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ORIGINAL SCIENTIFIC REPORT

Long-Term Outcomes of Parathyroidectomy in Hyperparathyroidism-Jaw Tumor Syndrome: Analysis of Five Families with *CDC73* Mutations

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Abstract

Background Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is a rare disease caused by *CDC73* germline mutations, with familial primary hyperparathyroidism (pHPT), ossifying jaw tumors, genito-urinary neoplasms. The present study was aimed at determining the long-term postoperative outcome of parathyroidectomy in HPT-JT.

Methods A retrospective analysis of a single-center series of 20 patients from five unrelated HPT-JT families undergoing parathyroid surgery was performed.

Results Pathology confirmed a single-gland involvement in 95% of cases at onset. Parathyroid carcinoma occurred in three patients undergoing en-bloc parathyroidectomy and thyroid lobectomy: parathyroid benign lesions in 17 patients undergoing subtotal parathyroidectomy for evident multiglandular involvement ($n = 1$) or selective parathyroidectomy for single-gland involvement ($n = 16$), during bilateral ($n = 13$) or targeted unilateral neck exploration ($n = 7$). At a median overall follow-up of 16 years (range 2.5–42), patients with parathyroid carcinoma had a persistent/recurrent disease in 66.6%; patients with benign lesions had recurrent pHPT in 23.5% after a prolonged disease-free period; recurrent benign pHPT occurred slightly more often in cases of discordant preoperative localization (60% vs 9%; $p = 0.06$).

Conclusion pHPT in HPT-JT is generally characterized by a benign and single-gland involvement, with a relatively increased risk of malignancy (15%). Parathyroid carcinoma needs extensive surgery because of high risk of permanent/recurrent disease (66.6%). In benign involvement, targeted unilateral exploration with selective parathyroidectomy may be effective in cases of concordant single-gland localization at preoperative localization imaging techniques. Bilateral neck exploration with subtotal parathyroidectomy might be preferred in cases of negative or discordant preoperative localization, because of the increased risk of multiglandular involvement and long-term recurrences (23.5%).

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Introduction

Hyperparathyroidism-jaw tumor syndrome (HPT-JT) (OMIM#145001) is a rare hereditary autosomal dominant disorder with variable and incomplete penetrance, characterized by familial primary hyperparathyroidism (pHPT) due to single or multiple parathyroid involvement, increased risk of malignancy, and associated tumors, including ossifying fibroma of maxilla/mandible, uterine and renal tumors [1, 2].

HPT-JT syndrome ensues from inactivating germline mutation of the cell division cycle protein 73 homolog (*CDC73*) gene (OMIM 607393), a tumor suppressor gene encoding parafibromin, a nuclear protein with antiproliferative properties [3–6].

At variance with hereditary variants of pHPT that have systematic multiglandular involvement and subsequently need bilateral neck exploration and extensive parathyroidectomy, a single-gland parathyroid involvement has been frequently reported in HPT-JT syndrome in a setting similar to sporadic pHPT; thus, it might be theoretically cured by targeted exploration and selective parathyroidectomy [3, 4, 7]. However, more extensive exploration and parathyroidectomy have also been suggested because of possible long-term metachronous multiglandular involvement and risk of malignancy [8, 9]. For these reasons, the optimal surgical strategy remains controversial.

The present study was aimed at evaluating the long-term outcome of parathyroid surgery in HPT-JT syndrome according to the extent of neck exploration and parathyroidectomy.

Material and methods

A retrospective analysis of follow-up medical files of subjects from five unrelated HPT-JT syndrome families including three to five generations, diagnosed at the Endocrine Surgery Unit of Padua University Hospital and previously published in part [3, 4], was performed. HPT-JT syndrome was defined by the presence of germline *CDC73* mutations, and/or coexistent personal and/or familial history of HPT-JT syndrome (according to the coexistence of pHPT, ossifying jaw fibromas, and other associated typical conditions, such as genito-urinary involvement) [10].

