

Causes and Treatment of Recurrent Hyperparathyroidism After Subtotal Parathyroidectomy in the Presence of Multiple Endocrine Neoplasia 1

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Abstract

Background Subtotal parathyroidectomy (SPTX) is the treatment of choice for hyperparathyroidism in a patient with multiple endocrine neoplasia type 1 (HPT-MEN-1). There are scarce data on the causes, timing, and appropriate surgical treatment of patients with recurrent HPT-MEN-1. The aim of this study was to investigate the timing, causes, site of recurrence, and surgical treatment of recurrent HPT-MEN-1 in patients who underwent SPTX.

Methods The study was a retrospective review of prospectively collected data on patients with HPT-MEN-1 with SPTX at two referral institutions. The data collected included the following: demographics, duration of follow-up, weight of resected parathyroid tissue, type of remnant, time to reoperation, cause/site of recurrence, and surgical treatment. We studied prognostic factors of recurrence.

Results A total of 69 patients underwent SPTX and were followed for a mean of 75.3 months. After the surgery, 15 patients were left with a single “normal” gland and 54 with a 50- to 70-mg remnant of a partially excised abnormal gland. Nine patients (13%) had a recurrence within a mean of 85 months (12–144 months). Patients with a recurrence had been followed longer (115 vs. 66 months; $p = 0.005$). Five recurrences occurred in a parathyroid remnant, 3 in a previously “normal” gland; the fifth recurrence was in both a hyperplastic remnant and a fifth gland. Remedial surgery

included five subtotal resections and four immediate parathyroid autotransplantations. Two patients had a second recurrence due to a supernumerary gland. Factors related with recurrence are the follow-up time ($p < 0.01$) and thymectomy ($p < 0.003$).

Conclusions Recurrence of HPT-MEN-1 usually is located in preserved parathyroid tissue with no preference for a previously normal gland or a remnant. A second recurrence is most likely seen in a supernumerary gland. Recurrence is associated with the follow-up time and thymectomy.

Introduction

Hyperparathyroidism (HPT) is the most common feature of multiple endocrine neoplasia type 1 (MEN-1) syndrome, affecting more than 80% of the carriers of the mutation that causes this disease [1]. This is the first manifestation of the disease and usually occurs between the ages of 30 and 50 years but may appear even before [2].

HPT in patients with MEN-1 is characterized by parathyroid hyperplasia, although it has been suggested that its main feature is the formation of sequential adenomas [3]. Parathyroid glands are typically asymmetric in size, and one or two glands of normal size and aspect are frequently found. Supernumerary glands are found in 20 to 30% of cases [3, 4]. Therefore, successful surgical treatment is difficult, and recurrence rates are high (10–80%). It is not uncommon for the MEN-1 patient to have hypocalcemia, which can cause more severe disturbance than moderate hypercalcemia.

The treatment of choice is debatable: total parathyroidectomy versus subtotal parathyroidectomy (SPTX). Some experienced groups believe that SPTX is the most appropriate treatment, but recurrence is common in those

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patients followed over long periods of time. There are scarce data on the causes, timing, and appropriate surgical treatment of patients with recurrent HPT-MEN-1 [5].

The objective of this study was to report our experience with MEN-1 patients who had HPT treated using SPTX by investigating the timing, causes, site, and surgical treatment of recurrence.

Patients and methods

A retrospective study has been carried out of patients treated for primary hyperparathyroidism (PHPT) belonging to families with MEN-1 syndrome who were operated on using SPTX, with a focus on those that had a relapse during follow-up. All were diagnosed and treated at two referral university hospitals: Hospital Universitario Virgen de la Arrixaca in Murcia, Spain and Hospital del Mar of Barcelona, Spain.

Between 1980 and 2008, a total 101 patients were diagnosed with MEN-1 using genetic and/or clinical studies. In all, 78 were diagnosed with HPT, and 69 of them underwent SPTX. Of the latter, 9 (13%) patients experienced recurrent disease during the follow-up. The following data were recorded.

