n)	Renal lesions (n)	Uterine lesions (n)
Carpten [1]	14	66	66/66	NA	NA	NA	NA	30/66	11/66	18/66	NA
Shattuck [6]	3	3	3/3	NA	NA	NA	NA	NA	3/3	NA	NA
Howell [7]	3	7	7/7	NA	NA	0/7	NA	0/7	3/7	0/7	NA
Simonds [8]	1	4	4/4	4/4	0/4	0/4	NA[a]	0/4	1/4	0/4	NA
Cetani [9]	2	4	4/4	3/4	1/4	NA	NA	0/4	0/4	0/4	NA
Villablanca [10]	2	9	9/9	7/9	2/9	3/9	7.44	0/9	0/9	0/9	NA
Cavaco [11]	6	11	9/11	5/9[b]	1/9[b]	0/9	5.56	2/11	0/11	2/11	NA
Howell [12]	1	2	2/2	2/2	0/2	0/2	NA	1/2	0/2	NA	NA
Gimm [32]	1	3	3/3	NA	NA	1/3	NA	NA	1/3	NA	NA
Bradley [2]	2	11	9/11	NA	NA	NA	NA	0/11	2/11	0/11	6/7
Moon [14]	1	2	2/2	2/2	0/2	NA	NA	1/2	2/2	NA	NA
Mizusawa [15]	3	7	7/7	6/7[c]	NA[c]	1/7	5.43	1/7	1/7	0/7	0/3
Aldred [16]	1	3	3/3	3/3	0/3	0/3	NA	2/3	0/3	NA	NA
Bradley [17]	5	5	5/5	4/5	1/5	NA	NA	2/5	0/5	0/5	1/4
Juhlin [18]	1	1	1/1	1/1	0/1	NA	NA	NA	0/1	NA	NA
Guarnieri [19]	1	5	4/5	4/4	0/4	1/4	2	NA	1/5	0/4	2/3
Kelly [20]	1	2	2/2	1/2	1/2	2/2	1.25	NA	2/2	NA	NA
Yamashita [21]	1	1	1/1	1/1	0/1	0/1	2	1/1	0/1	NA	NA
Cetani [22]	1	1	1/1	1/1	0/1	1/1	19	0/1	0/1	0/1	NA
Cetani [23]	2	3	3/3	NA	NA	NA	NA	NA	3/3	NA	NA
Raue [24]	1	2	2/2	1/2	1/2	NA	NA	1/2	1/2	NA	NA
Cetani [25]	1	1	1/1	1/1	0/1	NA	10	0/1	1/1	NA	NA

(continued)

Table 20.1 (continued)

Reference	Family (n)	Affected patients (n)	Patients with PHPT (n)	Single-gland involvement (n)	Synchronous multiglandular involvement (n)	Recurrences (n)	Follow-up (average years)	Jaw-tumor (n)	Parathyroid carcinoma (n)	Renal lesions (n)	Uterine lesions (n)
Sarquis [26]	3	11	11/11	5/11	6/11	8/11[d]	6.54	1/11	1/11	4/11	5/6
Guarnieri [27]	4	9	6/9	6/6	0/6	3/6	NA[e]	0/9	3/9	3/9	NA
Howell [28]	1	1	1/1	1/1	0/1	0/1	1	NA	NA	NA	NA
Iacobone [29]	3	17	16/17	15/16[f]	0/16[f]	3/16	8.60	1/17	1/17	1/17	8/13
Rekik [33]	1	1	1/1	1/1	0/1	0/1	NA	1/1	0/1	0/1	1/1
Panicker [34]	1	6	5/6	NA	NA	0/5	6	1/6	0/6	0/6	1/2
Cavaco [35]	2	2	2/2	2/2	0/2	1/2	NA	0/2	2/2	0/2	0/2
Pichardo-Lowden [36]	1	1	1/1	1/1	0/1	1/1	7	0/1	0/1	1/1	NA
Domingues [37]	1	1	1/1	1/1	0/1	0/1	1	0/1	0/1	0/1	NA
Bricaire [38]	15	13	12/13	NA	NA	NA	NA	3/15	2/15	2/15	2/6
Mehta [30]	7	16	16/16	11/16	5/16	4/16	5.12	2/16	6/16	3/16	2/6
Kong [39]	4	12	10/12	7/9	2/9	5/9	13.76	1/9	1/9	0/9	3/5
Korpi-Hyövälti [3]	1	8	8/8	6/7	1/7	NA	NA	0/7	2/7	2/7	NA
Total	98	251	238/251	79.7%	17.4%	28.0%	–	22.2%	20.0%	16.3%	53.5%