CDC73 gene was analyzed after informed consent as described elsewhere [5]. Patients' medical records were reviewed to gather relevant demographics, genetics, clinical features, pre- and postoperative work-up including pHPT and associated tumors features, details of operative and pathology reports, and the postoperative course. Follow-up data were obtained by clinical, laboratory, and radiological records or personal/general practitioner telephone interview designed to elicit all information regarding the patient's current state of health.

pHPT was biochemically diagnosed by the presence of inappropriately increased serum parathormone (PTH) and calcium levels (normal range 2.1–2.55 mmol/L), normal or high 24 h urine calcium levels. PTH reference normal levels varied over time and were not comparable; thus, PTH values were scored as multiples of the upper level of the normal range.

Preoperative parathyroid localizing studies were systematically performed: in each patient, at least two imaging techniques were used, including sestaMIBI/thallium–technetium scintigraphy and/or neck ultrasonography, computed tomography, magnetic resonance imaging.

Preoperative imaging results were categorized as "concordant" in suggesting a single-gland involvement when at least two different localizing studies showed a unique focus at the same anatomical site: "discordant" or "negative" when imaging results were not concordant or when no pathological gland localization was available, respectively.

The pHPT surgical explorative strategy was categorized as "bilateral neck exploration" (aimed at the identification of parathyroid glands at both sides), or "targeted unilateral exploration" (aimed at the identification of a single gland, according to the results of preoperative imaging). In some cases, intraoperative PTH was measured; preoperative (at induction of anesthesia) and postoperative (15 min after the removal of the last affected gland) assays were performed, and the degree of the decrease was calculated as percentage.

The histologic diagnosis was revised according to the World Health Organization guidelines [11].

At follow-up, pHPT evaluation included at least biochemical data (serum calcium, PTH, 24 h urine calcium) and neck ultrasonographic assessment. Only patients undergoing surgery for pHPT with complete outcome follow-up data (> 6 months) were included in the analysis.

The end-points of the study were the outcomes in terms of cure or persistent/recurrent disease and survival/mortality, as assessed at the time of the last available follow-up. Cure was defined as a disease-free status > 6 months with postoperative normalization of serum calcium and appropriate PTH levels in the absence of clinical and radiological signs of the disease: persistent disease as pHPT occurring within 6 months after surgery and recurrent disease as pHPT occurring after curative surgery (normocalcemia > 6 months). Overall survival was defined as time to the last follow-up and eventual specific disease-related mortality.

The study was approved by the Institution review board. Results have been expressed as absolute numbers,

percentage, median, and range. Statistical analysis was performed using Fisher's exact test, Mann–Whitney *U* test, Wilcoxon signed-rank test, and Spearman's correlation test, Kaplan–Meier as appropriate. Differences were considered statistically significant at $p < 0.05$.

Results

Fifty-nine subjects underwent clinical examination and genetic assessment (Fig. 1). Five different germline inactivating mutations of *CDC73* were identified. A frameshift mutation in exon 6 (c.433_442delinsAGA) in kindred A, a missense c.188T > C transition in exon 2 (resulting in the substitution Leu63Pro) in kindred B, a five nucleotides deletion in exon 2 (c.136_144 del5) in kindred C, a frameshift mutation (c.276delA p.Asp93Ilefs*16) in kindred D, and a mutation of the untranslated (UTR) sequence (5′UTR: c.-2insG (g.5182insG) in kindred E were found (Fig. 2).

Genetic and/or clinical features of HPT-JT were detected in 37 patients; 22 subjects were considered unaffected and excluded from further investigations. At the last available follow-up, 15 out of 37 affected subjects (median age 29 years, range 20–64) had no biochemical and clinical manifestations of pHPT; pHPT occurred in 22 patients (8 men and 14 women; median age at diagnosis 38 years, range 11–71). Two patients refused any surgical treatment, and the remaining 20 underwent surgery for symptomatic pHPT (Table 1). pHPT occurred in 68% (15 out of 22 patients) of affected patients older than 30 years. The median total calcium level in patients undergoing surgery was 3.24 mmol/L (range 2.56–4.57): the median PTH level 2.29-fold (range 1.04–57.1) higher than upper normal value (Table 2). Associated neoplasms were detected in 16 patients: a jaw ossifying fibroma ($n = 2$), a renal metastatic tumor ($n = 1$), and uterine involvement ($n = 14$; 60.8% of affected women).