- *Clinical and diagnostic data:* age at diagnosis, sex, presence (or not) of secondary symptoms of HPT; serum calcium (s-Ca) and intact parathyroid hormone (iPTH) levels.
- *Surgical treatment:* Four parathyroid glands were found in each the patients, and SPTX was performed. SPTX is defined as the resection of at least three glands, leaving a remnant of approximately 50 to 60 mg (equivalent to the size of a normal gland). Thus, we differentiated between two groups: one in which a “normal” parathyroid gland was left in situ (parathyroidectomy of three glands) and another in which a 50- to 60-mg remnant of diseased gland was left. In all cases, the remnant was marked with a nonresorbable suture. The association (or not) of transcervical thymectomy was also assessed. Surgical complications (recurrent paralysis and hypoparathyroidism)—both transitory and definitive—were also recorded.
- *Follow-up.* The following definitions were used.
 - Cure: a patient with normal s-Ca and iPTH values or with hypoparathyroidism at least 6 months after the intervention
 - Recurrence: a patient with high calcium and iPTH levels after a normal period of at least 6 months after surgery
 - Persistence: a patient whose s-CA and PTH levels remained high after the initial surgery

The following variables were recorded in patients who had recurrent disease.

- Age and sex.
- Time to recurrence after surgery.
- Laboratory tests (s-Ca and iPTH).
- Imaging tests: MIBI scan and ultrasonography/computed tomography (US/CT) scan.
- Cause of the recurrence.
- Intervention carried out during the initial surgery on the parathyroid glands as well as the thymus.
- Reintervention: findings and technique carried out; mean weight of the resected tissue; localization of the recurrence; morbidity (recurrent paralysis and hypoparathyroidism, transitory or recurrent).
- Cure rate and recurrence after the second surgical intervention.

Possible prognostic factors of recurrence were studied in patients treated for HPT-MEN-1 after appropriate SPTX. The chi-squared test, Student's *t*-test, and logistic regression were used for statistical analysis. Significance was set at $p < 0.05$.

Results

There were 69 patients with SPTX included in the study. Their mean age was 40.8 years (range 17–75 years), and 35 were female (50.7%). At the time of diagnosis 35 (50.7%) were symptomatic; the most common symptoms were bone pain in 68.2%, ureteral colic in 60.2%, and neurologic symptoms in 30%.

SPTX was carried out on all of these patients, after identifying of all four glands, a normal-sized parathyroid gland was left in place in 15 patients and a 50- to 70-mg remnant of an enlarged gland was left in the remaining 54 cases. Thymectomy was also done in 60 cases (87%).

No patient had persistent HPT. Three patients experienced permanent hypoparathyroidism, and none had a definitive recurrent laryngeal nerve lesion.

After a mean follow-up time of 75.3 months (range 9–300 months), 60 patients (87%) had normal calcium and iPTH levels. The remaining 9 patients (13%) had recurrence of the HPT. Table 1 provides a summary of the general results of the patients treated with SPTX.

HPT recurrence

The mean age of the patients with recurrent disease was 36.3 years (range 23–48 years); eight were female (88.9%). The clinical characteristics of cases with recurrence are shown in Table 2.

Table 1 Demographic and clinical data for 69 patients with HPT-MEN-1 undergoing SPTX

Age (years), mean and range	40.9 years (17–75)
Sex (F/M)	35/34
Clinical symptoms	
None	34 (49.3%)
Some	35 (50.7%)
Calcium, serum (mg/dl)	11.5 (10.2–16.0)
iPTH (pg/ml)	164 (67–610)
SPTX with	
Remnant of a hyperplastic gland	54 (78.3%)
“Normal” gland	15 (21.7%)
Thymectomy	60 (87.0%)
Weight of resected tissue (mg)	1380
Cure rate	87% (60/69)
Recurrence rate	13% (9/69)

HPT hyperparathyroidism, *MEN-1* multiple endocrine neoplasia type 1, *iPTH* intact parathyroid hormone, *SPTX* subtotal parathyroidectomy

Time to recurrence after surgery was 85 months (range 12–144 months). The mean s-Ca and iPTH values were 11.4 mg/dl and 188 pg/ml, respectively. During the first surgical intervention, we left a hyperplastic parathyroid remnant in six patients (66.7%) and a “normal” parathyroid gland in three (33.3%). In five of the nine cases (55.6%), thymectomy was performed as well.

The cause of recurrence was hyperplasia of the parathyroid remnant in five patients, hyperplasia of the normal gland in three, and the presence of a fifth gland and hyperplasia of the remnant in the remaining case.

Recurrence was diagnosed by a ^{99m}Tc-methoxyisobutylisonitrile (MIBI) scan in all cases. In the eight cases with one-site recurrence, the diseased parathyroid tissue was correctly located. In the remaining case, in which there was a fifth ectopic gland and remnant hyperplasia, only the fifth

thymic gland was identified. US (five cases) and CT (five cases) scans were all positive for the parathyroid lesion.