[a]A range of 3–29 years of normocalcemia was reported. No median follow-up time provided
[b]Three patients with known PHPT were not operated on; pathology (number of glands, histology) unknown
[c]Information concerning gland involvement not available for the patient with PHPT and parathyroid carcinoma
[d]Two of the patients had persistent disease after surgical intervention
[e]Individual data, not available. Each family had 2–4 years of follow-up
[f]One patient with known PHPT was not operated on; pathology (number of glands, histology) unknown

curative surgery. Iacobone et al. achieved cure by selective parathyroidectomy in 93.3% of patients. One patient had persistent disease after en-bloc parathyroidectomy and thyroid lobectomy. This patient was suspected and later diagnosed with parathyroid carcinoma. Aside from the patient with parathyroid carcinoma, the remaining patients were cured for an average of 12.3 years. Three patients had recurrent PHPT and were found to have metachronous single parathyroid tumors [29]. In another large series, Sarquis et al. had a higher rate of recurrence compared to the literature with eight out of 11 patients recurring after parathyroidectomy with an average disease free interval of 5 years. In the largest family, two out of the nine patients had persistent disease, and four out of the nine patients had recurrent disease. The average time to recurrence was 4.6 years for the six patients who had recurrence. One out of the nine patients had a second recurrence 30 years after her initial surgery [26]. Mehta et al. reported that one patient had persistent disease and three patients had recurrent disease. All four of these patients were found to have parathyroid carcinoma at either initial operation or subsequent operations. The average time to recurrence was 3.3 years for the three patients who were cured with their initial surgery [30]. In patients with HPT-JT, the rate of persistent/recurrent disease is approximately 28% based on review of the literature (Table 20.1).

In order to maximize the success of focused parathyroidectomy, preoperative localization studies should be reliable and accurate for demonstrating single gland disease. The evidence for the accuracy of localization in HPT-JT syndrome has not been reported extensively. To our knowledge, the study by Mehta et al. is the only study that analyzed preoperative imaging study results, surgical approaches, final pathology and patient outcome. Eleven patients with single gland disease and two patients with synchronous multigland disease were identified accurately by preoperative imaging and confirmed after bilateral neck exploration and on pathology. One patient was thought to have single gland involvement by preoperative localizing studies, but was found to have synchronous multigland disease intraoperatively [30]. Given the paucity of preoperative localization data in HPT-JT syndrome, evaluating preoperative localization data in other familial PHPT syndromes such as MEN1 may be helpful. Nilubol et al. analyzed the accuracy of neck ultrasonography, sestamibi parathyroid scan, parathyroid protocol CT scan, and neck MRI relative to the total number of enlarged parathyroid glands found intraoperatively in patients with MEN1. Preoperative imaging was found to be not helpful in this cohort of patients, who like HPT-JT syndrome, had a high rate of synchronous multigland involvement [31].

The main risks of parathyroidectomy are bleeding, recurrent laryngeal nerve injury and hypoparathyroidism. Unfortunately, due to the rarity of the disease and lack of uniformity in reporting of case series, there is minimal data regarding complications specifically in patients with HPT-JT. Mehta et al. did report that two out of 16 patients had postoperative permanent hypoparathyroidism. In their series, although there were no permanent recurrent laryngeal nerve injuries and/or hematomas at initial operation, one patient did have a recurrent laryngeal nerve injury during their second operation. Many of these patients will have recurrent disease, and the risk of recurrent laryngeal nerve injury in reoperative parathyroid surgery is higher [30]. This fact emphasizes the importance of patients with HPT-JT being

treated by an experienced endocrine surgeon. The importance of reporting complications and outcome data cannot be over emphasized and evaluation of this information by surgeons is important in determining what the optimal surgical approach is for parathyroidectomy in patients with HPT-JT.

Recommendations

The evidence for selecting focused parathyroidectomy or bilateral neck exploration with four gland identification and removal of enlarged parathyroid gland(s) in patients with HPT-JT syndrome is based on limited retrospective data. There are no prospective or randomized controlled trials and they are unlikely to be conducted given the rarity of HPT-JT syndrome, even at referral centers. Thus, the recommendation on the optimal surgical approach is based on the high rates of synchronous multigland disease, higher rate of parathyroid carcinoma at initial presentation or at the time of recurrent disease, and the overall higher rate of recurrence. In our own series of patients where we reported localizing data, surgical approach and final pathology, and follow up data, we believe that bilateral neck exploration with identification of all parathyroid glands and removal of enlarged glands is the optimal approach. In selected subjects a focused approach may be considered if (1) multiple localizing studies suggest single gland disease, (2) the biochemical profile and imaging studies are not suspicious for parathyroid carcinoma, (3) intraoperative PTH monitoring will be used as an adjunct to confirm biochemical cure, (4) the patient is young with no family members who had parathyroid carcinoma, and (5) the patient prefers a focused approach, or has had a previous thyroid or parathyroid operation and presents with persistent/recurrent disease. In our opinion, the morbidity of parathyroid carcinoma and the high rate of synchronous multigland disease outweigh the morbidity of bilateral neck exploration, especially when done by specialized endocrine surgeons.

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