Bilateral neck and targeted unilateral explorations were performed in 13 and 7 patients, respectively. No conversion from targeted unilateral to bilateral neck exploration was needed. A gross multiglandular hyperplastic involvement was evident at bilateral neck exploration in one patient (5%) who subsequently underwent subtotal parathyroidectomy (excision of 3 and half gland + bilateral transcervical thymectomy). In the remaining 19 patients (95%), a single-gland involvement was found and treated by selective parathyroidectomy. Among them, 3 patients also underwent an "en-bloc" unilateral parathyroidectomy with ipsilateral thyroid lobectomy, transcervical thymectomy, and clearance of the surrounding lymph-fatty tissue because of the suspicion of parathyroid carcinoma.

These findings were further confirmed at pathology and by the postoperative course: a parathyroid multiglandular hyperplastic involvement ($n = 1$), single adenomas ($n = 16$), and single carcinomas ($n = 3$) were diagnosed (Table 2, Fig. 3).

Intraoperative PTH measurements were available in 8 patients; the median decay was 94.5% (range 81–98) and predicted cure in all cases, even if a recurrent pHPT occurred two years later in a patient affected by parathyroid carcinoma.

The overall early cure rate was 95%; persistent pHPT occurred in one patient with parathyroid carcinoma who died 2.5 years later because of metabolic complications of hypercalcemia, instead of iterative surgery, as previously described [12, 13]. Another patient with parathyroid carcinoma experienced a pHPT recurrence 2 years after successful initial surgery due to local and distant metastases and was never cured instead of multiple reoperations; he is alive with persistent metastatic disease at a follow-up of 5 years after initial surgery. The last parathyroid carcinoma patient is currently disease free at a 2-year follow-up. Thus, the persistent/recurrent pHPT rate in parathyroid carcinoma was 66.6%.

All patients with benign parathyroid involvement were cured after initial surgery, but a metachronous recurrent pHPT occurred in patients (23.5%) due to a novel single-gland benign recurrent disease. All these patients underwent initial successful selective parathyroidectomy performed during a bilateral neck exploration; they experienced a recurrent pHPT after a disease-free interval of 5, 8, 9, and 27 years and were cured again by a targeted selective excision of a single parathyroid adenoma, guided by concordant preoperative localization at imaging techniques. To date, they are all disease free at a follow-up of 24, 6, 20, and 15 years after the reoperation, respectively. Thus, all patients with benign pHPT are disease free, at a median follow-up of 17.7 years (range 7–42) since initial surgery.

Patients with parathyroid malignancy had a significantly shorter long-term overall cure rate (33.4% vs 100%; $p = 0.016$), higher PTH (median 37.4 vs 2.18-fold; $p = 0.014$) and serum calcium levels (median 4.12 vs 3.15 mmol/L; $p = 0.02$), and larger tumors (median 40 vs 20 mm; $p = 0.03$) compared to benign pHPT involvement.

No significant differences in term of demographics and preoperative calcium and PTH levels were detected between patients with single and multiglandular involvement or between patients cured after a single operation and those who underwent reoperations for recurrent/persistent pHPT.

At initial surgery, preoperative localization studies suggested a concordant single-gland involvement in 70% of patients (11 benign and 3 malignant pHPT); they were