All nine patients underwent reoperation. In four cases parathyroidectomy and autotransplantation in the forearm was carried out, and in five cases SPTX of the hyperplastic gland was done, leaving a remnant of approximately 50 to 60 mg. The mean weight of the resected parathyroid tissue at reoperation was 938 mg, similar to the weight of the tissue resected during the first surgical intervention after SPTX (three or three and a half glands), which was 1380 mg.

One case of permanent hypoparathyroidism (8.3%) was the only complication reported as a result of reintervention. There were no cases of recurrent nerve paralysis.

After reoperation, seven of the nine patients remained normocalcemic, with normal PTH levels, during a follow-up of 124 months (range 48–180 months). Two patients had a further relapse due to the presence of supernumerary glands, one located in the upper mediastinum and another in the intercricothyroidal region (a sixth gland) (Fig. 1).

The two factors affecting recurrence rates were (1) thymectomy not carried out during the first surgical intervention ($p < 0.003$) and (2) the follow-up time ($p < 0.01$) (Table 3).

Discussion

The surgical management of HPT in MEN-1 is complex. Unlike primary sporadic HPT, which is curable in more than 90% of cases, parathyroidectomy for HPT-MEN-1 is followed by recurrence in 20% to 80% of cases. In patients without previous suspicion of MEN-1 and with incomplete surgery, the persistence/recurrence rate reaches 100% [6, 7].

HPT-MEN 1 is being diagnosed earlier because of the increased awareness of the importance of a family history

Table 2 Demographic and clinical data for patients with recurrence

Age (years)	Sex	Symptoms	s-Ca (mg/dl)	iPTH (pg/ml)	SPTX ^a	Thymectomy	Cause of recurrence	Reoperation	Cured
32	F	No	11.0	210	Hyperplastic	No	HR	PTX + AUTX	No
48	F	Yes	12.0	300	Hyperplastic	No	HR	PTX-R	Yes
23	F	No	11.4	137	Normal	Yes	HR	PTX-R	Yes
31	F	Yes	11.8	138	Normal	No	HR	PTX-R	Yes
42	F	No	10.9	125	Hyperplastic	Yes	HR	PTX-R	Yes
32	F	Yes	12.6	273	Hyperplastic	Yes	HR	SPTX + AUTX	No
36	F	Yes	11.4	–	Normal	Yes	HR	SPTX + AUTX	Yes
45	M	Yes	10.8	–	Hyperplastic	Yes	HR	SPTX + AUTX	Yes
38	F	No	10.7	135	Hyperplastic	No	HR + 5th gland	SPTX-R + 5th gland	Yes

Hyperplastic hyperplastic parathyroid remnant, *Normal* normal parathyroid left in situ, *HR* hyperplasia of remnant, *PTX + AUTX* parathyroidectomy + autotransplant, *SPTX-R* subtotal parathyroidectomy of remnant

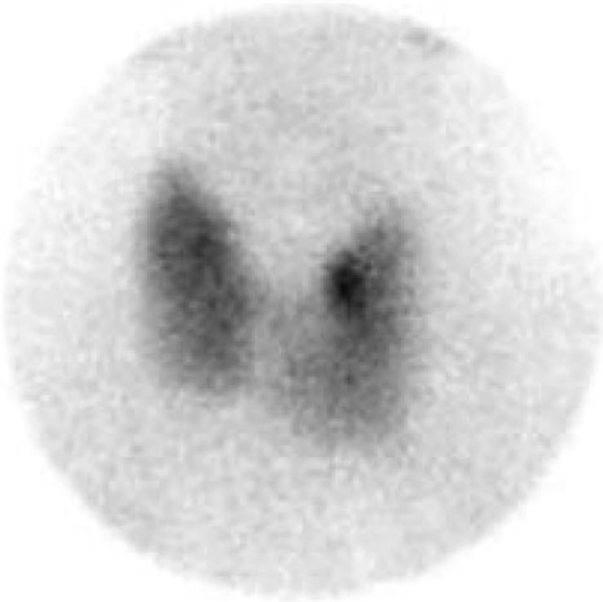


Fig. 1 ^{99m}Tc -MIBI (pinhole) parathyroid scan of a sixth gland (in the intercricothyroidal area) causing a second recurrence in a patient with hyperparathyroidism and multiple endocrine neoplasia 1

and widespread use of genetic analysis [8, 9]. The indication for surgery is obvious in patients with symptoms or with severe hypercalcemia; and in these circumstances there appears to be a good risk/benefit balance. In young patients with asymptomatic, mild hypercalcemia, however, the timing of surgery is controversial, given that recurrence rates increase in relation to the follow-up time. These patients sometimes have reduced bone mineral density due to the fact that HPT occurs during the bone mass accretion period. Thus, bone assessment by densitometry is essential.