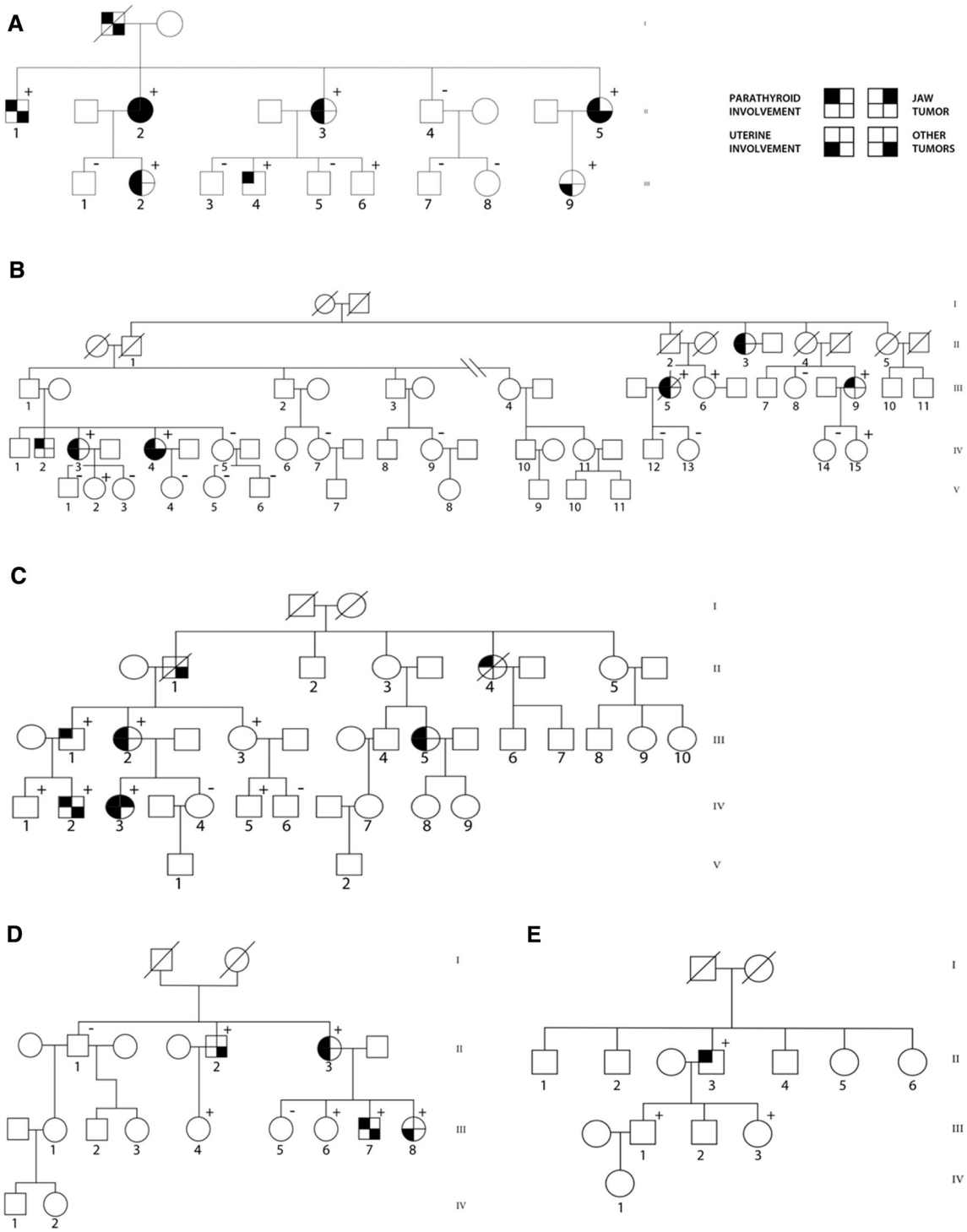

Fig. 1 Pedigrees of the families with HPT–JT. Square symbols indicate males, and round symbols indicate females. A diagonal slash mark through the symbol means deceased. The generations are labeled in roman numerals, and the individuals within each generation are designated with arabic numerals. Filled quadrants indicate a diagnosis or history of the trait indicated in the legend. The sign on the upper right of the symbol marks the subjects that have been tested for germline *CDC73* mutations: + indicates the presence of a *CDC73* mutation; − indicates the absence of the mutation

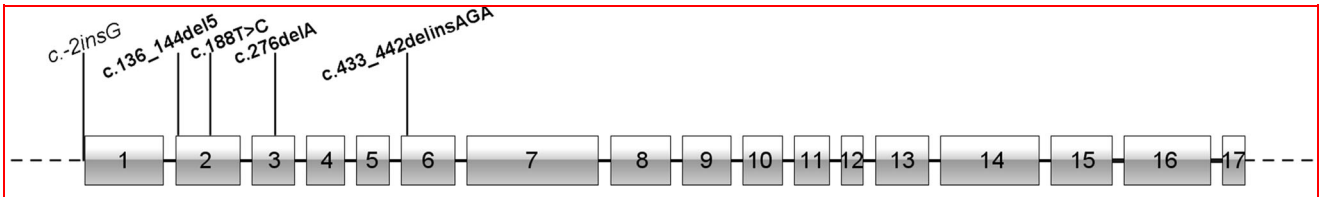

Fig. 2 Schematic of the *CDC73* gene with the 5 germline mutations identified in the HPT-JT kindreds. The exons are represented as gray-scale rectangles and the UTR as dashed lines. Mutations in coding sequences are reported in bold, and the UTR variant is in italic

negative in 1 patient with multiglandular parathyroid involvement and discordant in 5 patients with single adenoma. In patients with recurrent benign pHPT, a concordant single-gland localization was evident before reoperation in all cases.

When focusing on patients with single benign involvement at initial operation, all patients with preoperative concordant localization undergoing a targeted approach were cured; 3 out of 4 recurrences occurred in patients with discordant localization undergoing selective parathyroidectomy after bilateral exploration. Thus, a trend toward increased recurrent pHPT rate was observed in patients with preoperative discordant localization compared to concordant one (60% vs 9%; $p = 0.06$).

Morbidity comprised two cases of recurrent nerve palsy (one patient with a parathyroid carcinoma in which the nerve was infiltrated by the tumor and another case with a transient recurrent laryngeal nerve palsy after a bilateral exploration, fully recovered within 6 months after surgery) and five cases of transient postoperative hypoparathyroidism, which occurred more frequently in patients undergoing bilateral exploration compared to targeted approach (54% vs 0%, respectively; $p = 0.04$).

Discussion

pHPT represents the main finding in HPT-JT syndrome, occurring in more than 95% of mutation carriers, with frequent occurrence in early adulthood (68% of subjects older than 30 years in the present series), even if incomplete penetrance of the disease has been demonstrated also by the identification of some older healthy mutation carriers [14]. Despite the nomenclature of the syndrome, jaw tumors may be found only in approximately 30% of cases [2, 4, 8, 9, 15–20], while uterine involvement occurs in more than half of affected women (5.4% and 60.8% in the present series, respectively).

The variable expressivity of the disease is possibly related to the tumor suppressor role of *CDC73*, requiring a biallelic inactivation for tumor development; germline *CDC73* mutations may offer a predisposition to neoplastic progression, and a second genetic or epigenetic hit is necessary for the development of parathyroid tumors [4, 14, 16, 17, 21], as also previously demonstrated by the absence of parafibromin expression in affected parathyroid tumors, but not in normal glands from the same HPT–JT patients [3, 4].

These findings may explain the frequently reported higher rate of single-gland parathyroid involvement in HPT-JT at variance with other variants of hereditary pHPT. In fact, the literature reports approximately 140 HPT-JT syndrome kindred and 350 pHPT patients [2, 4, 8, 9, 15–20]; a single-gland involvement at onset was confirmed in approximately 80% of cases, with a synchronous multiglandular involvement in less than 20%, even though a metachronous multiglandular involvement leading to recurrent pHPT may occur in 25% of cases. Malignant parathyroid involvement is another distinctive feature of HPT-JT, being reported in 20% of cases in the literature [2, 4, 8, 9, 15–20]; it leads to increased rates of persistent and recurrent disease, thus needing a more aggressive surgical treatment.

For these reasons, the optimal surgical approach to *CDC73*-related pHPT has not yet been established and remains controversial, varying between bilateral or targeted neck exploration, and extensive or limited parathyroidectomy.