Surgery is the most effective way to preserve bone mass in patients with HPT [10].

Although it has been difficult to establish a genotype–phenotype relation, aggressive HPT at an early age is more common in some families [11–13]. In our series, two cases of recurrence occurred in the same four members of a family.

Surgery for HPT-MEN-1 can be difficult. Although it always evolves toward four-gland disease, this is not necessarily synchronous; therefore, glands can be found with a normal appearance. There are differences in terms of the volume, size, and weight of the affected parathyroid glands. If MEN-1 has not been diagnosed preoperatively, surgical treatment is probably inappropriate [14–16] owing to failure to explore the four glands or missing a supernumerary gland, which occurs in up to 30% of cases [17].

The surgical technique should involve identification of the four glands and resection of all but 50 to 70 mg of the parathyroid tissue. The aims of surgery are to (1) obtain and maintain levels of normocalcemia for as long as possible; (2) prevent recurrence; (3) avoid hypocalcemia as a surgical complication; and (4) facilitate further surgery in case of recurrence [6].

Total parathyroidectomy with autotransplantation has been proposed for HPT-MEN-1 due to the fact that, theoretically, resection of all parathyroid tissue reduces the need for neck reexploration. Graft function and graft-dependent recurrence can be assessed by the Casanova test [18]. However, total parathyroidectomy is followed by severe hypocalcemia, requiring treatment with calcium and calcitriol, until the graft begins to function; furthermore, the chance of cervical recurrence cannot be completely eliminated with this technique. Consequently, there is an increase in the possible number of recurrence sites, and reintervention

Table 3 Univariate study of factors related to recurrence

Factor	Recurrence		<i>p</i>
	Yes (<i>n</i> = 9)	No (<i>n</i> = 60)	
Age at diagnosis of HPT (years)	36.3	41.54	NS
Clinical symptoms			
Asymptomatic (<i>n</i> = 34)	4 (11.7%)	30 (88.2%)	NS
Symptomatic (<i>n</i> = 35)	5 (14.3%)	30 (85.7%)	
s-Ca (mg/dl)	11.4	11.5	NS
iPTH (pg/ml)	188	160	NS
Surgical technique			
Leave hyperplastic gland remnant (<i>n</i> = 54)	6 (11.1%)	48 (88.9%)	
Leave “normal” gland (<i>n</i> = 15)	3 (20%)	12 (80%)	NS
Weight of resected tissue	938	1380	NS
Bilateral thymectomy			
Yes (<i>n</i> = 60)	5 (9%)	30 (91%)	0.003
No (<i>n</i> = 9)	4 (80%)	27 (20%)	
Follow-up (months), mean	144.9	66.6	0.01

due to graft recurrence can be technically difficult. Hypocalcemia rates, unlike recurrence rates, are usually high, reaching 40 to 50% [17]. On the other hand, Kivlen et al. [7] reported a 30% nonfunctional autotransplantation rate (definitive hypoparathyroidism), with better results if grafting is carried out immediately [7]. Moreover, in this series, the mean time to graft-dependent recurrence was 15 months, with three cases occurring within 6 months.

Currently, there seems to be an evolving consensus among experienced groups that SPTX is the technique of choice to treat hyperparathyroidism associated with MEN-1. Its advantages are that it allows precise location of the neck remnant, surgery is not more complex, and there is less hypocalcemia. However, the term “SPTX” is a little ambiguous and may include several degrees of parathyroid resection, with varying results [19]. We have considered SPTX as the exeresis of at least three parathyroid glands, leaving a remnant of approximately 50 to 60 mg (equivalent to the size of a normal gland) [17, 19, 20]. We recommend leaving a remnant of the upper gland, preserving its irrigation and leaving the gland with the most normal appearance. The remnant is marked with a clip or a non-reabsorbable suture so it can be easily identified should the patient require reexploration. In our series, remnants corresponded to an enlarged gland in 54 cases (of which 6 had recurrence) and a “normal” parathyroid gland in 15 cases (of which 3 had a recurrence). We did not find a difference in the recurrence rates for the two procedures. On the other hand, only one patient with a hyperplastic gland remnant had permanent hypoparathyroidism after surgery,