Theoretically, the definitive cure can be obtained only by a complete bilateral neck exploration and total parathyroidectomy, resulting in permanent hypoparathyroidism; however, total parathyroidectomy is clearly not always successful, and the morbidity related to permanent hypoparathyroidism in young patients remains unacceptable. Thus, the surgical strategy should be aimed—whenever feasible—to a pragmatic compromise achieving the longest possible normocalcemia without permanent hypoparathyroidism, minimizing surgical morbidity and facilitating possible future surgery for recurrent disease [1, 4, 14]. For these reasons, bilateral neck exploration and subtotal parathyroidectomy or total parathyroidectomy with autotransplantation were proposed in the past [8, 20]. However, autotransplantation has been considered a risky procedure because it may allow the seeding and dissemination of eventual parathyroid malignancy [9].

Table 1 Clinical features of 20 patients undergoing surgery for primary hyperparathyroidism in HPT-JT syndrome

Kindred patient	Sex	Age at diagnosis (years)	Preoperative single-gland localization	Neck exploration	Parathyroidectomy	Parathyroid tumors (number and pathology)	Morbidity	Operative outcome
A I/1	M	56–58[a]	Concordant	Bilateral	Selective	1 Carcinoma + metastases[a]	Definitive RLNP	Persistence—deceased 2.5 years after initial surgery
A II/1	M	30	Discordant	Bilateral	Selective	1 Adenoma		Cured
A II/2	F	18–45[a]	Discordant	Bilateral	Selective	1 Adenoma + 1 adenoma[a]		Recurrence after 27 years—cured[a]
A II/3	F	42	Discordant	Bilateral	Selective	1 Adenoma	Transient HypoPTH	Cured
A II/5	F	21–30[a]	Discordant	Bilateral	Selective	1 Adenoma + 1 adenoma[a]		Recurrence after 9 years—cured[a]
A III/2	F	11	Concordant	Bilateral	Selective	1 Adenoma	Transient HypoPTH	Cured
B II/3	F	52	Concordant	Unilateral	Selective	1 Adenoma		Cured
B III/7	F	44	Concordant	Bilateral	Selective	1 Adenoma		Cured- deceased for ovarian cancer
B III/11	F	32	Concordant	Bilateral	Selective	1 Adenoma		Cured
B IV/2	M	43	Concordant	Unilateral	Selective	1 Adenoma		Cured
B IV/3	F	38	Concordant	Bilateral	Selective	1 Adenoma	Transient RLNP	Cured
B IV/4	F	25–30[a]	Discordant	Bilateral	Selective	1 Adenoma + 1 adenoma[a]		Recurrence after 5 years—cured[a]
C III/1	M	52	Negative	Bilateral	Subtotal	4 Multiglandular hyperplasia	Transient HypoPTH	Cured
C III/2	F	38	Concordant	Bilateral	Selective	1 Adenoma	Transient HypoPTH	Cured
C III/5	F	37	Concordant	Unilateral	Selective	1 Adenoma		Cured
C IV/2	M	22	Concordant	Unilateral	Selective	1 Adenoma		Cured
C IV/3	F	23–31[a]	Concordant	Bilateral	Selective	1 Adenoma + 1 adenoma[a]	Transient HypoPTH	Recurrence after 8 years—cured[a]
D II/3	F	41	Concordant	Unilateral	Selective	1 Adenoma		Cured
D III/7	M	22–24[a]	Concordant	Unilateral	Selective	1 Carcinoma + metastases[a]		Recurrence after 2 years—persistence[a]
E II/2	M	52	Concordant	Unilateral	Selective	1 Carcinoma		Cured

M Male, *F* Female, *NA* not available, *RLNP* recurrent laryngeal nerve palsy, *HypoPTH* hypoparathyroidism

[a]At reoperation

Table 2 Summary of features at initial surgery of 20 patients undergoing parathyroidectomy for *CDC73*-related pHPT

Sex *n* = (%)	
Male	7 (35%)
Female	13 (65%)
Age at surgery (years) median [range]	37.5 [11–58]
Serum calcium levels (mmol/L) median [range]	3.24 [2.56–4.57]
PTH-fold increase median [range]	2.29 [1.04–57.1]
Preoperative localization *n* = (%)	
Concordant	14 (70%)
Discordant	5 (25%)
Negative	1 (5%)
Neck exploration *n* = (%)	
Bilateral	13 (65%)
Unilateral	7 (35%)
Parathyroidectomy *n* = (%)	
Selective	19 (95%)
Subtotal	1 (5%)
Pathology *n* = (%)	
Benign	17 (85%)
Carcinoma	3 (15%)
Gland involvement *n* = (%)	
Single	19 (95%)
Multiglandular	1 (5%)
Recurrence *n* = (%)	6 (30%)

Sarquis [8] in a multicenter series of 11 patients from 3 kindred with *CDC73* germline mutations noted a synchronous multiglandular involvement at initial operation in 54.5% of patients, with a single-gland involvement in 45.4%; parathyroid malignancy in 9% and an overall persistence/recurrence rate of 80%; thus, a bilateral exploration with subtotal parathyroidectomy was suggested as initial approach. More recently, Mehta [9] in another multicenter series of 16 individuals from 7 HPT-JT families found a multiglandular involvement only in 31% of patients, a single-gland involvement in 69%, parathyroid carcinoma in 37.5% and recurrent pHPT in 20%, suggesting a bilateral neck exploration with selective removal only of abnormal gland/s. Routine subtotal or total parathyroidectomy was found to confer no benefit and likely leading to increased risk of permanent hypoparathyroidism.

The present study, at the best of our knowledge, reported the largest monocentric series including 20 HPT-JT operated patients. It represents a further analysis of previously published data [3, 4], including 2 additional kindred and 15 new patients undergoing genetic *CDC73* assessment, with a significantly longer follow-up. At initial surgery, a prevalent single-gland involvement (95%), malignancy in 15% and an overall persistence/recurrence rate of 30% were found, as demonstrated at a prolonged follow-up (median 16 years; range 2.5–42) by the intraoperative finding, pathology and postoperative course.