SPTX results vary according to published studies (Table 4). For example, Goudet et al. [18] reported a persistent hypercalcemia rate of 9% and a recurrence rate of 15%, with 15% of the treated cases remaining hypocalcemic. In 1998, in a prospective study by Hellman et al. [17], there was a 22% persistence rate and 44% recurrence, with no patients having permanent hypocalcemia. Leaving a remnant of 25 mg, Burgess et al. [21] obtained a lower recurrence rate (19%) at the expense of a higher prevalence of permanent hypocalcemia (24%). In our series, with a

mean follow-up time of 75 months, the recurrence rate was 13%.

It has been suggested that intraoperative PTH determination can ensure that all diseased parathyroid tissue was resected. Its use in HPT-MEN-1 patients is controversial [22, 23] mainly because decreases of >50% have been reported after resecting the first gland in cases of multi-glandular disease [24, 25]. Because of this high rate of false-positive intraoperative PTH tests, there are some who believe that the cure criteria in patients with MEN-1 should be stricter—even as high as PTH declining > 80% [26].

Transcervical thymectomy is recommended given the possibility that parathyroid cell nests within the cervical prolongations of the thymus may become enlarged owing to the same stimulus that caused hyperplasia in normal glands. We carried out 60 thymectomies (87%) in our series and found a relation between the recurrence of HPT and leaving the thymus in situ. Thus, thymectomy should be considered to be an essential part of SPTX [27].

The most significant factor causing recurrence in HPT-MEN-1 is the follow-up time: Patients with a longer follow-up time had higher recurrence rate [16, 17, 19]. Other prognostic factors of recurrence proposed are inadequate surgery, age at intervention, and associated thymectomy [16, 19, 27, 28]. In our series, only the follow-up time and thymectomy were related to recurrence, whereas age at surgery, type of remnant, and weight of resected tissue had no influence on the relapse rate.

The indications for reintervention are the same as those for primary intervention: severe hypercalcemia, the presence of symptoms, and/or alterations in bone mineral density. Reinterventions for HPT-MEN-1 are technically difficult. There is a high risk of persistent/recurrent hypercalcemia, definitive hypoparathyroidism, or recurrent paralysis. Therefore, patients should be referred to specialized units. These patients should be studied using a MIBI scan (preferably with single photon emission computed tomography (SPECT) and a noninvasive radiologic technique. In our series, the ^{99m}Tc-MIBI scan identified the residual parathyroid tissue in all nine cases. However, in

Table 4 Results of various series of SPTX for HPT-MEN-1

Study	No. of patients	Persistence (%)	Recurrence (%)	Hypocalcemia (%)
Hellman [17]	27	22	44	0
Goudet [19]	53	19	–	15
Burgess [28]	37	8	19	24
O’Riordain [16]	54	0	17	8
Kraimps [31]		14	36	–
Lambert [11]	16	–	43	7
Hubbard [6]	21	–	10	1
Lee [32]	6	–	16.7	50
Balsalobre	69	–	13	4.3

the case with a double recurrence (a fifth ectopic gland and remnant hyperplasia) only the fifth thymic gland was located. These results agree with those of Shepperd et al. [29] in 13 cases of reintervention. Thus, a positive scan does not always imply that a selective approach will be successful, particularly if the initial surgery was incomplete (i.e., without thymectomy). Intraoperative PTH determinations could be useful in cases of recurrence. Kivlen et al. [7] reported 14 patients, 4 of whom had high PTH levels after resection of a first enlarged gland and required a more extensive examination than the one indicated by the scan.

In our series, results of the first reintervention were similar whether resection and grafting in the forearm or trimming of the hyperplastic gland were carried out. In two patients, a second recurrence was due to supernumerary glands, as has been reported by others [17]. Complications in this series of reinterventions are minimal, with only one case of hypoparathyroidism being registered.

Medical treatment has also been proposed for patients with recurrent disease who are at high surgical risk. Shoback et al. [30] published a randomized study using cinacalcet versus placebo and found a persistent decrease in s-CA and PTH levels.

Conclusions

SPTX is a good technique for treating HPT-MEN-1 and has an acceptable rate of recurrence (13% at 85 months). Relapse is usually related to the initially preserved parathyroid tissue with no preference for a previously normal gland or a remnant. The recurrence rate increases with the length of follow-up and not having carried out a thymectomy. A second recurrence is most probably due to a supernumerary gland.

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