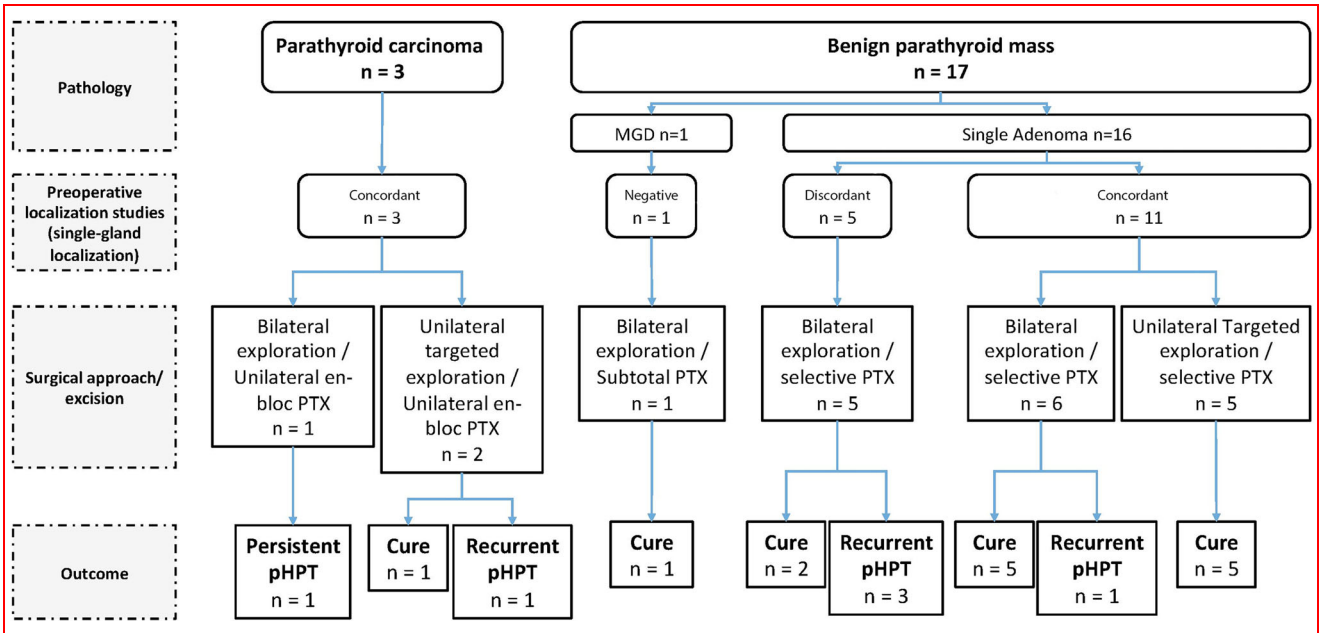

Fig. 3 Flowchart showing pathology, surgical approach, results of preoperative localizing imaging and outcomes in 20 patients undergoing parathyroidectomy for HPT-JT Syndrome. *MGD* multiglandular hyperplastic parathyroid disease, *PTX* parathyroidectomy, *pHPT* primary hyperparathyroidism

The outcome was significantly worse in parathyroid carcinoma compared to benign involvement (overall cure rate 33.3% vs 100%), confirming the need for an aggressive approach in the case of malignancy. Parathyroid carcinoma may be preoperatively suspected by higher calcemia and PTH levels, and larger tumor size. These finding should lead to "en-bloc" resection of the affected gland with the surrounding soft lymph-fatty tissues, the ipsilateral thyroid lobe, the remaining normal parathyroid and thymus in an "unilateral complete parathyroid clearance," in order to prevent capsular spillage and local seeding [12], and to decrease the possibility of recurrent disease and the risk of reoperation at the same side [12–14].

By contrast, targeted unilateral approach with selective parathyroidectomy and intraoperative PTH measurement might be the preferred strategy, in the same setting of sporadic HPT, when malignancy is unlikely and a single-gland involvement is preoperatively suggested by concordant localizing imaging techniques (as occurred in 70% of case of the present series) [1, 4, 7]. This strategy might achieve a high cure rate (100% in the present experience); it might have the potential advantage of causing lower risk of hypoparathyroidism and minimal tissue trauma, facilitating reoperations in the case of remedial surgery for recurrent pHPT. However, a long-term follow-up is required in HPT-JT patients because of the risk of recurrent and/or new disease even in the case of benign involvement. In the present experience, it occurred in 23.5% after a long disease-free period (median 8.5 years; range 5–27); in all cases, recurrences occurred in a single gland with benign involvement, and long-term cure (median 17.5 years, range 6–24) was achieved again at reoperation by limited parathyroidectomy. Moreover, 75% of benign recurrences in the present study occurred with preoperative discordant imaging results. For these reasons, in agreement with the European Society of Endocrine Surgeons guidelines [14], a targeted unilateral approach with selective parathyroidectomy might be proposed in the case of preoperative localization showing a concordant single-gland involvement; eventual recurrent disease could be more easily treated by targeted exploration and limited excision, facilitated by previous focused approaches. In case of negative or discordant preoperative localization or intraoperative suspicion of multiglandular involvement, a bilateral exploration with subtotal parathyroidectomy might be preferred, in order to decrease the risk of recurrent pHPT and need for reoperation in a scarred neck, because of the risk of morbidity related to iterative surgery.

Conclusion

HPT-JT syndrome is generally characterized by a parathyroid benign and single-gland involvement, with a relatively increased risk of malignancy (15%). Parathyroid carcinoma needs extensive surgery because of the high risk of persistent or recurrent disease (66%). In benign involvement, targeted unilateral exploration with selective parathyroidectomy may be effective for concordant single-gland localization at preoperative localizing techniques. Bilateral neck exploration with subtotal parathyroidectomy might be preferred in cases of negative or discordant preoperative localization, because of the increased long-term recurrence rate (23.5%).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study has been approved by the Institution review board.

Informed consent Informed consent was obtained from all individual participants included in the study.

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